National Guideline Centre

Final

Glaucoma

Glaucoma: diagnosis and management

NICE guideline 81

Appendices A–T

2017

Final draft

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians

The Royal College of Surgeons of England

Royal College of General Practitioners

Royal College of Nursing

NGC National Guideline Centre

NICE accredited

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Contents

Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline scope

Glaucoma: diagnosis and management

Topic

NICE intends to partially update the guideline on the diagnosis and management of chronic open angle glaucoma (CG85). This will include case finding and referral from primary to secondary care. Other areas for update are set out in the surveillance review decision.

Some areas of the guideline are not being updated – for details see key areas that will be covered and areas that will not be covered.

The guideline is for use in the NHS in England.

The guideline will be developed using the methods and processes outlined in Developing NICE guidelines: the manual.

For more information about why this guideline is being developed, and how the guideline will fit into current practice, see the context section.

Who the guideline is for

- People using services, families and carers and the public.
- Optometrists.
- Ophthalmologists.
- Orthoptists.
- Pharmacists.
- Nurses.
- GPs.

It may also be relevant for:

- Commissioners of services.

NICE guideline: Glaucoma final scope 1 of 14

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive.

Equality considerations

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to age, family origin, socioeconomic status, and moving from place to place (for example, people who are homeless and Gypsies and Travellers).

1 What the guideline is about

1.1 Who is the focus?

Groups that will be covered:

- Adults (18 and over) with confirmed chronic open angle glaucoma.
- Adults (18 and over) with suspected chronic open angle glaucoma.
- Adults (18 and over) with ocular hypertension.
- Adults (18 and over) with chronic open angle glaucoma or ocular hypertension associated with pseudoexfoliation or pigment dispersion.
- Populations with a higher prevalence of chronic open angle glaucoma and groups who may have worse clinical outcomes, including:
  - adults with a family history of chronic open angle glaucoma
  - older people (over 70 years)
  - adults of black African or black Caribbean family origin
  - adults living in areas of socioeconomic deprivation
  - younger adults with chronic open angle glaucoma or ocular hypertension (under 50 years).

Groups that will not be covered

- Children and young people under 18 years.
- People with secondary glaucoma, for example, neovascular or uveitic glaucoma. (Chronic open angle glaucoma or ocular hypertension variants associated with pseudoexfoliation or pigment dispersion are not excluded.)
- People with, or at risk of, primary or secondary angle closure glaucoma.
- People with primary congenital, infantile or childhood glaucoma.

1.2 Settings

Settings that will be covered

- All settings in which NHS-funded healthcare is received.

1.3 Activities, services or aspects of care

We will look at evidence on the areas listed below when developing the guideline, but it may not be possible to make recommendations on all the areas. The decisions relating to which areas from the published guideline will be updated by this update and which areas will not be updated have been fully explained in the surveillance review decision. Areas from the published guideline which will not be updated as part of this update may be considered by future updates.

Key areas that will be covered

Areas from the published guideline that will be updated

1 The diagnostic accuracy of tests[1] used for the provisional and definitive identification and monitoring of chronic open angle glaucoma, suspected chronic open angle glaucoma and ocular hypertension in people

[1] Visual field assessments are an integral part of diagnostic assessment. This update is not reviewing visual field assessments because there is no new evidence (as identified by the surveillance review decision). Recommendations from CG85 on visual field assessment will be carried forward as part of this update.

presenting to community optometrists and those referred to hospital eye services. Tests will involve 1 or more of the following:

- measuring intraocular pressure
- assessing the optic nerve head
- assessing the anterior chamber angle
- measuring the central corneal thickness.

2 The use of pharmacological interventions for people with chronic open angle glaucoma, suspected chronic open angle glaucoma or ocular hypertension (for example, when treatment should be started and how long it should be continued). Treatments considered will include:

- eye drops, including
  - prostaglandin analogues
  - carbonic anhydrase inhibitors
  - beta-blockers
  - sympathomimetics
  - miotics
  - preservative-free solutions
  - fixed-combination solutions
- systemic carbonic anhydrase inhibitors.

3 Frequency of monitoring for people with confirmed chronic open angle glaucoma, suspected chronic open angle glaucoma or ocular hypertension.

4 The most appropriate service models, where evidence of clinical and cost effectiveness is available (only in relation to the service models to support repeat measures, enhanced case finding and referral refinement).

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

Areas not in the published guideline that will be included in the update

1. Repeat measures, enhanced case finding and referral refinement.
2. Thresholds for referral to secondary care.

Areas that will not be covered

1. Population-based screening programmes for glaucoma.

Areas from the published guideline that will not be updated

1. The accuracy of visual field assessments[2] for the provisional and definitive identification of chronic open angle glaucoma and ocular hypertension in people presenting to community optometrists and those referred to hospital eye services.
2. The effectiveness of procedures (penetrating and non-penetrating) for surgical drainage with and without pharmacological augmentation or drainage devices.
3. The effectiveness of drain manipulation after surgery with and without pharmacological augmentation.
4. The effectiveness of laser procedures to facilitate aqueous outflow or reduce aqueous production.
5. The information, education and support needed to achieve adherence to treatment.

Recommendations in areas that are not being updated may be edited to ensure that they meet current editorial standards, and reflect the current policy and practice context.

1.4 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so

[2] Visual field assessments are an integral part of diagnostic assessment. This update is not reviewing visual field assessments because there is no new evidence (as identified by the surveillance review decision). Recommendations from CG85 on visual field assessment will be carried forward as part of this update.

whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and personal social services (PSS) perspective.

1.5 Key issues and questions

While writing this scope, we have identified the following key issues, and key questions based on the surveillance review decision:

1 Tests for diagnosis and monitoring

1.1 What is the diagnostic accuracy of tests for diagnosis and monitoring in people with ocular hypertension or suspected chronic open angle glaucoma, including tests for:

- measuring intraocular pressure
- assessing the optic nerve head
- assessing the anterior chamber angle
- measuring central corneal thickness.

1.2 What is the diagnostic accuracy of tests for diagnosis and monitoring in people with chronic open angle glaucoma, including tests for:

- measuring intraocular pressure
- assessing the optic nerve head
- assessing the anterior chamber angle
- measuring the central corneal thickness.

2 Prognosis and monitoring intervals

2.1 What is the accuracy of risk tools for identifying people who are at increased risk of developing chronic open angle glaucoma?

2.2 What is the accuracy of risk tools for identifying people with chronic open angle glaucoma who are at increased risk of vision loss?

2.3 What are the optimum intervals for monitoring in people with chronic open angle glaucoma, people with suspected chronic open angle glaucoma and people with ocular hypertension?

3 Treatment

3.1 Is treatment of ocular hypertension (in people who may also have suspected chronic open angle glaucoma) overall clinically and cost

effective? If so, which pharmacological treatment is the most clinically and cost effective and the least harmful, out of the following:

- eye drops
  - prostaglandin analogues
  - carbonic anhydrase inhibitors
  - beta-blockers
  - sympathomimetics
  - miotics
  - preservative-free solutions
  - fixed-combination solutions.
- systemic carbonic anhydrase inhibitors.

3.2 Which are the most clinically and cost effective and least harmful pharmacological treatments for lowering intraocular pressure and preserving visual field in people with chronic open angle glaucoma, out of the following:

- eye drops
  - prostaglandin analogues
  - carbonic anhydrase inhibitors
  - beta-blockers
  - sympathomimetics
  - miotics
  - preservative-free solutions
  - fixed-combination solutions.
- systemic carbonic anhydrase inhibitors.

4 Repeat measures, enhanced case finding and referral refinement

4.1 What are the most effective service models for finding people with chronic open angle glaucoma, suspected chronic open angle glaucoma and ocular hypertension?

4.2 Which tools should be used for repeat measures, enhanced case finding and referral refinement?

- 4.2.1 Which professionals and services should use these tools for repeat measures, enhanced case finding and referral refinement?

4.3 What are the thresholds for referral for repeat measures, enhanced case finding, referral refinement and hospital eye service evaluation?

The key questions may be used to develop more detailed review questions, which guide the systematic review of the literature.

1.6 Main outcomes

The main outcomes that will be considered when searching for and assessing the evidence are:

1. Health-related quality of life (validated scores).
2. Intraocular pressure.
3. Visual field defect.
4. Onset of chronic open angle glaucoma.
5. Progression of chronic open angle glaucoma.
6. Vision loss.
7. Treatment adherence and discontinuation.
8. Adverse events (for example, allergic reactions, irritation, respiratory difficulty).
9. Resource use and costs, including number of hospital visits.

2 Links with other NICE guidance, NICE quality standards, and NICE Pathways

2.1 NICE guidance

NICE guidance that will be updated by this guideline

- Glaucoma: diagnosis and management (2009) NICE guideline CG85

NICE guidance about the experience of people using NHS services

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to glaucoma:

- Patient experience in adult NHS services (2012) NICE guideline CG138
- Service user experience in adult mental health (2011) NICE guideline CG136
- Medicines adherence (2009) NICE guideline CG76

NICE guidance that is closely related to this guideline

Published

NICE has published the following guidance that is closely related to this guideline:

- Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009) NICE guideline CG76
- Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes (2015) NICE guideline NG5
- Canaloplasty for primary open-angle glaucoma (2008) NICE interventional procedure guidance 260
- Trabecular stent bypass microsurgery for open angle glaucoma (2011) NICE interventional procedure guidance 396
- Trabeculotomy ab interno for open angle glaucoma (2011) NICE interventional procedure 397

2.2 NICE quality standards

NICE quality standards that may need to be revised or updated when this guideline is published

- Glaucoma in adults (2011) NICE quality standard 7

2.3 NICE Pathways

When this guideline is published, the recommendations will update the current NICE Pathway on glaucoma. NICE Pathways bring together all related NICE guidance and associated products on a topic in an interactive topic-based flow chart.

3 Context

3.1 Key facts and figures

Adult glaucoma is a group of conditions in which the head of the optic nerve (within the eye) becomes damaged, resulting in problems with sight. In many, but not all cases, glaucoma is associated with increased pressure within the eye. Left untreated, or with inadequate treatment, glaucoma may lead to blindness. Around 10% of registrations for blindness are recorded as being primarily due to glaucoma.

Chronic open angle glaucoma is the most common form of glaucoma in the UK, affecting about 2% of people over 40 years. In England and Wales, around 500,000 people have chronic open angle glaucoma. Other forms of glaucoma include closed angle and secondary glaucomas. The prevalence of glaucoma rises rapidly with age; it is more common in people of black African or Caribbean family origin, and in those with a family history of the condition. There are often signs that something is wrong before vision is affected: increased pressure within the eye (called ocular hypertension) is found in around 3–5% of people over 40. When clinical signs are uncertain, the term 'COAG suspect' signifies a need for greater vigilance to detect any onset of chronic open angle glaucoma. The onset of visual damage from glaucoma is insidious and frequently goes unnoticed by those affected. This underlines the importance of timely identification and referral.

Most people with glaucoma are identified by community optometrists during routine sight tests. Identification of a possible problem is frequently followed by further optometric assessments in the community. Incrementally more complex assessments are undertaken by professionals with incremental

knowledge, skill and experience of glaucoma. Pathways may take the form of 1 or more of repeat measures (simply rechecking initial measurements), enhanced case finding (undertaking additional tests) or referral refinement (additional testing with added 'clinical value' in the form of clinical judgements). These service configurations help to minimise false-positive referrals to hospital eye services. Appropriate configuring of services allows people at low risk (people with ocular hypertension and people with suspected chronic open angle glaucoma) to be cared for in the community. People referred to hospital eye services usually have an assessment by an ophthalmologist. CG85 recommends that for people with chronic open angle glaucoma a diagnosis and management plan should be made by a consultant ophthalmologist.

The causes of chronic open angle glaucoma remain unclear. However, once vision has been lost from glaucoma it cannot be recovered. So treatment must be directed towards preserving remaining vision to maintain, as far as possible, some sight for a person's lifetime.

The only known effective treatment for glaucoma is lowering eye pressure, even when pressure is 'normal' to begin with (as in normal tension glaucoma). Treatment may take the form of eye drops, laser procedures, oral medicines or drainage surgery, either singly or in combination. People who are affected need lifelong monitoring to detect possible loss of disease control and/or disease progression. With changes in clinical status, treatments and diagnostic categories may need to be adjusted. A person with chronic open angle glaucoma can be expected to need an average of 40 follow-up visits for monitoring within their lifetime.

Most glaucoma care involves monitoring of chronic disease. This underlines the importance of appropriate monitoring intervals according to risk to maximise service efficiency. People with ocular hypertension or those with features suggesting but not diagnostic for chronic open angle glaucoma (that is, 'COAG suspects') may not need treatment but do need monitoring of their condition. The frequency of monitoring for glaucoma and related conditions should therefore be stratified according to the risk of progression to blindness

within the person's lifetime. People at a high risk need more frequent monitoring in services led by consultant ophthalmologists, with people at lower risk of blindness being monitored less frequently and not necessarily in hospital eye services. People with ocular hypertension and/or suspected chronic open angle glaucoma may thus be monitored in the community, in line with training and skill set requirements for non-medical healthcare professionals set out in CG85.

An unintended consequence of publication of CG85 in 2009 was high levels of false-positive referrals to hospital eye services. Recommendations for repeat measures and referral refinement were included in the NICE quality standard on glaucoma in adults (QS7), which helped but did not fully resolve this problem. A review of the evidence linked to case finding and thresholds for referral to hospital eye services has therefore been added to the scope of this update to guide NHS practice in these areas. Other areas in which there is new evidence since publication of CG85 have also been included.

3.2 Current practice

The surveillance review decision published in December 2015 outlined a number of areas of CG85 that need updating. Some drugs (for example, latanoprost) are now available in multiple generic products which may affect the findings of the health economic modelling conducted as part of CG85. A number of new questions have been identified and added to the scope to cover case finding, particularly in high-risk groups. New questions are needed to:

- clarify the threshold for referral to hospital eye services
- define and clarify repeat measures, enhanced case finding and referral refinement
- clarify the role of optometrists
- incorporate new technologies, including I-Care tonometry.

These new questions aim to clarify referral criteria and avoid 'flooding' of hospital eye services with referrals of people at low risk of blindness, which has happened since publication of CG85. Because there are targets for

seeing new patients, these people at low risk are given priority by NHS trusts ahead of people with advanced and potentially blinding glaucoma. It is therefore desirable to guide referral based on appropriate risk stratification.

3.3 Policy, legislation, regulation and commissioning

Legislation, regulation and guidance

There is legislation around independent prescribing for non-medically qualified healthcare professionals, including optometrists. Clarifying prescribing by optometrists in glaucoma care will avoid confusion about when such prescribing is appropriate.

Commissioning

Commissioning tools were developed as part of the NICE guideline on glaucoma: diagnosis and management (CG85) and the NICE quality standard for glaucoma in adults (QS7).

3.4 Glossary of terms used in this scope

Chronic open angle glaucoma

People with chronic open angle glaucoma have open or narrow (but not occludable or closed) anterior chamber angles with 1 or more of the following features:

- glaucomatous visual field loss
- glaucomatous optic neuropathy.

Ocular hypertension

Raised intraocular pressure.

Suspected glaucoma

People with suspected glaucoma have equivocal visual field loss and/or equivocal optic neuropathy suggesting possible glaucoma damage.

4 Further information

This is the final scope incorporating comments from registered stakeholders during consultation.

The guideline is expected to be published in July 2017.

You can follow progress of the guideline.

Our website has information about how NICE guidelines are developed.

Appendix B: Declarations of interest

The September 2014 version of the NICE code of practice for declaring and dealing with conflicts of interest policy was applied to this guideline.

John Sparrow (Chair)

GC meeting	Declaration of interest	Classification	Action taken
On application	NHS Consultant leading a Specialist Glaucoma Service	Non-specific, personal, financial	Declare and participate
	HTA Funded Local Principle Investigator on a glaucoma RCT of surgery versus medical treatment for advanced glaucoma at diagnosis	Non-specific, personal, non-financial	
	Trustee British Council for Prevention of Blindness and Chair, Grants Assessment Panel (unpaid)	Non-specific, personal, non-financial	
	Chair, GDG for Royal College of Ophthalmologists Glaucoma Commissioning Guideline published June 2016 (NICE Accredited)	Non-specific, personal, non-financial	
	Clinical Lead, HQIP funded NCAPOP National Ophthalmology Audit focussed on cataract with glaucoma components for visual field assessment and trabeculectomy glaucoma surgery	Non-specific, personal, non-financial	
	Family Interests: Wife, Angela Whitaker part time employed as Senior Lecturer, Independent Prescribing, Wales Optometry Postgraduate Education centre, University of Cardiff Other information: No private practice; no links with industry; no commercial interests	Non-specific, personal, financial	
First GC meeting 26/07/2016	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Augusto Azuara-Blanco

GC meeting	Declaration of interest	Classification	Action taken
On application	In 2015, his employer had a consultancy contract with Bayer that allowed him to join a panel of judges evaluating models of eye care in the UK. Personally, he did not receive any funds. He had a similar contract in 2016 Relevant publications in the past 12 months: McCann P, Hogg RE, Fallis R, Azuara-Blanco A. The Effect of Statins on Intraocular Pressure and on the Incidence and Progression of Glaucoma: A Systematic Review and Meta-Analysis. Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2729-48. doi:	Non-personal, non-specific financial Personal, non-specific, non-financial	Declare and participate Declare and participate

GC meeting	Declaration of interest	Classification	Action taken
	10.1167/iovs.15-18595. PubMed PMID: 27196321.		
	Banister K, Boachie C, Bourne R, Cook J, Burr JM, Ramsay C, Garway-Heath D, Gray J, McMeekin P, Hernández R, Azuara-Blanco A. Can Automated Imaging for Optic Disc and Retinal Nerve Fiber Layer Analysis Aid Glaucoma Detection? Ophthalmology. 2016 May;123(5):930-8. doi: 10.1016/j.ophtha.2016.01.041. Epub 2016 Mar 23. PubMed PMID: 27016459; PubMed Central PMCID: PMC4846823.	Personal, specific, non-financial	Declare and participate
	Azuara-Blanco A, Banister K, Boachie C, McMeekin P, Gray J, Burr J, Bourne R, Garway-Heath D, Batterbury M, Hernández R, McPherson G, Ramsay C, Cook J. Automated imaging technologies for the diagnosis of glaucoma: a comparative diagnostic study for the evaluation of the diagnostic accuracy, performance as triage tests and cost-effectiveness (GATE study). Health Technol Assess. 2016 Jan;20(8):1-168. doi: 10.3310/hta20080. PubMed PMID: 26822760; PubMed Central PMCID: PMC4781562.	Personal, specific, non-financial	Declare and withdraw from discussion and recommendation-making for the topics of service models and accuracy of structural tests. (This study was included in the evidence reviews for these topics.)
	Hernández R, Burr JM, Vale L, Azuara-Blanco A, Cook JA, Banister K, Tuulonen A, Ryan M; Surveillance of Ocular Hypertension Study group. Monitoring ocular hypertension, how much and how often? A cost-effectiveness perspective. Br J Ophthalmol. 2015 Dec 11. pii: bjophthalmol-2015-306757. doi: 10.1136/bjophthalmol-2015-306757. [Epub ahead of print] PubMed PMID: 26659710.	Personal, specific, non-financial	Declare and participate
	Garway-Heath DF, Crabb DP, Bunce C, Lascaratos G,	Personal, specific, non-financial	Declare and participate

GC meeting	Declaration of interest	Classification	Action taken
	Amalfitano F, Anand N, Azuara-Blanco A, Bourne RR, Broadway DC, Cunliffe IA, Diamond JP, Fraser SG, Ho TA, Martin KR, McNaught AI, Negi A, Patel K, Russell RA, Shah A, Spry PG, Suzuki K, White ET, Wormald RP, Xing W, Zeyen TG. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet. 2015 Apr 4;385(9975):1295-304. doi: 10.1016/S0140-6736(14)62111-5. Epub 2014 Dec 19. Erratum in: Lancet. 2015 Jul 11;386(9989):136. PubMed PMID: 25533656.		
First GC meeting 26/07/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	Published the following paper: Br J Ophthalmol. 2016 Sep;100(9):1263-8. doi: 10.1136/bjophthalmol-2015-306757. Epub 2015 Dec 11. Monitoring ocular hypertension, how much and how often? A cost-effectiveness perspective. Hernández R, Burr JM, Vale L, Azuara-Blanco A, Cook JA, Banister K, Tuulonen A, Ryan M; Surveillance of Ocular Hypertension Study group.	Personal, non-financial, specific	Declare and participate
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
28/03/2017			
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Anomika Bedi

GC meeting	Declaration of interest	Classification	Action taken
On application	None.	N/A	N/A
First GC meeting 26/07/2016	None	N/A	N/A
Second GC meeting 21/09/2016	None	N/A	N/A
Third GC meeting 25/10/2016	Did not attend.	N/A	N/A
Fourth GC meeting 29/11/2016	Appointed as specialist member for Eye Guard assisting the dissemination of patient data.	Non-specific, personal, non-financial	Declare and participate
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	Did not attend.	N/A	N/A
Seventh GC meeting 01/03/2017	Did not attend.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Jane Bell

GC meeting	Declaration of interest	Classification	Action taken
On application	Clinical Advisor for LOC Support Unit	Personal, financial, non-specific	Declare and participate
First GC	Did not attend.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
meeting 26/07/2016			
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Kamal Bishai

GC meeting	Declaration of interest	Classification	Action taken
On application	Part-time GP, Chigwell Medical Centre. General Practitioner with special interest in Ophthalmology contracting with West Essex CCG/Stellar Healthcare (a GP Provider Company) Vice Chair West Essex Clinical Commissioning Group Director of Ophthalmic Solutions Ltd company #06282864 (a non-trading company)	Personal, financial, non-specific Personal, financial, non-specific Personal, non-financial, non-specific Personal, non-financial, non-specific	Declare and participate
First GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
26/07/2016			
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	Did not attend.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	Did not attend.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Helen Doe

GC meeting	Declaration of interest	Classification	Action taken
On application	Nominated Moorfield's Governor, CQC Specialist Advisor, National Ophthalmology Data Audit Steering Group	Personal, non-financial, non-specific	Declare and participate
First GC meeting 26/07/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC	No change to existing	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
meeting 16/01/2017	declarations.		
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	Did not attend.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Clare Faulkner

GC meeting	Declaration of interest	Classification	Action taken
On application	None.	N/A	N/A
First GC meeting 26/07/2016	None.	N/A	N/A
Second GC meeting 21/09/2016	None.	N/A	N/A
Third GC meeting 25/10/2016	Did not attend.	N/A	N/A
Fourth GC meeting 29/11/2016	Newly appointed (Oct 2016) as co-chairperson of UK ophthalmic pharmacists group (UKOPG), who are a registered stakeholder in the glaucoma NICE guideline update. The other co-chair has registered UKOPG as a stakeholder and will act as chair of the group for the purposes of the being a stakeholder in the guideline.	Non-specific, personal, non-financial	Declare and participate
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting	No change to existing declarations.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
01/03/2017			
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	Did not attend.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Cecilia Fenerty

GC meeting	Declaration of interest	Classification	Action taken
On application	Attended an educational meeting for Xen glaucoma implants run by Thea on 13–14 May 2016 – who provided transport and overnight accommodation	Personal, financial, non-specific	Declare and participate
First GC meeting 26/07/2016	Did not attend.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Paul Foster

GC meeting	Declaration of interest	Classification	Action taken
On application	Trustee – British Council for the Prevention of Blindness	Non-specific, personal, non-financial	Declare and participate
	Shareholder (3%) – London Claremont Clinic (private sector healthcare provider)	Personal, financial, non-specific	
	Shareholder (80%) – Laser Precision Ltd (private healthcare delivery & consultancy)	Personal, financial, non-specific	
	ISA with exposure to healthcare (not at the level of individual companies)	Personal, financial, non-specific	
	Alcon Foundation Prize 2015 (unrestricted research grant) Foundation governance and selection of awardees – see https://www.myalcon.com/research-development/alcon-research-institute/index.shtml Key points are: No Alcon employee plays any role in the choice of the awardees; that is the responsibility of the Scientific Selection Committee (SSC). This committee is a group of outstanding independent ocular researchers chosen to represent the global research community. An Executive Committee (EC) chosen by the Chairman of the SSC administers the activities of the ARI, including funding, obtaining nominations for awards and planning of the biennial symposia. One non-voting Alcon executive serves on these committees as the secretary and facilitates the many administrative activities required throughout the year.	Non-personal, Specific, financial	
	Research collaboration – Topcon Research Laboratories (US), using TRL's automated OCT segmentation algorithm to process images from UK Biobank, to examine the epidemiology of common eye	Non-personal, non-financial, specific	

GC meeting	Declaration of interest	Classification	Action taken
	diseases in the UK.		
First GC meeting 26/07/2016	No change to existing declarations.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	Did not attend.	N/A	N/A
Fourth GC meeting 29/11/2016	Newly appointed to advise on Google's artificial intelligence on diagnosis and management of eye disease, to take effect in 2017.	Non-specific, personal, financial	Declare and participate
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Robert Harper

GC meeting	Declaration of interest	Classification	Action taken
On application	Received an honorarium from Allergan March 2016 for speaking on non-medical glaucoma care at one of their Athena glaucoma education events.	Personal, specific, financial	Do not participate in discussion or recommendation-making for pharmacological treatments until March 2017.
First GC meeting 26/07/2016	Did not attend.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting	Did not attend.	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
25/10/2016			
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	Did not attend.	N/A	N/A
Ninth GC meeting 29/03/2017	Did not attend.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

David Parkins

GC meeting	Declaration of interest	Classification	Action taken
On application	Director BP Eyecare Ltd - Optical Consultancy with wife Dr Susan Blakeney Self-employed locum working at Burnett Hodd and Jenkins, Kent - optical practice providing NHS services (General Ophthalmic Service) and enhanced services from NHS Bexley CCG Provider of sessional clinics for Kings College NHS Foundation Trust at Queen Mary's Hospital, Sidcup Immediate Past President - The College of Optometrists - the professional, scientific and examining body for optometry in the UK, working for the public benefit. Chair - Clinical Council for Eye Health Commissioning for England - brings together the leading professional, patient	Personal, financial, non-specific Personal, financial, non-specific, Personal, financial, non-specific Personal, non-financial, specific Personal, non-financial, specific	Declare and participate

GC meeting	Declaration of interest	Classification	Action taken
	and representative bodies involved in eye health, providing collective expertise to commissioners, providers, clinicians and policy-makers on the commissioning of eye health services, including social care and ophthalmic public health in England. Member of General Optical Council (regulator for the optical sector in the UK) Assistant Director of Quality, NHS Bexley CCG - assurance role for quality across all locally commissioned services	Personal, non-financial, specific Personal, financial, non-specific	
First GC meeting 26/07/2016	Did not attend.	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC meeting 29/11/2016	No change to existing declarations.	N/A	N/A
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	Lead author on a study included within the service model review: Parkins DJ, Edgar DF. Comparison of the effectiveness of two enhanced glaucoma referral schemes. Ophthalmic and Physiological Optics. 2011; 31(4):343-352.	Personal, non-financial, specific	Declare and withdraw from discussion and recommendation-making on service models.
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Rebecca Turner

GC meeting	Declaration of interest	Classification	Action taken
On application	None.	N/A	N/A
First GC meeting 26/07/2016	Did not attend.	N/A	N/A
Second GC meeting 21/09/2016	None.	N/A	N/A
Third GC meeting 25/10/2016	None.	N/A	N/A
Fourth GC meeting 29/11/2016	Did not attend.	N/A	N/A
Fifth GC meeting 16/01/2017	None.	N/A	N/A
Sixth GC meeting 28/02/2017	None.	N/A	N/A
Seventh GC meeting 01/03/2017	None.	N/A	N/A
Eighth GC meeting 28/03/2017	None.	N/A	N/A
Ninth GC meeting 29/03/2017	None.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

NGC team

GC meeting	Declaration of interest	Classification	Action taken
First GC meeting 26/07/2016	In receipt of NICE commissions	N/A	N/A
Second GC meeting 21/09/2016	No change to existing declarations.	N/A	N/A
Third GC meeting 25/10/2016	No change to existing declarations.	N/A	N/A
Fourth GC	No change to existing	N/A	N/A

GC meeting	Declaration of interest	Classification	Action taken
meeting 29/11/2016	declarations.		
Fifth GC meeting 16/01/2017	No change to existing declarations.	N/A	N/A
Sixth GC meeting 28/02/2017	No change to existing declarations.	N/A	N/A
Seventh GC meeting 01/03/2017	No change to existing declarations.	N/A	N/A
Eighth GC meeting 28/03/2017	No change to existing declarations.	N/A	N/A
Ninth GC meeting 29/03/2017	No change to existing declarations.	N/A	N/A
Tenth GC meeting 18/07/2017	No change to existing declarations.	N/A	N/A

Appendix C: Clinical review protocols

C.1 Prognostic risk tools

C.1.1 Increased risk of conversion to COAG

Review question	What is the accuracy of risk tools for identifying people in the community who are at increased risk of developing chronic open-angle glaucoma?
Objective	To evaluate which risk tool can best identify those people in the community at increased risk of developing COAG
Population	• Adults (18 and over) with ocular hypertension (OHT), including people with ocular hypertension associated with pseudoexfoliation or pigment dispersion: ○ people with consistently or recurrently elevated IOP (greater than 21 mmHg) in the absence of clinical evidence of optic nerve damage or visual field defect. • Adults (18 and over) with suspected COAG: ○ people with possible visual field loss and/or optic neuropathy that suggest possible glaucomatous damage, regardless of the level of the IOP. • Adults who were not previously treated for OHT (exclude populations where <80% were untreated).
Risk tool	Derived and validated risk tools or tests identified in literature for predicting increased risk of developing COAG
Target condition(s)	COAG conversion: • Visual field defect (confirmed by any method) • Abnormal optic nerve (confirmed by any method)
Statistical outcomes	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values; c-statistic) • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) • Reclassification • Other statistical measures: for example, D statistic, R^2 statistic and Brier points
Study types	Prospective and retrospective cohort studies, externally or temporarily validated
Exclusions	• Derivation studies • Split validation studies • People with confirmed COAG • People with secondary glaucoma, for example, neovascular or uveitic glaucoma. • People with, or at risk of, primary or secondary angle closure glaucoma. • People with primary congenital, infantile or childhood glaucoma. • People with angle closure
Search study	Databases: Medline, Embase • Dates/cut-offs: None
Review strategy	Prospective and retrospective cohort studies, externally or temporarily validated Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values; c-statistic) For this review the committee would consider a risk tool for recommendation only if evidence showed an acceptable c-statistic of 70% or above with corresponding thresholds for sensitivity and specificity of 60% and 90% respectively • Area under the ROC curve (c-statistic)

	• Predicted risk versus observed risk (calibration) • Reclassification • Other statistical measures: for example, D statistic, R^2 statistic and Brier points.
Analysis	Analysis: the ability of a risk tool to predict each of the target conditions will be analysed separately. Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST. Indirectness: risk tools will be downgraded for indirectness if the definition of target conditions varies from one of the definitions of above.

C.1.2 Increased risk of COAG progression

Review question	What is the accuracy of risk tools for identifying people with chronic open-angle glaucoma who are at an increased risk of vision loss?
Objective	To evaluate which risk tool can best identify people with confirmed COAG at an increased risk of vision loss
Population	Adults (18 and over) with confirmed COAG Chronic open-angle glaucoma (COAG): people who, in the presence of open or narrow (but not occludable or closed) anterior chamber angles have glaucomatous visual field loss or glaucomatous optic neuropathy
Risk tools	Derived and validated risk tools or tests identified in literature for predicting risk of vision loss in people with confirmed COAG
Target condition(s)	COAG progression: • Advanced glaucomatous visual field loss; progression of visual field defect (confirmed by any method) • Progression of optic nerve head damage (confirmed by any method)
Exclusions	• Studies without a minimum follow-up period of 6 months • Derivation studies • Split validation studies • People with suspected COAG • People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with, or at risk of, primary or secondary angle closure glaucoma • People with primary congenital, infantile or childhood glaucoma • People with angle closure
Search strategy	Databases: Medline, Embase Cut-off dates: None
Review strategy	Prospective and retrospective cohorts, externally or temporarily validated. Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) For this review the committee would consider a risk tool for recommendation only if evidence showed an acceptable c-statistic of 70% or above with corresponding thresholds for sensitivity and specificity of 80% and 70% respectively • Area under the ROC curve (c-statistic) • Predicted risk versus observed risk (calibration) • Reclassification • Other statistical measures included D statistic, R^2 statistic and Brier score
Analysis	Analysis: the ability of each risk tool to predict each of the target conditions will be analysed separately Appraisal of methodological quality: methodological quality of each risk tool will be assessed using PROBAST Indirectness: risk tools will be downgraded for indirectness if the definition of the target

Review question	What is the accuracy of risk tools for identifying people with chronic open-angle glaucoma who are at an increased risk of vision loss?
	conditions varies from definitions of above

C.2 Tests used in case finding, diagnosis and reassessment

C.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

Component	Description
Review question	What is the accuracy of tests for identifying closed or occludable anterior chamber angle?
Objectives	To evaluate the accuracy of tests for identifying closed or occludable anterior chamber angle In current practice, gonioscopy is used to assess the anterior chamber angle. This test is used to diagnose people with COAG, alongside visual field tests and assessment of the optic nerve head.
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-sectional studies)
Population	Adults (18 and over)
Setting	Any
Target condition	Closed or occludable anterior chamber angle on 2 or more quadrants Closed angle: angle 0^{o} CG 85 definition: 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[454] Occludable angle: trabecular meshwork not visible for at least half of the angle's circumference.
Index test	• Anterior segment optical coherence tomography (AS-OCT) • Scheimpflug anterior segment photography or Scheimpflug photographic angle assessment • Ultrasound biomicroscopy (UBM) or (ultra) high resolution B-scan • van Herick's test or angle assessment or limbal anterior chamber depth measurement
Reference standard	Gonioscopy conducted by a trained clinician
Statistical measures	2x2 tables Specificity Sensitivity C-statistic (ROC curve or AUC)
Other exclusions	• People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with primary congenital, infantile or childhood glaucoma • People with neurodegenerative diseases • Diagnostic RCTs (included in separate review) • Case-control studies
Search strategy	Databases: Date limits for search: From 2009 cut-off guideline search onwards (4 August 2008) Language: English only
Review strategy	Data for closed and occludable anterior chamber angles to be analysed together Subgroups (to be investigated if heterogeneity is identified):

	○ Different manufacturers of tests ○ People of Chinese family origin ○ People with suspected COAG; people with confirmed COAG ○ People with OHT; people without OHT ○ Who conducts the test ○ Setting of test The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Diagnostic meta-analysis will be conducted using hierarchical methods where appropriate when ≥3 studies report data at a threshold Primary measure for decision-making (with consideration of the paired accuracy value): • Community – specificity (acceptable threshold 95%) • Retesting and monitoring – sensitivity (acceptable threshold 95%)

C.2.2 Accuracy of IOP tests

Component	Description
Review question	What is the accuracy of tests for measuring IOP and monitoring changes in IOP, including repeat measures?
Objectives	To evaluate the accuracy of tests for measuring IOP and monitoring changes in IOP, and to identify thresholds for referral and treatment In current practice, Goldmann applanation tonometry (GAT) is used to diagnose OHT. To aid the interpretation of IOP measurements, measurements of IOP are made alongside measurement of the central corneal thickness (CCT). The measurement of CCT is important as corneal thickness can affect the accuracy of IOP measurements; IOP may be underestimated in people with thinner CCT, and overestimated in people with thicker CCT. OHT is also a risk factor for developing COAG.
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-sectional studies)
Population and target condition	Adults (18 and over) Detection of any level of IOP
Setting	Any
Index tests	• Dynamic Contour Tonometry or Pascal Dynamic Contour Tonometer • Icare or rebound tonometry • Impression or (electronic) indentation tonometry or Tono-Pen • Ocular Response Analyzer (ORT) • Perkins applanation tonometry • Non-contact or air puff tonometry • Pneumotonometry Include repeat measures for any of the above tests
Reference standard	Goldmann applanation tonometry (GAT) completed by a trained clinician, slit lamp mounted
Statistical measures	2x2 tables Specificity Sensitivity C-statistic (ROC curve or AUC)

Other exclusions	• People with primary congenital, infantile or childhood glaucoma • People with neurodegenerative diseases • Diagnostic RCTs (included in a separate review) • Case-control studies
Search strategy	Databases: Date limits for search: From 2009 cut-off guideline search onwards (4 August 2008) Language: English only
Review strategy	Subgroups (to be investigated if heterogeneity is identified): • Different manufacturers of tests • People with OHT; people without OHT • People with suspected COAG; people with confirmed COAG • Thick or thin central corneal thickness • Black African or Caribbean descent • Who conducts the test • Setting of test The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Studies with a time interval of greater than 1 hour between taking the index test measurement and the reference test measurement will be excluded. Diagnostic meta-analysis will be conducted using hierarchical methods where appropriate when ≥3 studies report data at a threshold Primary measure for decision-making: • Community – specificity (acceptable threshold 95%) • Retesting and monitoring – sensitivity (acceptable threshold 95%)

C.2.3 Central corneal thickness measurement evidence

None.

C.2.4 Visual field evidence

None.

C.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

Review question: What is the accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head and macular and retinal nerve fibre layer)?	
Objectives	To evaluate the accuracy of structural tests for identifying COAG and monitoring progression of glaucoma damage In current practice, a trained clinician uses a biomicroscopic slit-lamp examination and stereo photography to assess the optic nerve and to identify optic neuropathy. People with suspected COAG are identified using this test alongside visual field tests. People with COAG are diagnosed using a biomicroscopic slit-lamp examination and stereo photography, alongside visual field tests, assessment of the optic nerve head, and assessment of the anterior angle.
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-

Review question: What is the accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head and macular and retinal nerve fibre layer)?	
	sectional studies)
Population	Adults (18 and over)
Target conditions	Glaucoma damage: • optic nerve head or disk damage • macular and retinal nerve fibre layer damage Progression of glaucoma damage
Setting	Any
Index test	• Optic disc examination with stereo photography or stereoscopic disc photography • Heidelberg Retinal Tomography (HRT) or scanning laser ophthalmoscopy (SLO) • Optical coherence tomography (OCT) • Monoscopic photography • Direct ophthalmoscopy
Reference standard	Biomicroscopic slit lamp examination by a trained clinician • With or without stereo photography • With or without glaucomatous visual field loss (as measured by standard automated perimetry [SAP] or Swedish Interactive Threshold Algorithm [SITA])
Statistical measures	2x2 tables Specificity Sensitivity C-statistic (ROC curve or AUC)
Other exclusions	• Visual field tests • Tests for monitoring the optic nerve head (separate review) • People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with, or at risk of, primary or secondary angle closure glaucoma • People with primary congenital, infantile or childhood glaucoma • People with neurodegenerative diseases • Diagnostic RCTs (included in a separate review) • Case-control studies
Search Strategy	Databases: Date limits for search: From 2009 cut-off guideline search onwards (4 August 2008) Language: English only
Review Strategy	Strata: different types of glaucomatous damage when reported separately Subgroups (to be investigated if heterogeneity is identified): • Different manufacturers of tests • People with suspected COAG; people with confirmed COAG • Severity of COAG • Who conducts the test • Setting of test The methodological quality of each study will be assessed using the QUADAS-2 checklist (per target condition). Diagnostic meta-analysis will be conducted using hierarchical methods where appropriate when ≥3 studies report data at a threshold

Review question: What is the accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head and macular and retinal nerve fibre layer)?	
	Primary measure for decision-making (in consideration with the paired measure): • Community – specificity (acceptable threshold 95%) • Retesting and monitoring – sensitivity (acceptable threshold 95%)

C.3 Reassessment intervals

C.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

Review question	What are the optimum intervals for monitoring people with ocular hypertension, suspected chronic open-angle glaucoma or both?
Objectives	To identify the optimum intervals for monitoring people with ocular hypertension, suspected chronic open-angle glaucoma or both
Review population	• Adults (18 and over) with ocular hypertension (OHT): people with consistently or recurrently elevated IOP (greater than 21 mmHg) in the absence of clinical evidence of optic nerve damage or visual field defect (including people with ocular hypertension associated with pseudoexfoliation or pigment dispersion) who are having or not having treatment for OHT • Adults (18 and over) with suspected COAG: people with suspected visual field loss or optic neuropathy that suggests possible glaucomatous damage, regardless of the level of the IOP
Interventions	Tests for monitoring IOP, optic nerve head, macular and retinal nerve fibre layer and visual field conducted at certain intervals
Comparators	Tests for monitoring IOP, optic nerve head, macular and retinal nerve fibre layer and visual field conducted at different intervals
Outcomes	<u>Critical outcomes</u> • Normal visual field to visual field defect (dichotomous; confirmed by any method) • Extent of glaucomatous visual field loss (continuous) • Development of glaucoma • Health-related quality of life (validated scores) <u>Important outcomes</u> • Optic nerve head damage (continuous); normal, suspicious or abnormal optic nerve (dichotomous; confirmed by any method) • IOP level • Patient and carer satisfaction (validated scores only)
Study design	Systematic review of RCTs RCT
Unit of randomisation	Any
Crossover study	Not permitted
Other exclusions	• People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with, or at risk of, primary or secondary angle closure glaucoma • People with primary congenital, infantile or childhood glaucoma • People with ocular comorbidities
Population stratification	• People with OHT on treatment • People with OHT off treatment

	• People with suspected COAG
Subgroup analyses if there is heterogeneity	• People with OHT and normal disc; people with suspected COAG • Central corneal thickness thin, thick or average • Adults with a family history of chronic open-angle glaucoma • Adults of black African or black Caribbean family origin • Age (under 50 years; 50–70 years; over 70 years)
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: From 2009 cut-off guideline search onwards (04 August 2008) Language: English language only

C.3.2 Optimum intervals for chronic open-angle glaucoma

Review question	**What are the optimum intervals for monitoring people with chronic open-angle glaucoma?**
Objectives	To identify the optimum intervals for monitoring people with chronic open-angle glaucoma
Review population	Adults (18 and over) with confirmed chronic open-angle glaucoma: people who, in the presence of open or narrow (but not occludable or closed) anterior chamber angles, have glaucomatous visual field loss or glaucomatous optic neuropathy. Including people with chronic open-angle glaucoma associated with pseudoexfoliation or pigment dispersion
Interventions	Tests for monitoring IOP, optic nerve head, macular and retinal nerve fibre layer and visual field conducted at certain intervals
Comparators	Tests for monitoring IOP, optic nerve head, macular and retinal nerve fibre layer and visual field conducted at different intervals
Outcomes	<u>Critical outcomes</u> • Normal visual field to visual field defect (dichotomous; confirmed by any method) • Extent of glaucomatous visual field loss (continuous) • Health-related quality of life (validated scores) <u>Important outcomes</u> • Optic nerve head damage (continuous); normal, suspicious or abnormal optic nerve (dichotomous);confirmed by any method • IOP level • Patient and carer satisfaction
Study design	Systematic review of RCTs RCT
Unit of randomisation	Any
Crossover study	Not permitted
Other exclusions	• People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with, or at risk of, primary or secondary angle closure glaucoma • People with primary congenital, infantile or childhood glaucoma • People with ocular comorbidities
Population stratification	None
Subgroup analyses if there is heterogeneity	• Central corneal thickness thin, thick or average • Adults with a family history of chronic open-angle glaucoma • Adults of black African or black Caribbean family origin • Age (under 50 years; 50–-70 years; over 70 years)
Search criteria	Databases: Medline, Embase and the Cochrane Library

	Date limits for search: From 2009 cut-off guideline search onwards (04 August 2008) Language: English language only

C.4 Overview of Treatment

None.

C.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

C.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

Review question	**Which are the most clinically, cost-effective and least harmful pharmacological treatments for people with OHT, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma?**
Objectives	To see which are the most clinically, cost-effective and least harmful pharmacological treatments people with people with OHT, suspected, chronic open-angle glaucoma (COAG) and confirmed COAG
Review population	• Adults (18 and over) with OHT: people with consistently or recurrently elevated IOP (greater than 21 mmHg) in the absence of clinical evidence of optic nerve damage or visual field defect. Including people with ocular hypertension associated with pseudoexfoliation or pigment dispersion • Adults (18 and over) with suspected COAG: people with suspected visual field loss or optic neuropathy that suggest possible glaucomatous damage, regardless of the level of the IOP • Adults (18 and over) with confirmed COAG: people whom, in the presence of open or narrow (but not occludable or closed) anterior chamber angles have glaucomatous visual field loss or glaucomatous optic neuropathy. Including people with chronic open-angle glaucoma associated with pseudoexfoliation or pigment dispersion
Interventions	• Topical solutions (eye drops) ○ prostaglandin analogues: Bimatoprost (all doses), Tafluprost (all doses), Travoprost (all doses) and latanoprost ○ carbonic anhydrase inhibitors (all doses): brinzolamide and dorzolamide ○ beta-blockers (all doses): Betaxolol, Carteolol hydrochloride, levobunolol hydrochloride and Timolol maleate ○ sympathomimetics(all doses): apraclonidine and brimonidine tartrate ○ miotics - Pilocarpine ○ fixed-combination solutions (of different classes): prostaglandin analogue with beta-blockers; carbonic anhydrase inhibitors and sympathomimetics and carbonic anhydrase inhibitors with beta-blockers ○ topical solutions with any of the following preservatives: Benzalkonium chloride or SofZia • Systemic carbonic anhydrase inhibitors (all doses): Acetazolamide
Comparators	• Compared to each other (different class) • Treatment with preservative versus preservative-free solutions • Fixed combination versus fixed combination • Fixed combination versus monotherapy • Fixed combination versus single doses • Frequency of administration (for example, carbonic anhydrase inhibitors administered 2 times per day versus 3 times per day)

	• No treatment or placebo
Outcomes	<u>Critical outcomes</u> • Glaucomatous visual field loss (continuous; NMA outcome; duration of study) • Normal visual field to visual field defect (dichotomous; confirmed by any method; NMA outcome – to be analysed if insufficient data on continuous visual field loss outcome; (duration of study) • Progression of glaucomatous visual field defect (confirmed by any method; NMA outcome – to be analysed if insufficient data on continuous visual field loss outcome; duration of study) • Vision loss (confirmed by any method; duration of study) • Health-related quality of life (validated scores; duration of study) • Adverse events (duration of study): ○ Allergic reaction or intolerance (including hyperaemia; NMA outcome) ○ Breathing difficulties ○ Cardiovascular events <u>Important outcomes</u> • Optic nerve head damage (continuous; confirmed by any method; duration of study) • Progression of optic nerve head damage (continuous; confirmed by any method; duration of study) • Normal or suspicious-to-abnormal optic nerve head (dichotomous; confirmed by any method; duration of study) • IOP level (NMA outcome to be analysed if insufficient data on dichotomous visual field loss outcome; duration of study) • Treatment adherence (duration of study) • Treatment discontinuation (duration of study)
Study design	Systematic Review of RCTs RCT
Unit of randomisation	Any
Crossover study	Not permitted
Minimum duration of study	6 months
Other exclusions	• People with secondary glaucoma, for example, neovascular or uveitic glaucoma • People with, or at risk of, primary or secondary angle closure glaucoma • People with primary congenital, infantile or childhood glaucoma • People with angle closure
Population stratification	None
Subgroup analyses if there is heterogeneity	Intervention or comparison: • Timing of administration (daytime; night time) • No treatment; placebo Population: • People with normal IOP; people with elevated IOP • People with OHT and normal disc; people with suspected COAG • Pseudoexfoliation; none • Pigment dispersion; none • Adults with a family history of chronic open-angle glaucoma • Adults of black African or black Caribbean family origin • Age (under 50 years; 50-70 years; over 70 years)

	• Socioeconomic status • Living in area of socioeconomic deprivation • Access to commercial healthcare services • Rural; urban
Search criteria	Databases: Medline, Embase and the Cochrane Library Date limits for search: From the 2009 cut-off guideline search onwards (4 August 2008) Language: English language only

C.5.2 Laser treatment for COAG

None.

C.5.3 Surgical treatment for COAG

None.

C.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

C.6 Complementary and alternative interventions

None.

C.7 Organisation of care

C.7.1 Service models for case finding, referral filtering and diagnosis

Objectives	To identify the best tests or combinations of tests for identifying people who require onward referral from the first contact with primary care To identify the best tests or combinations of tests from first point of contact to a referral to confirm or exclude a diagnosis of OHT, suspect status or COAG
Population	Adults (18 and over)
Subgroups	• Conductor of the tests • Setting of tests
Interventions	Single or combinations of the following tests, including repeat measures, enhanced case finding, and referral refinement, triage stations in primary and secondary care: **For measuring intraocular pressure** • Goldmann applanation tonometry (GAT) by trained clinician • Dynamic contour tonometry or PASCAL Dynamic Contour Tonometer (DCT) • Icare or rebound tonometry • Impression or (electronic) indentation tonometry or Tono-Pen • Ocular response analyser • Perkins applanation tonometry • Non-contact or air puff tonometry **For detection and monitoring of glaucoma damage (damage of optic nerve head and macular and retinal nerve fibre layer)**

	• Biomicroscopic slit lamp examination by a trained clinician • Stereo photography • Optic disc examination with stereo photography or stereoscopic disc photography • Heidelberg Retinal Tomography (HRT) or scanning laser ophthalmoscopy (SLO) • Optical coherence tomography (OCT) • Monoscopic photography • Direct ophthalmoscopy **For assessing the anterior chamber angle** • Gonioscopy conducted by a trained clinician • Anterior Segment Optical Coherence Tomography (AS-OCT) • Scheimpflug anterior segment photography or Scheimpflug photographic angle assessment • Ultrasound biomicroscopy (UBM) or (ultra) high resolution B-scan • van Herick's test or angle assessment or limbal anterior chamber depth measurement **For measuring central corneal thickness** • Corneal pachymetry • Scheimpflug photography • Optical Coherence Tomography • Optical Coherence Pachymetry **For assessing visual field** • Standard automated threshold perimetry or full threshold perimetry • Frequency doubling technology (FDT)
Comparisons	• Single tests versus single tests • Single tests versus combinations of tests • Combinations of test versus other combinations of test For single tests: • Different thresholds for referral Within combinations: • Different types of test technology (for example, Goldmann, air puff) • Test conducted once; repeat measures using same method on same occasion; repeat measures using same method on different occasion; repeat measures using different method on same occasion; repeat measures using different method on different occasion • Different thresholds for referral
Outcomes	<u>Critical outcomes</u> • Appropriate referral (for OHT, suspected COAG, COAG) or non-referral • Missed OHT, suspected COAG, COAG • Vision loss as a result of incorrect non-referral <u>Important outcomes</u> • Long-term glaucomatous visual field loss (continuous); normal visual field to visual field defect (dichotomous; confirmed by any method) • Long-term optic nerve head damage (continuous); normal or suspicious to abnormal

	optic nerve (dichotomous; confirmed by any method) • Health-related quality of life (validated scores) • Participant satisfaction (validated scores)
Study design	RCT Systematic review of RCTs If no RCTs, cohort studies (prospective and retrospective) will be considered
Setting	All settings
Search Strategy	Date limits for search: none Language: English only

C.7.2 Skills required by healthcare professionals

None.

C.8 Provision of information for patients

None.

Appendix D: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocols in Appendix E above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001 and studies from non-OECD countries or the USA will be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2012 NICE guidelines manual.[488] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to exclude the remaining studies selectively. All studies excluded based on applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

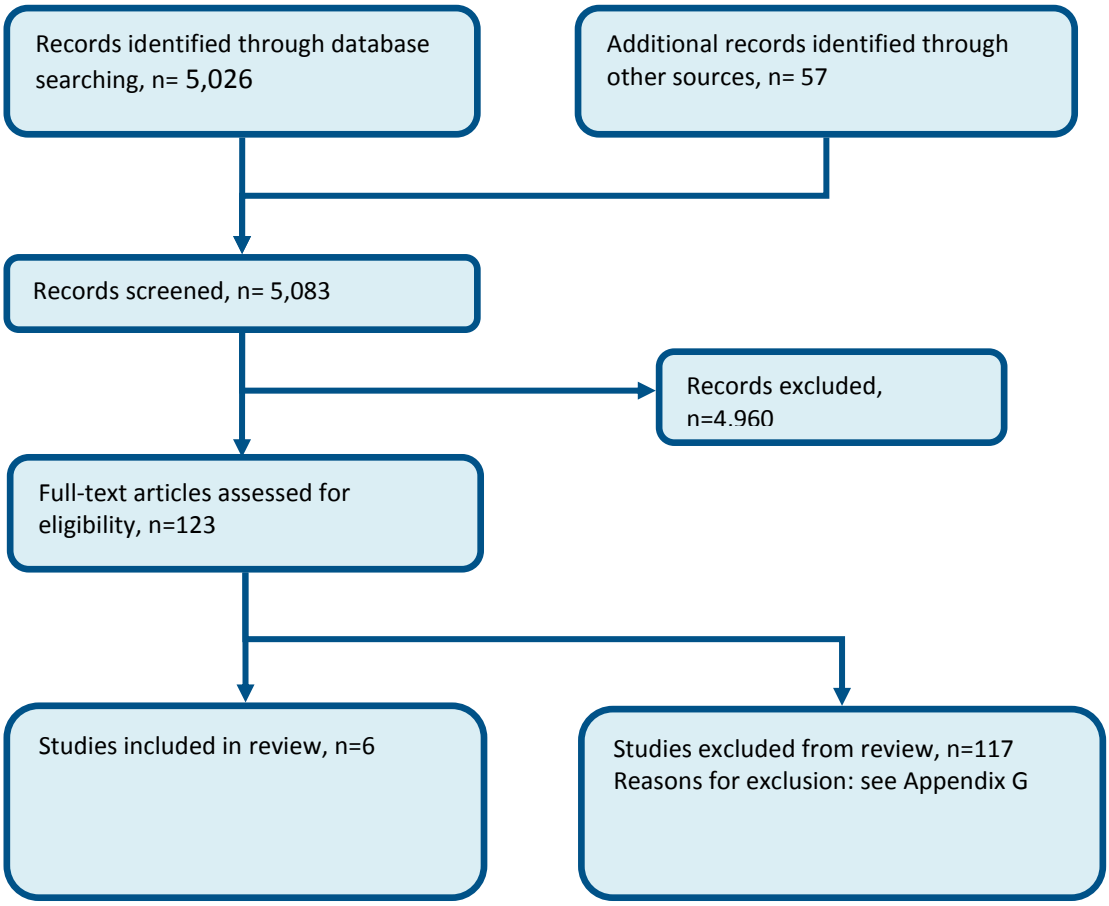
	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as 'Not applicable'. • Studies published before 2001 will have been excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix E: Clinical study selection

E.1 Prognostic risk tools

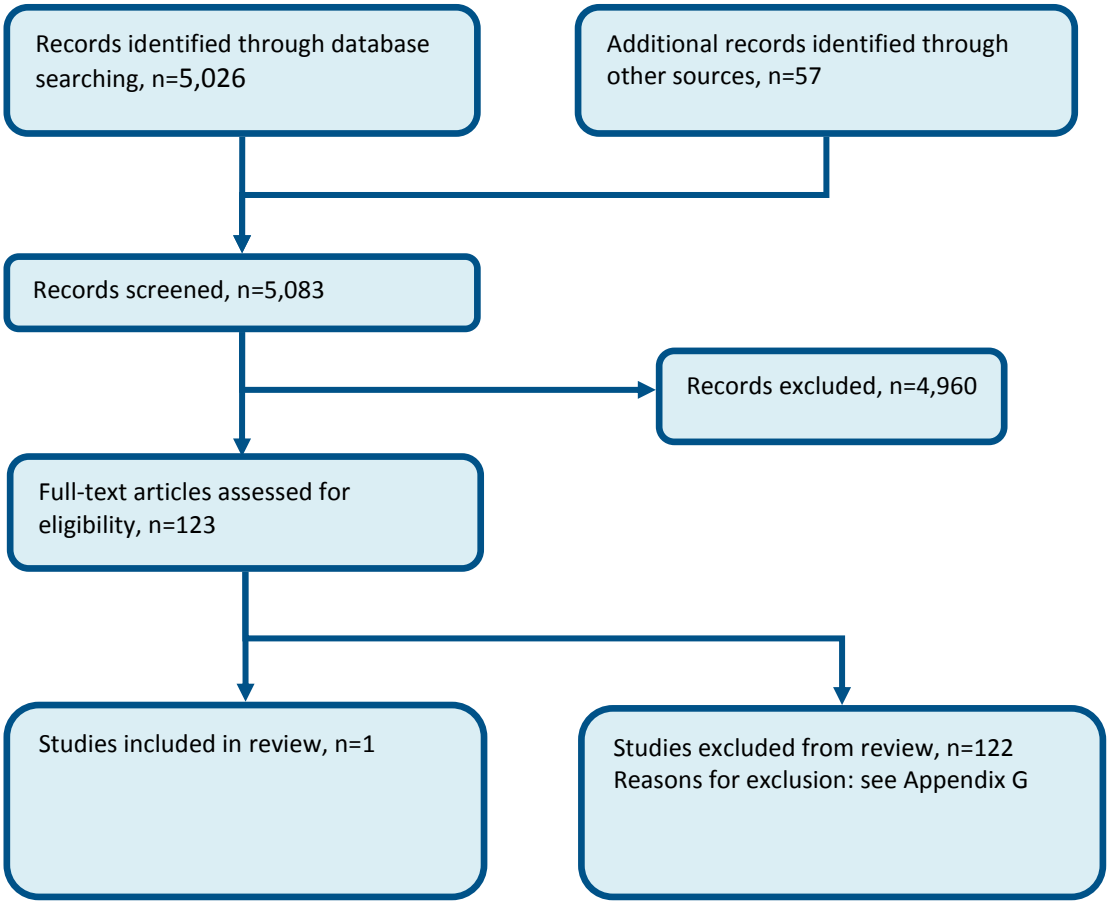
E.1.1 Increased risk of conversion to COAG

Figure 1: Flow chart of clinical article selection for the review of: What is the accuracy of risk tools for identifying people in the community who are at increased risk of developing chronic open-angle glaucoma?



E.1.2 Increased risk of COAG progression

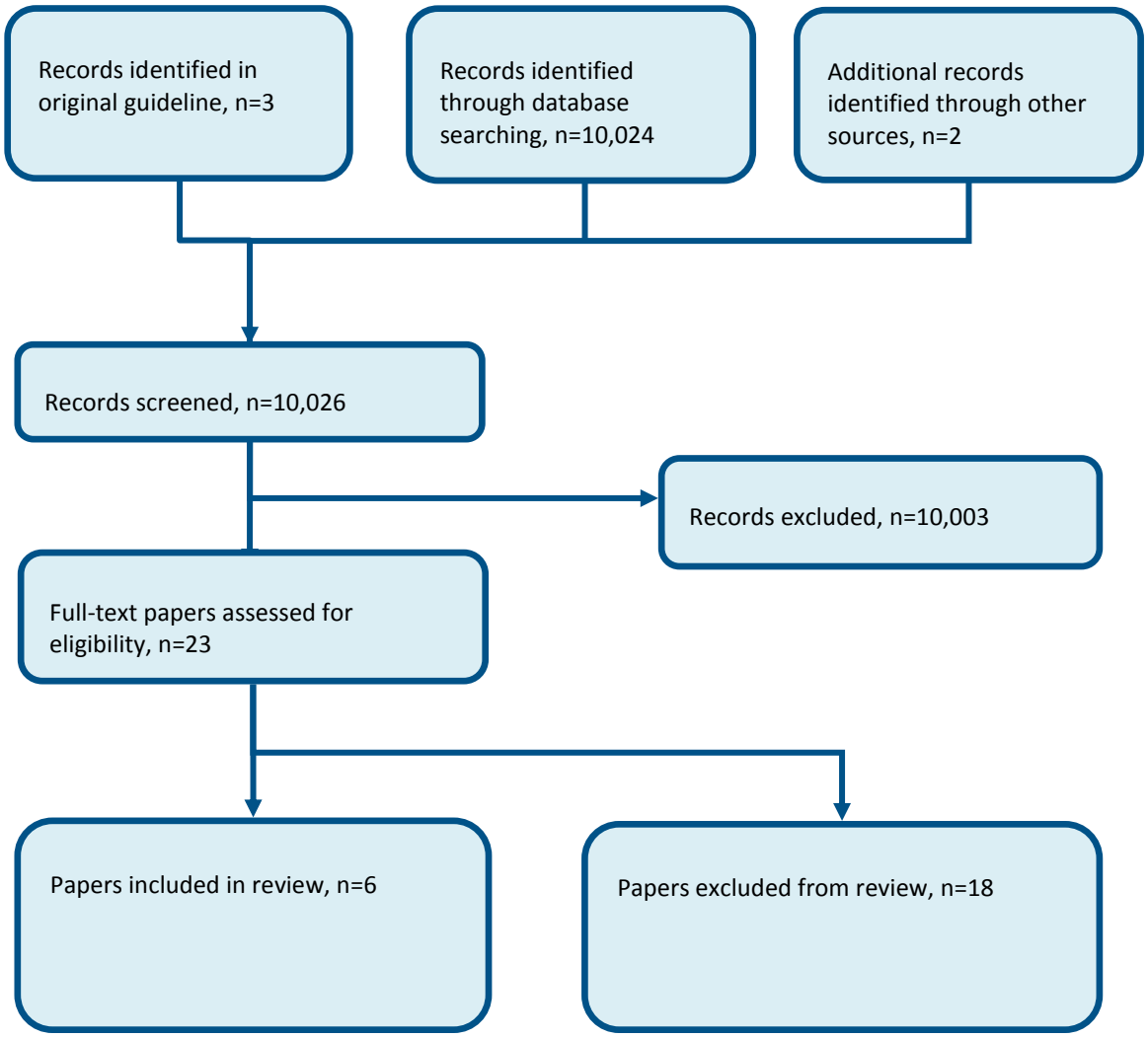
Figure 2: Flow chart of clinical article selection for the review of: What is the accuracy of risk tools for identifying people with chronic open-angle glaucoma who are at an increased risk of vision loss?



E.2 Tests used in case finding, diagnosis and reassessment

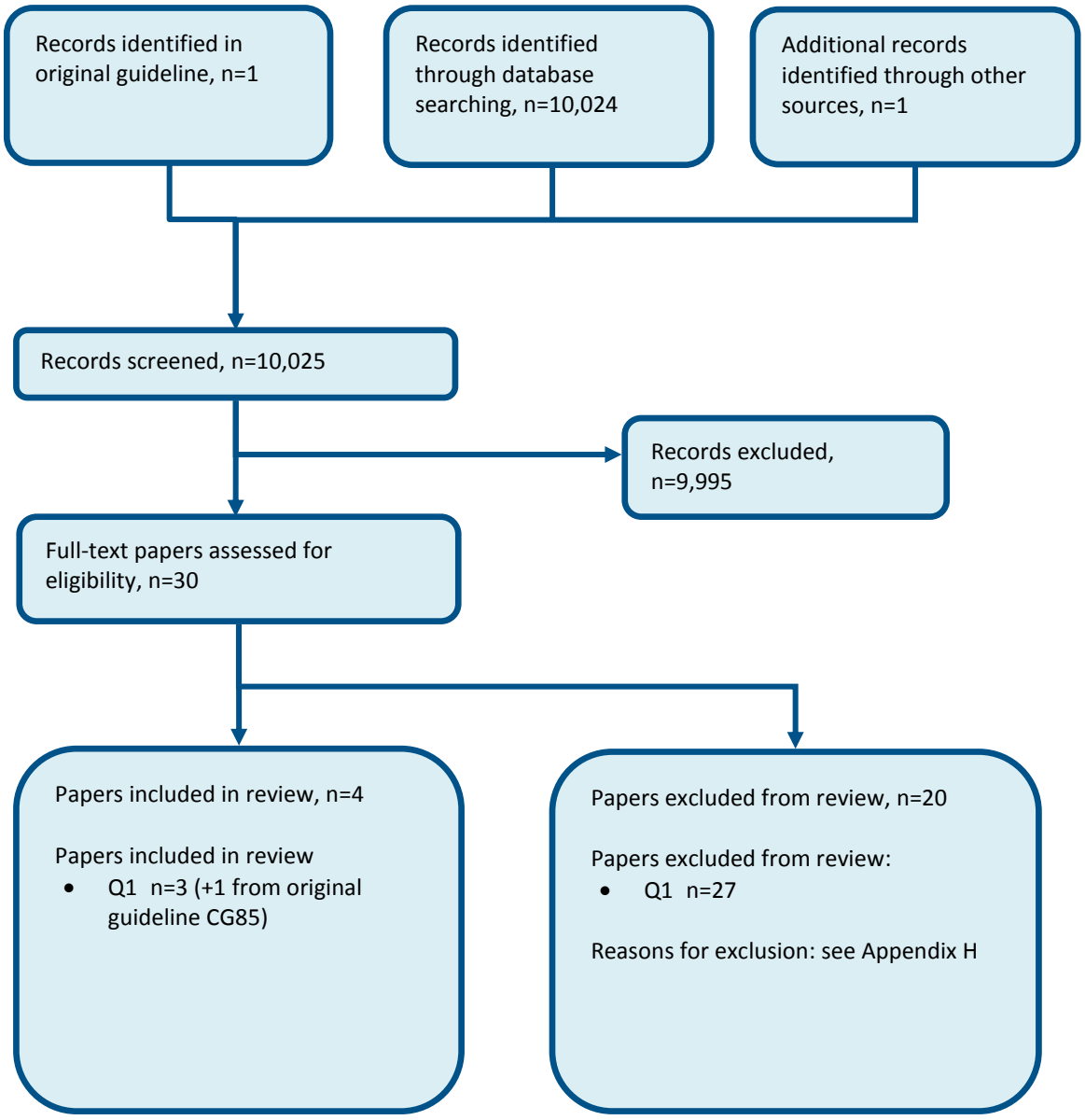
E.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

Figure 3: Flow chart of clinical study selection for the review of 'What is the accuracy of tests for identifying closed or occludable anterior chamber angle?'



E.2.2 Accuracy of IOP tests

Figure 4: Flow chart of clinical study selection for the review of the accuracy of tests for measuring IOP and monitoring changes in IOP, including repeat measures



E.2.3 Central corneal thickness measurement evidence

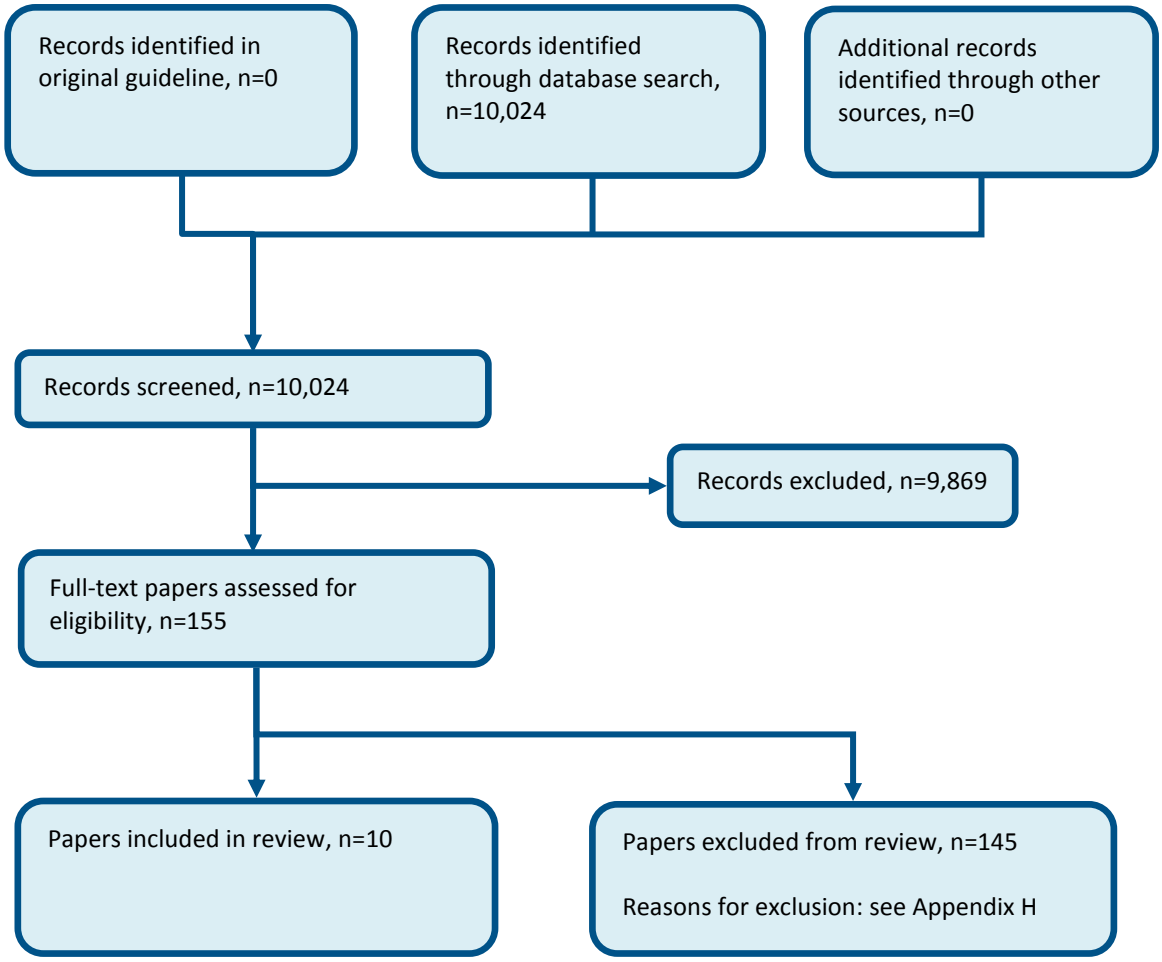
None.

E.2.4 Visual field evidence

None.

E.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

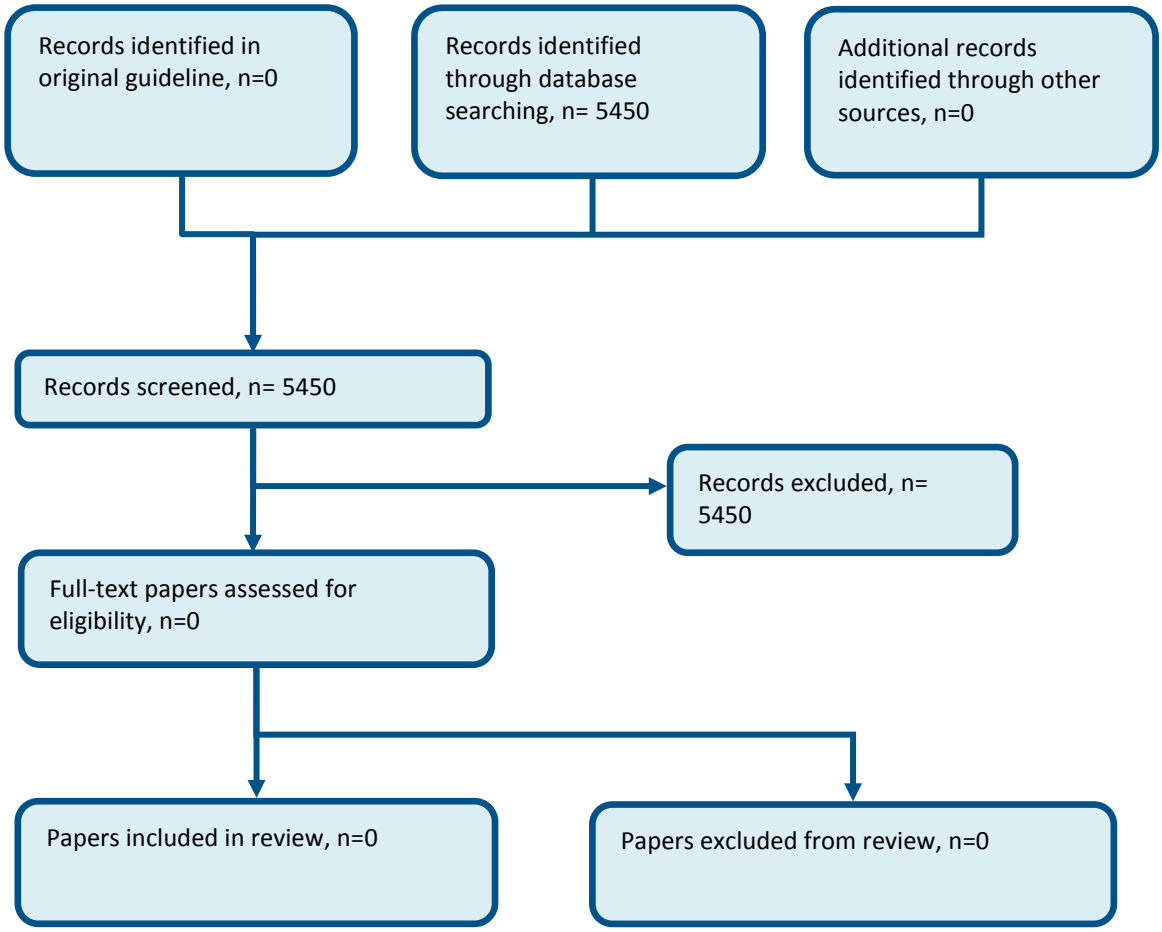
Figure 5: Flow diagram of clinical article selection for the review of the accuracy of structural tests for identifying and monitoring progression of glaucoma damage (damage of the optic nerve head and macular and retinal nerve fibre layer).



E.3 Reassessment intervals

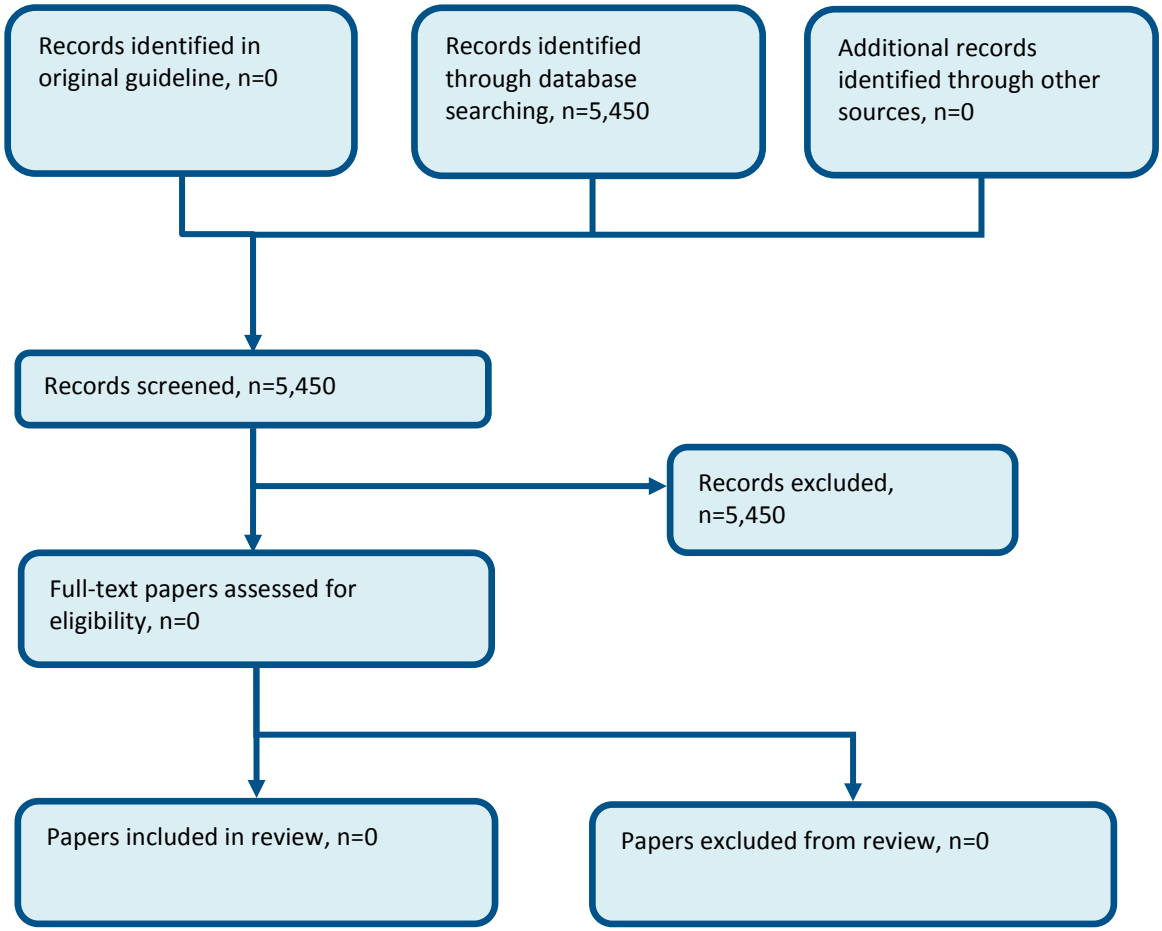
E.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

Figure 6: Flow chart of clinical study selection for the review of: What are the optimum intervals for monitoring people with ocular hypertension, suspected chronic open-angle glaucoma or both?



E.3.2 Optimum intervals for chronic open-angle glaucoma

Figure 7: Flow chart of clinical study selection for the review of: What are the optimum intervals for monitoring people with chronic open-angle glaucoma?



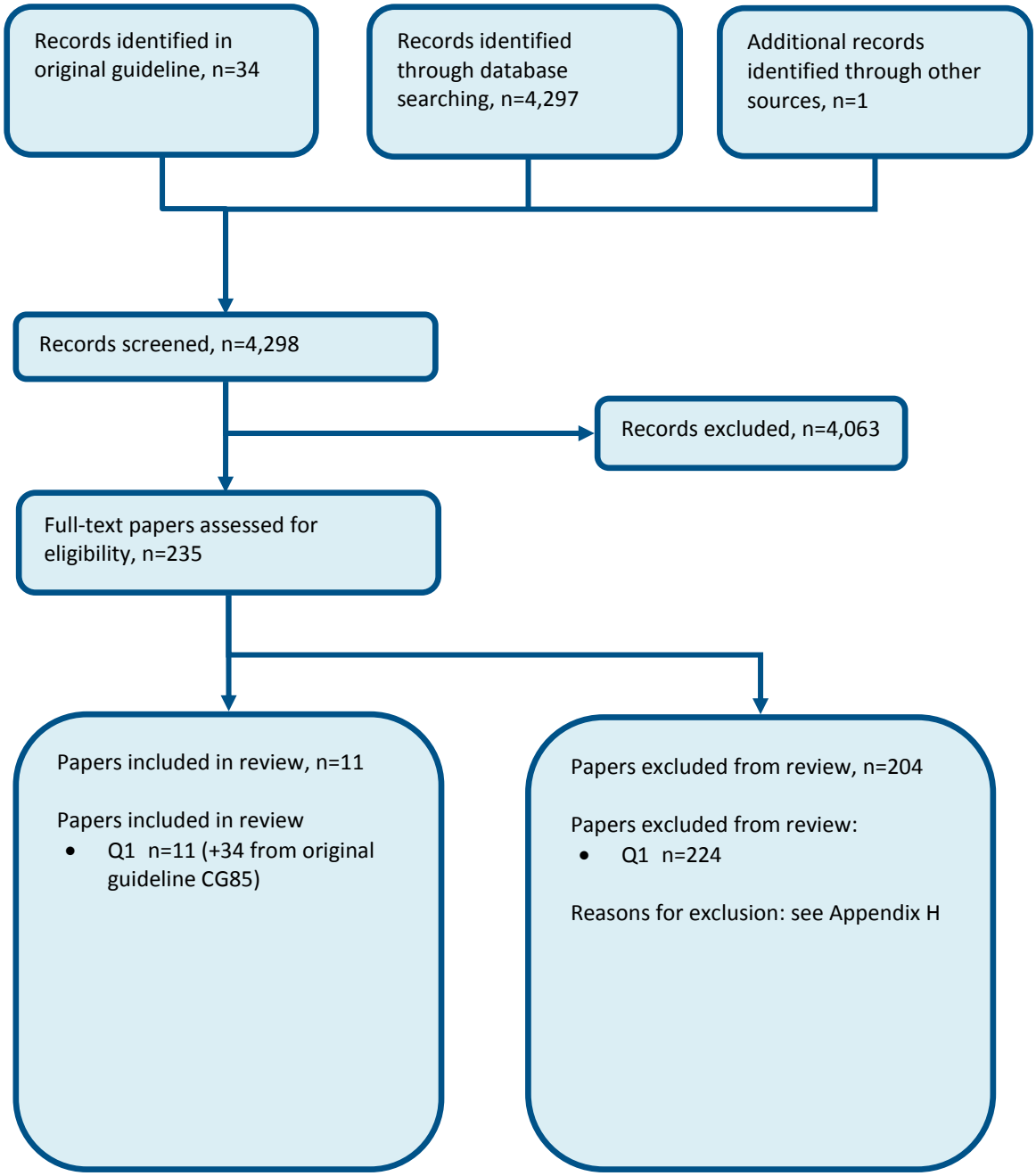
E.4 Overview of Treatment

None.

E.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

E.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

Figure 1: Flow chart of clinical study selection for the review of pharmacological treatment of chronic open-angle glaucoma



E.5.2 Laser treatment for COAG

None.

E.5.3 Surgical treatment for COAG

None.

E.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

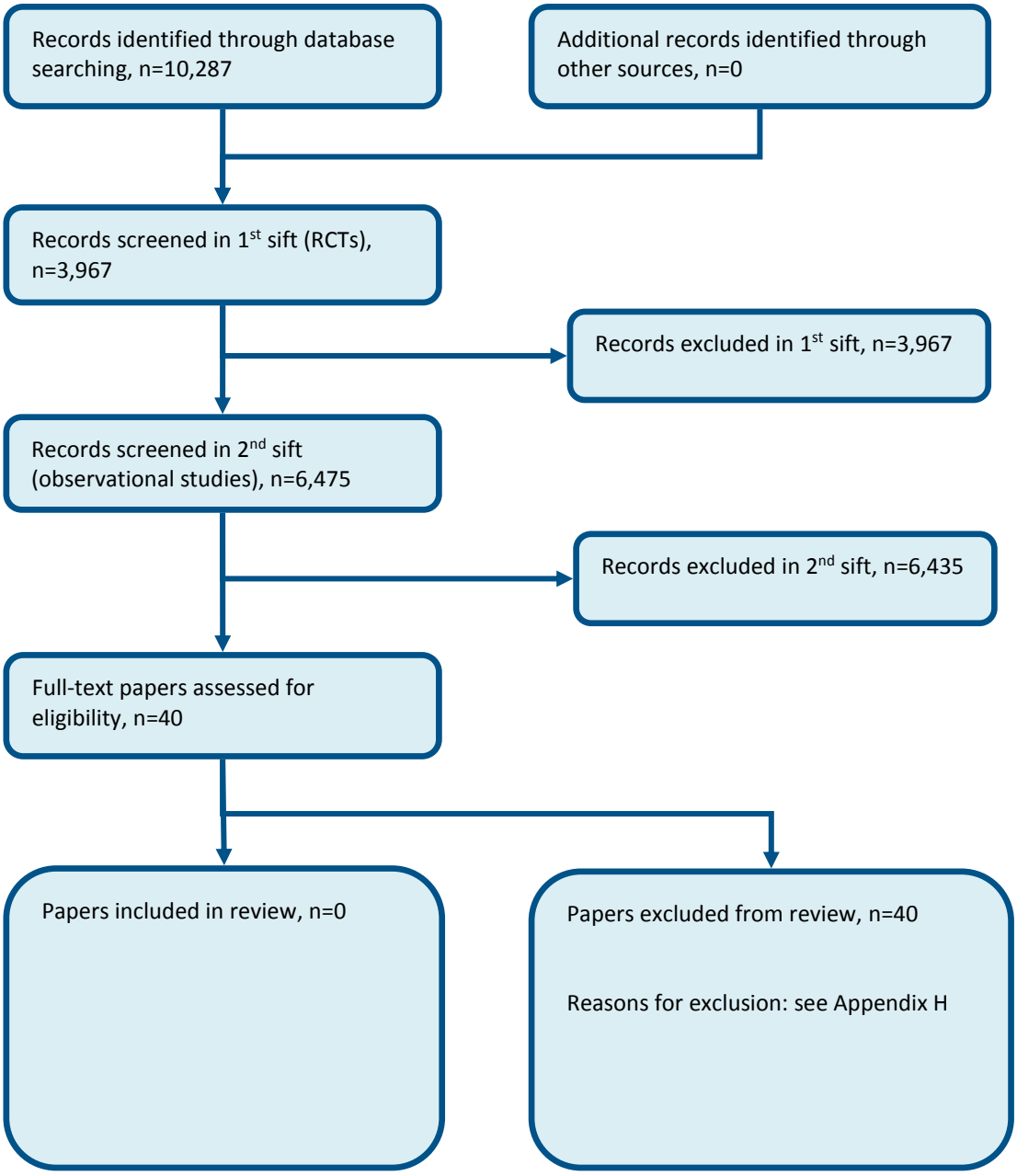
None.

E.6 Complementary and alternative interventions

E.7 Organisation of care

E.7.1 Service models for case finding, referral filtering and diagnosis

Figure 8: Flow chart of clinical study selection for the review of 'What is the clinical and cost-effectiveness of performing different tests or combinations of tests (including repeat measures of individual tests) for identifying people who require onward referral from the first contact with primary care to a confirmed diagnosis?'

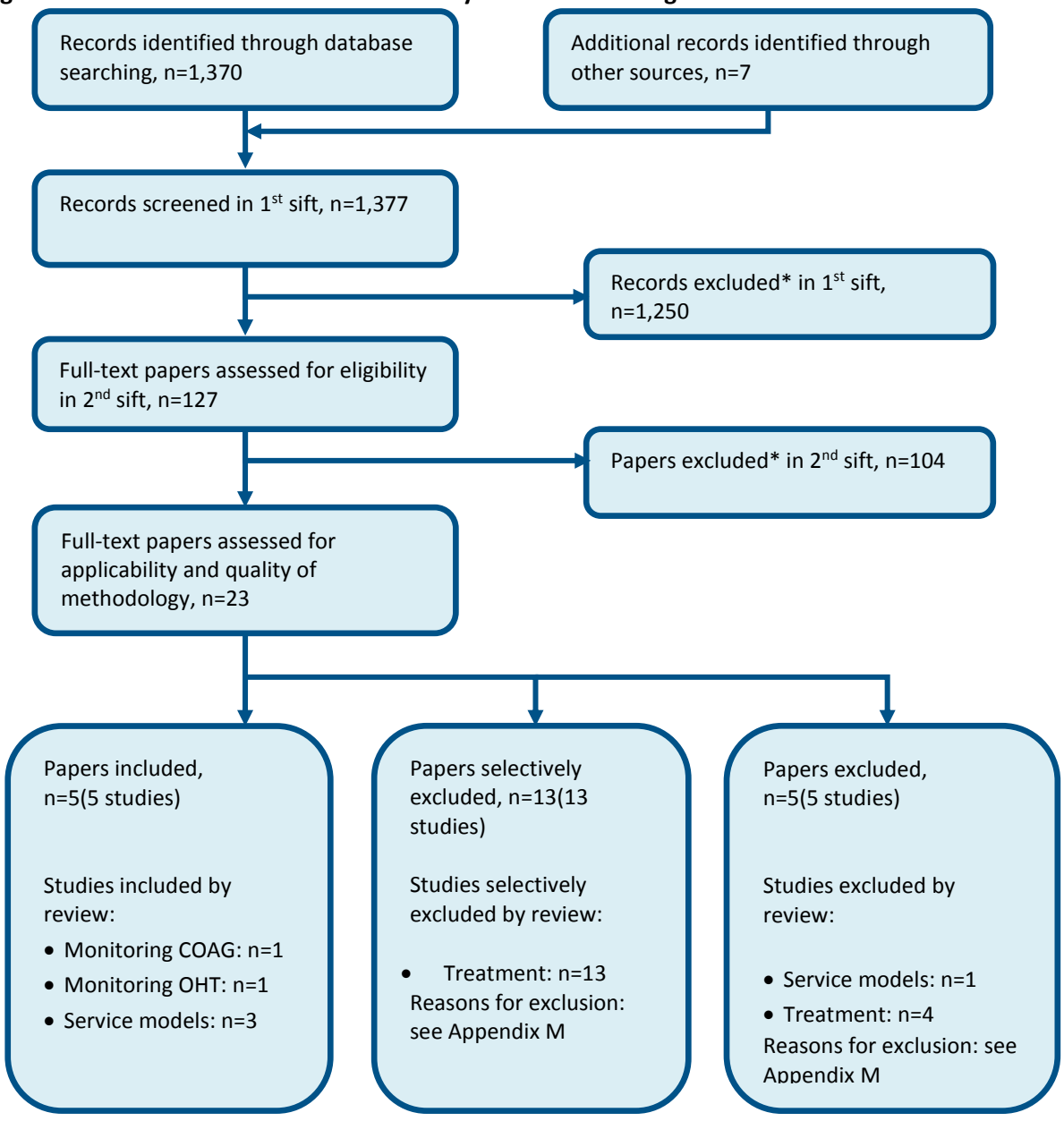


E.7.2 Skills required by healthcare professionals

E.8 Provision of information for patients

Appendix F: Health economic study selection

Figure 9: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

G.1 Contents

Search strategies used for the glaucoma guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2014, available from https://www.nice.org.uk/article/pmg20/. All searches were run up to 24th January 2017 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley), see Table 1.

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Searches for **prognostic studies** were usually constructed combining population terms with prognostic variable terms and sometimes outcomes. Search filters were added to the search where appropriate.

Table 1: Databases searched

Diagnosis accuracy	G.4.2	Medline, Embase and the Cochrane Library
Monitoring	G.4.3	Medline, Embase and the Cochrane Library
Prognostic risk tools	G.4.1	Medline & Embase
Service provision	G.4.5	Medline, Embase and the Cochrane Library
Treatment	G.4.4	Medline, Embase and the Cochrane Library

Searches for the clinical reviews were run in Medline, Embase and the Cochrane Library for all questions except prognostic risk tools, where Medline and Embase only were searches as the protocol did not include randomised controlled trials study types.

Searches for the health economic reviews were run in Medline, Embase, the NHS Economic Evaluations Database (NHS EED), and the Health Technology Assessment (HTA) database. NHS EED and HTA databases are hosted by the Cochrane Library. The NHS EED database has not been updated since 2015.

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in NHS EED and HTA were constructed using population terms only.

G.2 Population search strategies

G.2.1 Standard glaucoma population

Medline search terms

1.	exp ocular hypertension/ or ocular hypotension/
2.	low tension glaucoma/
3.	intraocular pressure/
4.	glaucom*.ti,ab,kw.
5.	(ocular adj (hypertension or hypotension)).ti,ab.
6.	or/1-5

Embase search terms

1.	exp glaucoma/
2.	exp intraocular hypotension/
3.	intraocular pressure/
4.	glaucom*.ti,ab,kw.
5.	(ocular adj (hypertension or hypotension)).ti,ab.
6.	or/1-5

Cochrane search terms

#1.	MeSH descriptor: [ocular hypertension] explode all trees
#2.	MeSH descriptor: [ocular hypotension] explode all trees
#3.	MeSH descriptor: [low tension glaucoma] explode all trees
#4.	glaucom*:ti,ab,kw
#5.	(ocular next (hypertension or hypotension)):ti,ab

#6.	(or #1-#5)

G.3 Study filter search terms

G.3.1 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

G.3.2 Randomised controlled trials [RCT]

Medline search terms

(Based on the sensitivity and precision maximising version reported in the Cochrane Handbook (http://handbook.cochrane.org/)).

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ti,ab.
4.	placebo.ab.
5.	randomly.ab.ti
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

G.3.3 Systematic reviews [SR]

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.

4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.3.4 Health economic studies [HE]

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

G.3.5 Quality of life studies [QoL]

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.
7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.

22.	or/1-21

G.3.6 Diagnostic test accuracy studies [DIAG]

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(roc curve* or auc).ti,ab.
8.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(roc curve* or auc).ti,ab.
7.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

G.3.7 Health economic modelling [MOD]

Medline search terms

1.	exp models, economic/
2.	*models, theoretical/
3.	*models, organizational/
4.	markov chains/
5.	monte carlo method/
6.	exp decision theory/
7.	(markov* or monte carlo).ti,ab.
8.	econom* model*.ti,ab.
9.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
10.	or/1-9

Embase search terms

1.	statistical model/
2.	exp economic aspect/

3.	1 and 2
4.	*theoretical model/
5.	*nonbiological model/
6.	stochastic model/
7.	decision theory/
8.	decision tree/
9.	monte carlo method/
10.	(markov* or monte carlo).ti,ab.
11.	econom* model*.ti,ab.
12.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
13.	or/3-12

G.3.8 Observational studies [OBS]

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

G.4 Searches for specific questions

G.4.1 Prognostic risk tools

Searches for the following two questions were run as one search:

- What is the accuracy of risk tools for identifying people in the community who are at increased risk of developing chronic open angle glaucoma?
- What is the accuracy of risk tools for identifying people with chronic open angle glaucoma who are at increased risk of vision loss?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	predict.ti.
5.	(validat* or rule*).ti,ab.
6.	(predict* and (outcome* or risk* or model*)).ti,ab.
7.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
8.	decision*.ti,ab. and logistic models/
9.	(decision* and (model* or clinical*)).ti,ab.
10.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
11.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
12.	roc curve/
13.	or/4-12
14.	epidemiologic studies/
15.	observational study/
16.	exp cohort studies/
17.	(cohort adj (study or studies or analys* or data)).ti,ab.
18.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
19.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
20.	controlled before-after studies/
21.	historically controlled study/
22.	interrupted time series analysis/
23.	(before adj2 after adj2 (study or studies or data)).ti,ab.
24.	or/14-23
25.	3 and (13 or 24)
26.	model*.ti,ab.
27.	algorithms/
28.	algorithm*.ti,ab.
29.	tool*.ti,ab.
30.	calculat*.ti,ab.
31.	or/26-30

32.	25 and 31
33.	OHTS-EGPS.ti,ab.
34.	Ocular Hypertension Treatment Study-European Glaucoma Prevention Study.ti,ab.
35.	means prediction model.ti,ab.
36.	means plus asymmetry.ti,ab.
37.	worse eye model.ti,ab.
38.	or/33-37
39.	38 not 2
40.	32 or 39
41.	(glaucom* adj5 (risk* adj3 (score* or stratif* or assess* or calculat* or engine* or equation* or algorithm* or chart* or table* or predict* or function*))).ti,ab.
42.	(glaucom* adj5 ((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) adj3 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model*))).ti,ab.
43.	43 or 44
44.	43 not 2
45.	40 or 44
46.	Limit 45 to English language
	Date parameters: 1946 – 24 January 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	clinical study/
5.	observational study/
6.	family study/
7.	longitudinal study/
8.	retrospective study/
9.	prospective study/
10.	cohort analysis/
11.	follow-up/
12.	cohort*.ti,ab.
13.	11 and 12
14.	(cohort adj (study or studies or analys*)).ti,ab.
15.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
16.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
17.	(before adj2 after adj2 (study or studies or data)).ti,ab.
18.	or/4-10,13-17
19.	predict.ti.
20.	(validat* or rule*).ti,ab.
21.	(predict* and (outcome* or risk* or model*)).ti,ab.
22.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (predict* or model* or decision* or identif* or prognos*)).ti,ab.
23.	decision*.ti,ab. and statistical model/

24.	(decision* and (model* or clinical*)).ti,ab.
25.	(prognostic and (history or variable* or criteria or scor* or characteristic* or finding* or factor* or model*)).ti,ab.
26.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or auc or calibration or indices or algorithm or multivariable).ti,ab.
27.	receiver operating characteristic/
28.	or/19-27
29.	3 and (18 or 28)
30.	model*.ti,ab.
31.	exp algorithm/
32.	algorithm*.ti,ab.
33.	tool*.ti,ab.
34.	calculat*.ti,ab.
35.	or/30-34
36.	29 and 35
37.	OHTS-EGPS.ti,ab.
38.	Ocular Hypertension Treatment Study-European Glaucoma Prevention Study.ti,ab.
39.	means prediction model.ti,ab.
40.	means plus asymmetryl.ti,ab.
41.	worse eye model.ti,ab.
42.	or/37-41
43.	43 not 2
44.	36 or 43
45.	(glaucom* adj5 (risk* adj3 (score* or stratif* or assess* or calculat* or engine* or equation* or algorithm* or chart* or table* or predict* or function*))).ti,ab.
46.	(glaucom* adj5 ((decision or predict* or assess* or screen* or score* or scoring or stratif* or prognos* or logistic*) adj3 (tool* or rule* or instrument*1 or index* or test* or technique* or analys* or model*))).ti,ab.
47.	47 or 48
48.	47 not 2
49.	44 or 48
50.	Limit 49 to English language
	Date parameters: 1946 – 24 January 2017

G.4.2 Diagnostic accuracy

Searches for the following three questions were run as one search:

- What is the accuracy of tests for measuring IOP and monitoring changes in IOP, including repeat measures?
- What is the accuracy of structural tests for identifying and monitoring progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)?
- What is the accuracy of tests for identifying closed or occludable anterior chamber angle?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2

4.	Limit 3 to English language
5.	diagnostic techniques, ophthalmological/ or corneal pachymetry/ or gonioscopy/ or scanning laser polarimetry/ or slit lamp/ or tonometry, ocular/
6.	exp tomography, optical/
7.	(tonog* or tonom*).ti,ab.
8.	slit lamp*.ti,ab.
9.	((heidelberg or retina* or optical) adj2 tomog*).ti,ab.
10.	exp ophthalmoscopy/
11.	scanning laser.ti,ab.
12.	monoscopic photo*.ti,ab.
13.	gonioscop*.ti,ab.
14.	((iris eclipse or shadow or van herick*) adj2 (test* or assess*)).ti,ab.
15.	schiempflug*.ti,ab.
16.	(ultrasound or ultra sound).ti,ab.
17.	b-scan.ti,ab.
18.	pachymet*.ti,ab.
19.	(cornea* adj3 thick* adj2 (measure* or record*)).ti,ab.
20.	ocular response analy*.ti,ab.
21.	tono pen*.ti,ab.
22.	((direct or indirect) adj1 ophthalmosc*).ti,ab.
23.	(stereoscopic adj2 photo*).ti,ab.
24.	confocal microscop*.ti,ab.
25.	anterior chamber depth.ti,ab.
26.	optic disk imag*.ti,ab.
27.	optic disk assess*.ti,ab.
28.	optic nerve fib* analy*.ti,ab.
29.	or/5-28
30.	4 and 29
31.	Study filters RCT [G.3.2] or DIAG [G.3.6]
32.	30 and 31 - Date parameters: 1946 - 24 January 2017
33.	Study filter OBS [G.3.8]
34.	30 and 33 - Date parameters: 2008 - 24 January 2017
35.	32 or 34

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	visual system examination/
6.	gonioscopy/ or ophthalmoscopy/ or exp pachymetry/ or scanning laser ophthalmoscopy/ or scanning laser polarimetry/
7.	slit lamp/
8.	oculoplethysmography/
9.	eye photography/
10.	optical tomography/

11.	exp optical coherence tomography/
12.	(tonog* or tonom*).ti,ab.
13.	slit lamp*.ti,ab.
14.	((heidelberg or retina* or optical) adj2 tomog*).ti,ab.
15.	scanning laser.ti,ab.
16.	monoscopic photo*.ti,ab.
17.	gonioscop*.ti,ab.
18.	((iris eclipse or shadow or van herick*) adj2 (test* or assess*)).ti,ab.
19.	Schiempflug*.ti,ab.
20.	(ultrasound or ultra sound).ti,ab.
21.	b-scan.ti,ab.
22.	pachymet*.ti,ab.
23.	(cornea* adj3 thick* adj2 (measure* or record*)).ti,ab.
24.	ocular response analy*.ti,ab.
25.	tono pen*.ti,ab.
26.	((direct or indirect) adj1 ophthalmosc*).ti,ab.
27.	(stereoscopic adj2 photo*).ti,ab.
28.	confocal microscop*.ti,ab.
29.	anterior chamber depth.ti,ab.
30.	optic disk imag*.ti,ab.
31.	optic disk assess*.ti,ab.
32.	optic nerve fib* analy*.ti,ab.
33.	or/5-32
34.	4 and 33
35.	Study filters RCT [G.3.2] or DIAG [G.3.6]
36.	34 and 35 - Date parameters: 1974 - 24 January 2017
37.	Study filter OBS [G.3.8]
38.	34 and 37 - Date parameters: 2008 - 24 January 2017
39.	36 or 38

Cochrane search terms

#1.	Standard population [G.2.1]
#2.	[mh ^"diagnostic techniques, ophthalmological"]
#3.	[mh ^"corneal pachymetry"]
#4.	[mh ^gonioscopy]
#5.	[mh ^"scanning laser polarimetry"]
#6.	[mh ^"slit lamp"]
#7.	[mh ^"tonometry, ocular"]
#8.	[mh "tomography, optical"]
#9.	[mh ophthalmoscopy]
#10.	((heidelberg or retina* or optical) near/2 tomog*):ti,ab
#11.	scanning laser:ti,ab
#12.	(tonog* or tonom*):ti,ab
#13.	slit next lamp*:ti,ab
#14.	monoscopic next photo*:ti,ab

#15.	gonioscop*:ti,ab
#16.	(("iris eclipse" or shadow or van herick*) near/2 (test* or assess*)):ti,ab
#17.	schiempflug*:ti,ab
#18.	(ultrasound or "ultra sound"):ti,ab
#19.	b-scan:ti,ab
#20.	pachymet*:ti,ab
#21.	(cornea* near/3 thick* near/2 (measure* or record*)):ti,ab
#22.	tono pen:ti,ab
#23.	((direct or indirect) near/1 ophthalmosc*):ti,ab
#24.	(stereoscopic near/2 photo*):ti,ab
#25.	confocal next microscop*:ti,ab
#26.	anterior next chamber next depth:ti,ab
#27.	optic next disk next imag*:ti,ab
#28.	ocular next response next analy*:ti,ab
#29.	optic next disk next assess*:ti,ab
#30.	optic next nerve next fib* next analy*:ti,ab
#31.	(or #2-#30)
#32.	#1 and #31
	Date parameters: Inception - 24 January 2017

G.4.3 Monitoring intervals

Searches for the following two questions were run as one search:

- What are the optimum intervals for monitoring people with chronic open angle glaucoma?
- What are the optimum intervals for monitoring people with ocular hypertension, suspected chronic open angle glaucoma or both?

Medline search terms

1.	Search strategy G.4.2 lines 1-30
2.	Study filters RCT [G.3.2] or DIAG [G.3.6]
3.	1 and 2
	Date parameters: 2008 - 24 January 2017

Embase search terms

1.	Search strategy G.4.2 lines 1-34
2.	Study filters RCT [G.3.2] or DIAG [G.3.6]
3.	1 and 2
	Date parameters: 2008 - 24 January 2017

Cochrane search terms

#1.	Search strategy G.4.2 lines #1-#32
	Date parameters: 2008 - 24 January 2017

G.4.4 Treatment

- Which are the most clinically and cost effective and least harmful pharmacological treatments for people with OHT, suspected chronic open angle glaucoma and confirmed chronic open angle glaucoma?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filters RCT [G.3.2] or SR [G.3.3]
6.	4 and 5
	Date parameters: 2008 – 24th January 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filters RCT [G.3.2] or SR [G.3.3]
6.	4 and 5
	Date parameters: 2008 - 24th January 2017

Cochrane search terms

#1.	Standard population [G.2.1]
	Date parameters: 2008 - 24th January 2017

G.4.5 Service provision

- What is the clinical and cost-effectiveness of performing different tests or combinations of tests (including repeat measures of individual tests) for identifying people who require onward referral from first contact primary care to confirming diagnosis?

Medline search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	diagnostic techniques, ophthalmological/ or corneal pachymetry/ or gonioscopy/ or scanning laser polarimetry/ or slit lamp/ or tonometry, ocular/
6.	slit lamp*.ti,ab.
7.	((heidelberg or retina* or optical) adj2 tomog*).ti,ab.
8.	exp ophthalmoscopy/
9.	scanning laser.ti,ab.
10.	monoscopic photo*.ti,ab.
11.	gonioscop*.ti,ab.
12.	((iris eclipse or shadow or van herick*) adj2 (test* or assess*)).ti,ab.
13.	exp tomography, optical/
14.	(tonog* or tonom*).ti,ab.
15.	schiempflug*.ti,ab.
16.	(ultrasound or ultra sound).ti,ab.
17.	b-scan.ti,ab.
18.	pachymet*.ti,ab.

19.	(cornea* adj3 thick* adj2 (measure* or record*)).ti,ab.
20.	ocular response analy*.ti,ab.
21.	tono pen*.ti,ab.
22.	((direct or indirect) adj1 ophthalmosc*).ti,ab.
23.	(stereoscopic adj2 photo*).ti,ab.
24.	confocal microscop*.ti,ab.
25.	anterior chamber depth.ti,ab.
26.	optic disk imag*.ti,ab.
27.	optic disk assess*.ti,ab.
28.	optic nerve fib* analy*.ti,ab.
29.	visual field tests/
30.	(perimetr* or campimetr*).ti,ab.
31.	(frequency doubling technology or fdt).ti,ab.
32.	(visual field test* or vision field test* or visual field exam* or vision field exam*).ti,ab.
33.	(sita or humphrey or swedish interactive testing algorithm or henson).ti,ab.
34.	or/5-33
35.	Study filters RCT [G.3.2] or SR [G.3.3]
36.	epidemiologic studies/
37.	observational study/
38.	exp cohort studies/
39.	(cohort adj (study or studies or analys* or data)).ti,ab.
40.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
41.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
42.	controlled before-after studies/
43.	historically controlled study/
44.	interrupted time series analysis/
45.	(before adj2 after adj2 (study or studies or data)).ti,ab.
46.	or/36-45
47.	exp case control study/
48.	case control*.ti,ab.
49.	or/47-48
50.	cross-sectional studies/
51.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
52.	or/50-51
53.	35 or 46 or 49 or 52
54.	4 and 34 and 53
	Date parameters: 1946 - 24th January 2017

Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	visual system examination/

6.	gonioscopy/ or ophthalmoscopy/ or exp pachymetry/ or scanning laser ophthalmoscopy/ or scanning laser polarimetry/
7.	slit lamp/
8.	oculoplethysmography/
9.	eye photography/
10.	optical tomography/
11.	exp optical coherence tomography/
12.	(tonog* or tonom*).ti,ab.
13.	slit lamp*.ti,ab.
14.	((heidelberg or retina* or optical) adj2 tomog*).ti,ab.
15.	scanning laser.ti,ab.
16.	monoscopic photo*.ti,ab.
17.	gonioscop*.ti,ab.
18.	((iris eclipse or shadow or van herick*) adj2 (test* or assess*)).ti,ab.
19.	schiempflug*.ti,ab.
20.	(ultrasound or ultra sound).ti,ab.
21.	b-scan.ti,ab.
22.	pachymet*.ti,ab.
23.	(cornea* adj3 thick* adj2 (measure* or record*)).ti,ab.
24.	ocular response analy*.ti,ab.
25.	tono pen*.ti,ab.
26.	((direct or indirect) adj1 ophthalmosc*).ti,ab.
27.	(stereoscopic adj2 photo*).ti,ab.
28.	confocal microscop*.ti,ab.
29.	anterior chamber depth.ti,ab.
30.	optic disk imag*.ti,ab.
31.	optic disk assess*.ti,ab.
32.	optic nerve fib* analy*.ti,ab.
33.	perimetry/
34.	perimetr*and campimetr*.ti,ab.
35.	(frequency doubling technology or fdt).ti,ab.
36.	(visual field test* or vision field test* or visual field exam* or vision field exam*).ti,ab.
37.	(sita or humphrey or swedish interactive testing algorithm or henson).ti,ab.
38.	or/5-37
39.	Study filters RCT [G.3.2] or SR [G.3.3]
40.	clinical study/
41.	observational study/
42.	family study/
43.	longitudinal study/
44.	retrospective study/
45.	prospective study/
46.	cohort analysis/
47.	follow-up/
48.	cohort*.ti,ab.
49.	47 and 48

50.	(cohort adj (study or studies or analys* or data)).ti,ab.
51.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
52.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
53.	(before adj2 after adj2 (study or studies or data)).ti,ab.
54.	or/40-46,49-53
55.	exp case control study/
56.	case control*.ti,ab.
57.	or/55-56
58.	cross-sectional study/
59.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
60.	or/58-59
61.	39 or 54 or 57 or 60
62.	4 and 38 and 61
	Date parameters: 1946 - 24th January 2017

Cochrane search terms

#1.	MeSH descriptor: [ocular hypertension] explode all trees
#2.	MeSH descriptor: [ocular hypotension] explode all trees
#3.	MeSH descriptor: [low tension glaucoma] explode all trees
#4.	glaucom*:ti,ab,kw
#5.	(ocular next (hypertension or hypotension)):ti,ab
#6.	(or #1-#5)
#7.	[mh ^"diagnostic techniques, ophthalmological"]
#8.	[mh ^"corneal pachymetry"]
#9.	[mh ^gonioscopy]
#10.	[mh ^"scanning laser polarimetry"]
#11.	[mh ^"slit lamp"]
#12.	[mh ^"tonometry, ocular"]
#13.	[mh "tomography, optical"]
#14.	[mh Ophthalmoscopy]
#15.	((heidelberg or retina* or optical) near/2 tomog*):ti,ab
#16.	scanning laser:ti,ab
#17.	(tonog* or tonom*):ti,ab
#18.	slit next lamp*:ti,ab
#19.	monoscopic next photo*:ti,ab
#20.	gonioscop*:ti,ab
#21.	(("iris eclipse" or shadow or van herick*) near/2 (test* or assess*)):ti,ab
#22.	Schiempflug*:ti,ab
#23.	(ultrasound or "ultra sound"):ti,ab
#24.	b-scan:ti,ab
#25.	pachymet*:ti,ab
#26.	(cornea* near/3 thick* near/2 (measure* or record*)):ti,ab
#27.	tono pen:ti,ab
#28.	((direct or indirect) near/1 ophthalmosc*):ti,ab

#29.	(stereoscopic near/2 photo*):ti,ab
#30.	confocal next microscop*:ti,ab
#31.	anterior next chamber next depth:ti,ab
#32.	optic next disk next imag*:ti,ab
#33.	ocular next response next analy*:ti,ab
#34.	optic next disk next assess*:ti,ab
#35.	optic next nerve next fib* next analy*:ti,ab
#36.	MeSH descriptor: [visual field tests] explode all trees
#37.	(perimetr* or campimetr*):ti,ab
#38.	((frequency next doubling next technology) or fdt):ti,ab
#39.	((visual or vision) near/2 (test* or exam*)):ti,ab
#40.	(sita or humphrey or henson):ti,ab
#41.	swedish interactive testing algorithm:ti,ab
#42.	(or #6-#41)
#43.	#5 and #42
	Date parameters: Inception - 24 January 2017

G.5 Health economics search terms

G.5.1 Health economic (HE) reviews

Economic searches were conducted in Medline, Embase and the Cochrane library

Medline & Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter HE [G.3.4]
6.	4 and 5
	Date parameters: 2000-2007 and 2014 - 23 January 2017

Cochrane search terms (NHS EED and HTA)

#1.	Standard population [G.2.1]
	Date parameters: 2000 - 23 January 2017

G.5.2 Quality of life (QoL) reviews

Quality of life searches were conducted in Medline and Embase only

Medline & Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter QOL [G.3.5]
6.	4 and 5
	Date parameters: 2008– 23 January 2017

G.5.3 Economic modelling (MOD)

Economic modelling searches were conducted in Medline and Embase

Medline & Embase search terms

1.	Standard population [G.2.1]
2.	Excluded study designs and publication types [G.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter MOD [G.3.7]
6.	4 and 5
	Date parameters: 2008– 23 January 2017

Appendix H: Clinical evidence tables

H.1 Prognostic risk tools

H.1.1 Increased risk of conversion to COAG

Reference	Alencar 2008[10]
Study type	Prospective cohort
Study methodology	Data source: Diagnostic Innovations in Glaucoma Study (DIGS) prospective cohort study. Eligible subjects were required to have had a visual field examination and optic disc stereo photograph taken close in time to a baseline HRT scan used for evaluation. Baseline was set at the first occurrence of this matching, and the HRT date was used as the baseline date. The average time interval between examinations was 1.4 months (median: 0.6 months, first quartile: 0.2 months, third quartile: 1.7 months). For each eye, central corneal thickness (CCT) was calculated as the average of three measurements obtained during the same visit using an ultrasound pachymeter (Pachette GDH 500; DGH Technology, Inc., Philadelphia, PA, USA). One eye of each patient was randomly selected for analysis. Only patients with normal and reliable visual fields on the baseline were included. Standard automated perimetry (SAP) visual fields were obtained using either 24-2 Full Threshold or Swedish Interactive Thresholding Algorithm (SITA; Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA, USA) strategies. Only tests with reliable results (≤33% fixation losses, false positives, and false negatives) were included. Simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ, USA) were reviewed with a stereoscopic viewer (Pentax Stereo Viewer II; Asahi Optical Co., Tokyo, Japan). Two masked, experienced graders evaluated baseline stereo photographs and classified them as glaucomatous or normal. Glaucomatous optic disc appearance was defined based on the presence of neuroretinal rim thinning, excavation, notching, or characteristic retinal nerve fibre layer defects. Vertical cup-to-disc ratio (CDR) was assessed by visually estimating the CDR based on the contour of the cup. The average value between examiners was calculated and used for analysis. For progression assessment, each patient's most recent stereo photograph was compared with the baseline. Each grader was masked to the temporal sequence of the photographs. Definition of change was based on focal or diffuse thinning of the neuroretinal rim, increased excavation, and the appearance or enlargement of RNFL defects. Discrepancies between the 2 graders either were resolved by consensus or by adjudication of a third experienced grader. Only photographs with adequate quality were included. From an initial group of 310 patients who fulfilled inclusion criteria, 5 (2%) subjects had poor-quality photographs at baseline, and 29 (9%) did not have follow-up stereo photographs to assess progression and were excluded from further analysis. CSLO images were acquired using either the HRT-I or –II (Heidelberg Engineering, GmbH) and analysed on each respective machine, using HRT-3

Reference	Alencar 2008[10]
	software. Only 15° images were used. For each patient, 3 topographical images were obtained, then combined and automatically aligned to make a single mean topography used for analysis. Magnification errors were corrected using patients' corneal curvature measurements. Good-quality images required a focused reflectance image with a standard deviation not greater than 50 micrometres and centred GPS analysis. From an initial group of 310 patients who fulfilled inclusion criteria, 15 (5%) were excluded because the 15° HRT baseline image could not be retrieved, 26 (8%) were excluded after quality control of the HRT mean image, 4 (1%) were excluded because the HRT was not able to run the GPS analysis, and 11 (4%) were excluded as a result of highly off-centred analysis of the GPS algorithm. Average follow-up was 63.3 months.
Number of patients	n=223
Patient characteristics	People with suspected glaucoma (according to the clinical examination by 2 glaucoma specialists) Age: 59.0 ± 12.7 Male to female ratio: not reported Family origin: not reported Setting: Hamilton Glaucoma Center (University of California, San Diego; UCSD). Country: USA IOP (mm Hg) 22.5 ± 5.7 CCT (micrometre) 565 ± 38 PSD (dB) 1.94 ± 0.68 Vertical cup/disc ratio 0.59 ± 0.19 Inclusion criteria: suspect optic disc appearance (as determined by subjective assessment) or elevated intraocular pressure (>21 mm Hg); normal and reliable standard automated perimetry (SAP) visual fields at baseline; open angles on gonioscopy Exclusion criteria: best-corrected visual acuity less than 20/40, spherical refraction outside ± 5.0 D or cylinder correction outside 3.0 D, or any other ocular or systemic disease that could affect the optic nerve or the visual field
Target condition(s)	Conversion to COAG, defined as development of either repeatable abnormal visual fields or glaucomatous deterioration in the appearance of the optic disc (whichever came first). Glaucomatous conversion by visual field was defined as the development of 3 consecutive abnormal examinations during follow-up, or 2 consecutive, when these were the last examination results available during follow-up. An abnormal result followed by a normal result was not

Reference	Alencar 2008[10]
	considered a conversion. An abnormal visual field was defined as a pattern standard deviation (PSD) with $p < 0.05$ or a glaucoma hemifield test (GHT; Humphrey Perimeter; Carl Zeiss Meditec, Inc., Oberkochen, Germany) with results outside normal limits. Two experienced glaucoma specialists verified that the visual field defects were consistent with glaucoma. Number of events n=54 eyes (24.2%)
Risk tool(s)	Glaucoma Prediction Score (GPS) Derivation: unclear
Statistical measures	Glaucoma Prediction Score (GPS) Global c-statistic 0.732
Source of funding	Supported in part by National Eye Institute Grants EY08208 (PAS) and EY11008 (LMZ) and participant retention incentive grants in the form of glaucoma medication at no cost (Alcon Laboratories Inc., Allergan, Pfizer Inc., and Santen Inc.).
Limitations	Risk of bias: high (no calibration data reported) Indirectness: none
Comments	

Reference	Medeiros 2005[442]
Study type	Prospective cohort
Study methodology	Data source: Diagnostic Innovations in Glaucoma Study (DIGS), a prospective longitudinal study. Consecutive people attending the glaucoma clinic at the Hamilton Glaucoma Center University of California, San Diego (UCSD) were recruited to participate in the DIGS. After entry in the study, patients in DIGS were longitudinally evaluated according to a pre-established protocol that included regular follow-up visits in which they underwent clinical examination and several other imaging and functional tests. All the data were entered in a computer database, which contained information on 1,876 subjects, including healthy subjects, patients with glaucoma, and patients suspected of having glaucoma. A cohort of untreated patients with OHT was retrospectively selected from the DIGS population. All patients with OHT who met the inclusion criteria described later were enrolled in the current study. Evaluation of structural damage to the optic disc at baseline was based on assessment of simultaneous stereoscopic optic disc photographs (TRC-SS; Topcon Instrument Corp of America, Paramus, NJ, USA). Stereoscopic sets of slides were examined using a stereoscopic viewer (Asahi Pentax, Golden, CO, USA). Two experienced graders, each masked to the subject's identity and to the other test results, evaluated the photographs. Each

Reference	Medeiros 2005[442]
	grader was previously trained using a set of standard reference photographs used in the Optic Disc Reading Center of the Hamilton Glaucoma Center UCSD. This set of photographs included multiple examples of normal and definite glaucomatous optic discs. After training, each grader completed a test to evaluate his or her grading skills before achieving certification. For inclusion, photographs needed to be graded of adequate quality or better. The graders visually estimated the horizontal and vertical cup-disc ratios based on the contour of the cup. For eye-specific variables, the mean for each eye was calculated and then the mean values from each eye were averaged to determine the baseline predictive factor for each participant. The IOP predictive factor was calculated from 2 to 4 baseline IOP measurements per eye obtained during the first 6 months of follow-up. Follow-up time (median and range): 76 months 14–198 months
Number of patients	n=126 (252 eyes)
Patient characteristics	People with OHT who did not receive treatment. None of the patients received any ocular hypotensive medication at baseline, and they were left untreated during follow-up. Fifteen (12%) of the 126 patients were assigned to treatment during follow-up for other causes than development of glaucoma, such as unacceptably high IOP (based on the attending ophthalmologist's decision). For these patients, only the period without treatment was evaluated in the study. Age: mean 56.3±13.1 Male to female ratio: 42:58 Family origin: White non-Hispanic 93.6%, African American 3.3%, Hispanic 1.6%, Asian 1.6% Setting: glaucoma clinic at the Hamilton Glaucoma Center University of California, San Diego (UCSD) Country: USA Diabetes mellitus 11% IOP mean 25.7±3.5 mm Hg CCT mean 576.8±36.7 m Vertical cup-disc ratio mean 0.43±0.15 Horizontal cup-disc ratio mean 0.43±0.15 PSD mean 1.78±0.36 dB Inclusion criteria: best-corrected visual acuity of 20/40 or better, spherical refraction within ±5.0 D and cylinder correction within ±3.0 D, and

Reference	Medeiros 2005[442]
	open angles on gonioscopy; OHT (baseline IOP greater than or equal to 24 mm Hg in one eye and greater than or equal to 21 mm Hg in the other eye on at least 2 occasions; normal-appearing optic discs and retinal nerve fibre layer on baseline stereo photographs of both eyes (no diffuse or focal rim thinning, haemorrhage, cupping, or nerve fibre layer defects indicative of glaucoma or other ocular pathologic features); and normal visual field test results. Normal visual field test results were defined as a mean deviation and PSD within 95% confidence limits and a Glaucoma Hemifield Test result within normal limits). Exclusion criteria: secondary causes of high IOP (for example, pseudoexfoliation, pigment dispersion syndrome, iridocyclitis, trauma), other intraocular eye disease, history of refractive surgery, or other diseases possibly affecting the visual field (for example, demyelinating diseases, pituitary lesions), patients with any evidence of diabetic retinopathy documented from a dilated ophthalmoscopic examination.
Target condition(s)	Conversion from OHT to POAG - defined as the development of a reproducible visual field defect or glaucomatous change in appearance of the optic disc in at least 1 eye. The time of the first abnormal SAP visual field test results or change in optic disc appearance (whichever came first) in the eye that developed POAG was defined as the end point for patients showing conversion. Glaucomatous change was defined as the development of focal or diffuse thinning of the neuroretinal rim, increased excavation, or appearance of retinal nerve fibre layer defects. Changes in rim colour, presence of disc haemorrhage, or progressive parapapillary atrophy were not sufficient for characterisation of progression. When grading photographs for progression, each examiner was masked to the temporal sequence of the photographs. Discrepancies between the 2 graders either were resolved by consensus or by adjudication of a third experienced grader. Abnormality on SAP was defined as the presence of a Glaucoma Hemifield Test result outside normal limits and/or PSD with p<.05. A confirmed visual field defect required 3 consecutive, abnormal visual field test results. A glaucoma specialist, who excluded other causes of nonglaucomatous visual field loss or presence of visual field artefacts as possible causes of the visual field abnormality, evaluated the visual field test results. Only reliable visual field test results were included in the analysis. This was defined as 33% or fewer false-positive results, false-negative results, and fixation losses. One hundred ninety-five (5.6%) of 3,509 visual field test results were classified as unreliable and excluded from the analysis. Number of events n=31 (25%)
Risk tool(s)	OHTS predictive model OHTS predictive model (reduced) Derivation: OHTS predictive model (full) was derived in the OHTS (Gordon 2002[240]) OHTS predictive model (reduced) was derived in the OHTS (Coleman 2004[136])

Reference	Medeiros 2005[442]
Statistical measures	OHTS predictive model C-statistic 0.68 OHTS predictive model (reduced) C-statistic 0.73 Calibration plot (see Calibration) Three studies produced calibration plots, which have been reproduced with permission. Calibration plots for the OHST full and reduced models[442] (Figure 1, OHTS-EPS model[504,650], Figure 2 and Figure 3). None of the studies reported the results of formal statistical tests, such as the Hosmer-Lemeshow test.
Source of funding	None stated
Limitations	Risk of bias: high (not a reasonable number of outcome events for both full and reduced OHTS predictive models) Indirectness: none
Comments	

Reference	Takwoingi 2014[650]
Study type	RCTs Prospective cohort
Study methodology	Data source: Data from placebo arm of 2 RCTs (Moorfields Eye Hospital, Rotterdam Eye Hospital) and 2 observational cohort studies (Queen Margaret Hospital Dunfermline, Queens Medical Centre Nottingham) Median follow up time: 2.7–9.3 years
Number of patients	n=879
Patient characteristics	People with OHT Rotterdam Eye Hospital (n=393) Age: no OAG 56.0 (11.0) Male to female ratio: 187:206

Reference	Takwoingi 2014[650]
	Family origin: White 100% Inclusion criteria: white family origin; both eyes IOP≥22mmHg and ≤32mmHg; normal visual fields on Humphrey automated perimetry; best-corrected Snellen visual acuity of at least 20/40 Exclusion criteria: any coexisting ocular or systemic disease; use of ocular hypertensives in preceding 3 months <u>Moorfields Eye Hospital (n=298)</u> Age: no OAG 59.3 (10.2) Male to female ratio: 174:124 Family origin: White 82.6%, African ancestry: 6.4%, Asian 1.6% Inclusion criteria: age >35 years IOP between 22mmHG and 35mmHg by GAT <u>Dunfermline Hospital (n=188)</u> Age: no development of OAG 62.9 (11.8), development of OAG 62.2 (9.2) Male to female ratio: 105:83 Family origin: White 100% Diabetes 9% Treated 1.9% Inclusion criteria: all referrals with confirmed OHT from 2000 to end of December 2010 collated from an electronic patient record system Data from 1 cohort study (Nottingham Queens Medical Centre) was excluded as 30.2% of people were treated.
Target condition(s)	Conversion from OHT to OAG (5 years) Rotterdam: defined as change from the initial Advanced Glaucoma Intervention Study (AGIS) score of 0 to an AGIS score of ≥1 on 3 consecutive reliable visual fields, with at least 1 of the locations consistently below the threshold for normality. Criteria defining a reliable field were <25% fixation losses, <30% FN errors and <30% FP errors. If the patient developed a visual field defect, the test was repeated within 1 month. If the same defect was then reproduced on a reliable second field, then a third test was performed 3–4 months after that. Conversion was confirmed if the field defect was present on 3 consecutive tests. Moorfields: defined as a reproducible defect in the visual field (standard automation perimetry) of 1 individual point below the 0.5% probability level, 2 clustered points below the 1% probability level, or 3 clustered points below the 5% probability level on either the total deviation or the pattern deviation probability plot.

Reference	Takwoingi 2014[650]
	Dunfermline: development of a repeatable visual field defector significant change in optic disc morphology. A visual field defect was defined as a reproducible defect of SAP of 1 individual point below the 0.5% probability level, 2 clustered points below the 1% probability level, or 3 clustered points below the 5% probability level on either the total deviation or the pattern deviation probability plot. At least 2 sets of fields were required to deem conversion. Nottingham: development of a repeatable visual field defect or significant change in optic disc morphology. The optometrist initially detected this on his or her annual review and confirmed it with a repeat visual field upon returning to hospital eye service for a consultant assessment. Number of events: Rotterdam n=28/393 (7.1%) Moorfields n=44/298 (14.8%) Dunfermline n=28/188 (14.9%)
Risk tool(s)	OHTS-EGPS means model Derivation: references The Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study Group 2007[504]
Statistical measures	<u>C-statistic</u> Rotterdam 0.83 (0.75 – 0.91) Moorfields 0.69 (0.59 – 0.78) Dunfermline 0.72 (0.63 – 0.82) <u>Calibration slope</u> Rotterdam 1.09 (0.75 – 0.91) Moorfields 0.69 (0.59 – 0.78) Dunfermline 0.72 (0.63 – 0.82)
Source of funding	Part of the Surveillance for Ocular Hypertension study funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme
Limitations	Risk of bias: Rotterdam – very high (not a reasonable number of outcome events; no calibration data reported)

Reference	Takwoingi 2014[650]
	Moorfields – high (no calibration data reported) Dunfermline –very high (not a reasonable number of outcome events; no calibration data reported) Indirectness: Rotterdam – no serious indirectness Moorfields – no serious indirectness Dunfermline – no serious indirectness
Comments	The proportion of missing values of CCT was high (between 23–100%). CCT was sporadically collected for Moorfields. CCT was not recorded in Dunfermline cohort, so the average value from the Nottingham cohort was imputed (556 micrometres). Also 52% PSA values were missing for Moorfields.

Reference	The Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study Group 2007 [504]
Study type	RCT, control arm
Study methodology	Data source: European Glaucoma Prevention Study (EGPS) placebo arm. Randomisation was from January 1997 to May 2004. Baseline data was collected prior to randomisation, apart from CCT, which were collected 1–3 years after randomisation.
Number of patients	n=406
Patient characteristics	People with OHT Age: no POAG 57.2±10, POAG 61.1±9.9 Male to female ratio 241:259 Family origin: White, not Hispanic 100% Treatment: with beta blockers 7.6% Country: 18 centres, Europe
Target condition(s)	Development of OAG (5 year), defined as the first abnormal visual field or optic disk that masked readers classified as meeting the definition for change Number of events n=61 (12.2%)

Reference	The Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study Group 2007 [504]
Risk tool(s)	OHTS prediction model. Derivation: Gordon 2002[240] OHTS-EGPS prediction model. Derivation: derived in this study using the control arm of the OHTS
Statistical measures	OHTS prediction model c-statistic 0.72 (0.63–0.80) OHTS-EGPS prediction model c-statistic 0.74 (0.70-0.78)
Source of funding	National Eye Institute, National Center for Minority Health and Health Disparities; National Institutes of Health, Bethesda, MD, USA; European Commission; Merck Research Laboratories; White House Station, New Jersey, USA; Pfizer; Research to Prevent Blindness, New York City, New York, USA
Limitations	Risk of bias: OHTS prediction model – high (no calibration data reported) OHTS-EGPS model – low Indirectness: none
Comments	

Reference	Weinreb 2010 [685]
Study type	Prospective cohort
Study methodology	Data source: Confocal Scanning Laser Ophthalmology (CSLO) Ancillary Study to the OHTS Operators certified by the CSLO Reading Center at the University of California, San Diego, USA obtained Heidelberg Retina Tomography (HRT; Heidelberg Engineering, GmbH, Heidelberg, Germany) images. Three 10-degree images were obtained on both eyes and three 15-degree images were obtained on the right eye at the annual OHTS dilated examination. If both 10-degree and 15-degree good quality images were available, the 10-degree images were used in this analysis. Corneal curvature measurements were used to correct images for magnification error. Corrective lenses were used during image acquisition when astigmatism was greater than 1 diopter. Mean images were used for statistical analyses.
Number of patients	n=438 (857 eyes)
Patient characteristics	People with OHT

Reference	Weinreb 2010 [685]
	Age: mean 55.4 (95% CI 54.5 to 56.2) Male to female ratio 185:253 Family origin: African American 17% Family history of glaucoma 32% Setting: 7 clinics Country: USA Inclusion criteria: IOP ranged from 24mmHg to 32mmHg in at least 1 eye and 21mmHg to 32mmHG in other eye; 2 normal, reliable automated achromatic 30–2 visual fields and normal appearing optic discs based on clinical examination and review of full-frame 35 mm pairs or a split-frame simultaneous stereoscopic optic disc photographs as assessed by 2 independent, masked, certified graders at the Optic Disc Reading Center The Optic Disc Reading Center (ODRC) graders estimated horizontal and vertical cup-to-disc ratios by contour.
Target condition(s)	Development of confirmed visual field abnormality Confirmed clinically significant stereograph-based optic disc deterioration attributed to POAG Masked, certified readers at the Visual Field or Optic Disc Reading Centers independently identified abnormalities. The masked Endpoint Committee then determined whether these confirmed abnormalities were attributable to POAG. Optic disc deterioration had to be clinically significant to be classified as an endpoint. The date for a POAG endpoint was the first date of 3 consecutive abnormal visual fields or the first date of 2 consecutive sets of stereo photographs that classified the eye as reaching a POAG endpoint. Number of events n=64/828 eyes (7.7%)
Risk tool(s)	<u>Glaucoma Probability Score (GPS):</u> The GPS is available with HRT 3.0 (or higher software). It does not depend on an operator-drawn contour line or a reference plane and is therefore operator independent. The GPS uses a geometric model to describe the shape of the optic disc/parapapillary retina (globally and locally) based on 5 parameters (cup size, cup depth, rim steepness, horizontal retinal nerve fibre layer curvature, and vertical retinal nerve fiber layer curvature). A relevance vector machine classifier then interprets these parameters, and the resulting output describes the probability that the eye is glaucomatous as between 0% and 100% (based on fit to training data from healthy and glaucoma eyes). GPS output is then automatically classified into 3 categories; outside normal limits (GPS > 64%), borderline (GPS between 24% and 64%) and within normal limits (GPS < 24%). <u>Moorfields Regression Analysis (MRA):</u>

Reference	Weinreb 2010 [685]
	Compares measured rim area to predicted rim area adjusted for disc size to categorize eyes as outside normal limits, borderline or within normal limits. Using the HRT 3.0 software, both the MRA and GPS classify eyes as within normal limits (WNL), borderline (BL) or outside normal limits (ONL) utilising the same normative database of 700 white eyes and 200 African American eyes. The comparison to the normative database is provided in 6 regions (superior temporal, inferior temporal, temporal, superior nasal, inferior nasal and nasal), and as an overall global classification. If any of the 6 regions are ONL, then the eye was classified as ONL. In addition, if any of the regional or global values are 'outside normal limits' then the MRA and GPS overall 'result' measurement is defined as 'outside normal limits'. Derivation: unclear
Statistical measures	GPS global Sensitivity 0.28 Specificity 0.73 C-statistic 0.75 (0.69-0.82) MRA Sensitivity 0.30 Specificity 0.78 C-statistic 0.76 (0.70-0.82)
Source of funding	NIH/NEI grants; Horncrest Foundation awards; NIH Vision Core Grant; Merck Research Laboratories; Pfizer Inc.
Limitations	Risk of bias: GPS – high (no calibration data reported) MRA – very high (unclear number of predictors and concerns regarding the reasonable number of outcome events; no calibration data reported) Indirectness: none
Comments	

H.1.2 Increased risk of COAG progression

Reference	Anton 2013 [24]
Study type	Prospective cohort
Study methodology	Data source: Subjects were initially included and prospectively followed for 3 years. All had been diagnosed with glaucoma (primary open-angle glaucoma, pigment dispersion glaucoma or pseudoexfoliative glaucoma). All subjects received a full ophthalmic examination that included visual acuity, refraction, slit-lamp examination of anterior segment, gonioscopy and intraocular pressure readings with a Goldmann tonometer. The posterior pole was examined with special care paid to optic nerve head morphology specifying vertical cup-to-disk ratio and the presence of rim thinning, disk haemorrhages and nerve fibre layer defects. This was performed every 6 months. The Humphrey Visual Field Analyser 24-2 SITA Standard assessed the functional damage (Carl Zeiss Meditec, Dublin, CA, USA). Structural damage was evaluated with nonstereo optic disc photographs.
Number of patients	n=50 (22 analysed;37 eyes)
Patient characteristics	People diagnosed with glaucoma: POAG: 32 eyes Pseudoexfoliative: 3 eyes Pigmentary: 2 eyes Age: 64.3 ± 10.3 years Male to female ratio: Not reported Family origin: Not reported Setting: Not reported Country: Spain Mean initial defect (MD): -5.6 ± 5.7 Mean initial VFI : 87.5 ± 17.4% Initial visual field damage (MD > -6 dB): 64.9% Inclusion criteria: Visual acuity equal to or better than 20/40 and glaucomatous structural and functional damage. Glaucomatous optic nerve was defined by the presence of a cup-disc ratio asymmetry 0.2 or more or optic disc rim thinning or 1 or more disc haemorrhages or a nerve fibre layer defect. Visual fields had to show a pattern standard deviation outside normal 95% confidence interval or glaucoma hemifield test outside

Reference	Anton 2013 [24]
	normal limits. Refractive errors below 6 dioptres (+5 to -5) or mild to moderate cataract were allowed. All recruited subjects needed 2 similar and reliable visual field tests (SITA Standard or Full Threshold) within 4 months, to set a baseline, and a minimum of 4 follow-up field tests. Exclusion criteria: Tests were considered unreliable and therefore discarded if fixation losses were above 30%, false-negatives above 30%, or false-positives above 15%. If 1 or more of the fields in the series did not accomplish these criteria, the subject was excluded from the study. Subjects with untreated intraocular pressure under 21mmHg or any other ophthalmic or neurologic disease were excluded.
Target condition(s)	Progression of glaucomatous visual field loss GPA I: presence of progression was considered with 3 contiguous full black triangles or non-contiguous but belonging to the same scotoma. Occurrence of 2 full black triangles in the GPA was considered suspicious of progression. Any other result was considered as absence of progression. Number of events: 7 (21.8%)
Risk tool(s)	Glaucoma progression event analysis (GPA I) Derivation: Glaucoma progression event analysis (GPA I) was derived in Heijl (2008)[265]
Statistical measures	<u>GPA I</u> Sensitivity: 0.83 Specificity: 0.93
Source of funding	Supported by Merck Sharp & Dome (Spain) and the Asociación para la Investigación en Glaucoma
Limitations	Risk of bias: Very high (concerns about whether there was a reasonable number of outcome events, no calibration data reported, attrition of study subjects) Indirectness: No indirectness Usability: Yes
Comments	None.

H.2 Tests used in case finding, diagnosis and reassessment

H.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

Study details	Participants	Diagnostic tools	Measure of Disorders	Results	Comments
Baskaran 2007[55] Study design: Diagnostic Evidence level: III	Participant group: Phakic participants attending glaucoma or general ophthalmology clinics at the Singapore National Eye Centre Exclusion criteria: Subjects with corneal disorders and uveitis excluded All participants N: 120 (120 eyes) Age (mean ± SD): 62.1 ± 11.3 M/F: 52/68 73% Chinese 7% Malay 20% Indian Drop outs: 0 Diagnosis: 44% PACG 56% POAG	Reference standard: Gonioscopy: static and indentation with 2 or 4 mirror prisms For gonioscopy: narrow angle defined as the presence of a Schaffer grade up to 1 (10° iridotrabecular angle) for at least 180° of the angle on gonioscopy with or without peripheral anterior synechiae Assessment tool under investigation: Scanning Peripheral Anterior Chamber Depth Analyzer (SPAC) and modified van Herick's grade van Herick's test. Peripheral anterior chamber depth of ≤25% of the corneal thickness at the temporal limbus with the slit beam directed to the ocular surface as angle closed and ≥40% angle open as optimal cut-off using standard photos.	Detection of angle-closure by eye using van Herick test at cut off ≤25% Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability + ve result Post-Test Probability - ve result	 85% (45/53) 90% (60/67) 87% (45/52) 88% (60/68) 44% (53/120) 8.13 0.17 0.44 87% (CI95% 76–93%) 12% (CI95% 7–20%)	Funding: National Medical research Council, Singapore Limitations: Asian population (73% Chinese) where PACG is more prevalent. It was not clear whether van Herick test was performed independently and in a masked fashion to gonioscopy Additional Outcomes: Notes: SPAC assessment observer was
			Detection of angle-closure by eye using van Herick test at cut off ≤5% to ≥15%	Sensitivity 30% (16/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using van Herick test at cut off ≤15% to ≥25%	Sensitivity 60% (32/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using van Herick test at cut off ≤40% to ≥75%	Sensitivity 96% (51/53) Specificity 76% (51/67)	
			Detection of angle-closure by eye using SPAC at cut off S, P =closed angle (N=open) Sensitivity Specificity Positive predictive value	 85% (45/53) 73% (49/67) 71% (45/63)	

Study details	Participants	Diagnostic tools	Measure of Disorders	Results	Comments
		For SPAC: 3 categorical grades for risk of angle closure S=suspect ≥4 points exceeding 95% CI; P=potential ≥4 points exceeding 72% CI; N=normal. Optimal cut-off is S or P as closed and N as open angle	Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability + ve result Post-Test Probability - ve result	868% (49/57) 44% (53/120) 3.16 0.21 0.44 71% (CI95% 62–79%) 14% (CI95% 8–24%)	masked to results of gonioscopy and van Herick test
			Detection of angle-closure by eye using SPAC at cut off S=closed angle (P, N=open)	Sensitivity 60% (32/53) Specificity 85% (57/67)	

Reference	Dabasia 2015[155]
Study type	Prospective
Study methodology	Adult participants recruited from glaucoma and general ophthalmology clinics.
Number of participants	n=78
Participant characteristics	Age: Median (IQR) 66 (53-79; range 30-83) Gender (male to female ratio): 34:44 Family origin: 56% white, 35% south Asian Based on gonioscopy Open angle 46% (n=36) Narrow angle 54% (n=42) Based on clinical opinion Narrow angle 21% (n=17)

Reference	Dabasia 2015[155]
	Setting: Ealing Hospital, Moorfields Eye Clinic Country: UK Inclusion criteria: Including those with suspected or confirmed primary angle closure, no current or previous history of ocular disease, or eye conditions not affecting angle configuration Exclusion criteria: Subjects receiving systemic or topical medicines known to affect the anterior segment and, in particular, those that may influence ACA configuration (for example, miotics). Anomalies of the anterior segment that affect ACA configuration. Phakic eyes were included for analysis.
Target condition(s)	Narrow angle using International Society of Geographical and Epidemiological Ophthalmology (ISGEO) definition of primary angle closure and a classification based on clinical opinion of occludability. Subjects diagnosed as primary angle closure suspect, primary angle closure (PAC) and primary angle closure glaucoma (PACG) were combined into a single category 'narrow or occludable' angle. ISGEO definition defined as an ACA in which the posterior (usually pigmented) trabecular meshwork was not visible for 270° or more of the angular extent on non-indentation gonioscopy and with the eye in the primary position. Clinical opinion of the consultant subspecialist ophthalmologist as to whether the angle was 'occludable'. This pragmatic criterion provides a measure of the ability of the index test to identify individuals who would be most likely to benefit from treatment.
Index test(s) and reference standard	Index test(s) van Herick Test – width of the corneal section compared with the adjacent anterior chamber space, first at the temporal limbus and then at the nasal limbus for each eye, but recorded as a percentage in accordance with the modified 7-point grading scale of Foster and colleagues. Visante AS-OCT Reference standard Gonioscopy by a consultant glaucoma subspecialist ophthalmologist with extensive experience in performing the technique and previously standardised against another consultant ophthalmologist. Time between measurement of index test and reference standard: same day
Statistical measures	Based on the eye as the unit of analysis van Herick (cut-off grade 2 or less ≤25% of the corneal thickness) Sensitivity 79.5 (64.5-89.2)

Reference	Dabasia 2015[155]
	Specificity 92.3 (79.7-97.3) Partial AUROC based on 95% specificity: 0.33 (0.09-0.80) Visante AS-OCT (ACA ≤20.7° – derived from the Youden Index) Sensitivity 87.2 (72.6-95.7) Specificity 86.8 (71.9-95.6) Partial AUROC based on 95% specificity: 0.62 (0.46-0.80) Visante AS-OCT (ACD ≤2.50mm – derived from the Youden Index) Sensitivity 71.8 (55.1-85.0) Specificity 84.6 (69.5-94.1) Partial AUROC based on 95% specificity: 0.30 (0.13-0.65)
Source of funding	Not reported
Limitations	Risk of bias: serious – unclear participant selection methods; index test cut-offs not pre-specified; not all participants included in final analyses but unclear on numbers for each index test. Indirectness: none
Comments	

Reference	Grewal 2011[243]
Study type	Cross-sectional
Study methodology	Recruitment: consecutive participants at comprehensive ophthalmology clinic at Grewal Eye Institute. The participants underwent SD-ASOCT and then Scheimpflug. SD-ASOCT performed in dark room (~1 lux using digital light meter) after allowing for dark adaption of 30 seconds, without the use of mydriatics, and with the subjects sitting in front of the instruments with their face in an upright position, by a single examiner who was masked to the gonioscopy results. 300 people were recruited, 35 were excluded because of undetectable scleral spur on SD-ASOCT.

Reference	Grewal 2011[243]
Number of participants	n=265 (265 eyes)
Participant characteristics	Age: ≥40 years, mean 55.2±5.1 Gender (male to female ratio): 49:51 Family origin: not reported Setting: Grewal Eye Institute Country: USA Inclusion criteria: ≥40 years Exclusion criteria: history of glaucoma, intraocular surgery, laser treatment, penetrating trauma, corneal disorders or abnormalities that precluded SD-ASOCT or Scheimpflug imaging
Target condition(s)	Narrow anterior chamber angles Defined as Shaffer grade ≤1 in all quadrants
Index test(s) and reference standard	Index test(s) Spectral domain (SD) AS-OCT (RTVue 100) Imaging with an auxiliary lens attachment, the corneal adaptor module long (CAM-L), which captured 1x1024 A-scan in 0.04s. Only images with Scan-Score Index >45 were included. Reference standard Gonioscopy Time between measurement of index test and reference standard: unclear
Statistical measures	Scheimpflug – ACV (criterion ≤113mm3) Sensitivity 0.90 (0.717-0.976) Specificity 0.8819 (0.834-0.92) AUC 0.935 (0.898-0.961) Scheimpflug – ACD (≤2.45mm)

Reference	Grewal 2011[243]
	Sensitivity 0.893 (0.718-0.976) Specificity 0.726 (0.664-0.781) AUC 0.880 (0.835-0.917) SD-ASOCT - parameter AOD500 temporal (criterion: ≤0.32mm) Sensitivity 0.678 (0.447-0.841) Specificity 0.8819 (0.834 – 0.92) AUC 0.808 (0.755-0.854) PPV 0.33 (0.186 – 0.51) NPV 0.963 (0.928 – 0.984) PLR 5.75 (4 - 8.2) NLR 0.45 (0.2 – 0.9) SD-ASOCT - parameter AOD500 nasal (criterion ≤0.34mm) Sensitivity 0.786 (0.590-0.917) Specificity 0.713 (0.651-0.770) AUC 0.761 (0.705-0.811) SD-ASOCT TISA500 – temporal (criterion ≤0.21mm2) Sensitivity 0.714 (0.513-0.867) Specificity 0.810 (0.754-0.858) AUC 0.738 (0.681-0.79) SD-ASOCT TISA500 – nasal (criterion ≤0.2mm2) Sensitivity 0.643 (0.441-0.813) Specificity0.787 (0.728-0.838) AUC 0.756 (0.700-0.807)
Source of funding	Not reported

Reference	Grewal 2011[243]
Limitations	Risk of bias: serious – concern that reference standard results interpreted with knowledge of the results of the index test Indirectness: none
Comments	

Reference	Khor 2010[326]
Study type	Cross-sectional
Study methodology	Recruitment: participants seeking treatment for non-ophthalmic reasons at a community clinic in Singapore. Two-thousand, one-hundred four people were recruited; 251 eyes were excluded, as at least 1 of the quadrants could not be classified due to poor image quality or poor definition of scleral spur on AS-OCT images
Number of participant	n=2,104 (1,853 eyes)
Participant characteristics	Age: Mean (SD) 63,4±8.11 years, range 50-93 Gender (male to female ratio): 48:52 Family origin: 89.5% Chinese, 2.1% Malaysian, 7.3% Indian Setting: community clinic Country: Singapore Inclusion criteria: aged 50 years or over Exclusion criteria: history of intraocular surgery or penetrating trauma in either eye; previous anterior segment laser treatment, history of glaucoma
Target condition(s)	Closed angles Gonioscopy- posterior TM could not be seen in the primary position without indentation (Scheie grade 3 or 4) Closed angles in at least 1 quadrant on gonioscopy n=380 eyes (nasal-temporal quadrants imaged)

Reference	Khor 2010[326]
Index test(s) and reference standard	Index test(s) AS-OCT (Visante) Acquisition rate of 8 frames per second (20,000 A-scans) with a transverse resolution of 60 micrometres and an axial resolution of 10-20 micrometres. After acquisition, the scanned images are processed by customised software. A single examiner, masked to the other test results, examined the seated participants before any procedure that involved contact with the eye. Reference standard Gonioscopy by a trained ophthalmologist with extensive experience in performing gonioscopy in a research setting. Performed in the dark by a single examiner masked to the AS-OCT findings. Static and dynamic gonioscopy was performed using a Goldmann 2-mirror lens and a Sussman 4-mirror lens, at x16 magnification with the eye in the primary position of gaze. Care was taken to avoid light falling on the pupil and to avoid accident indentation during the examination. Slight tilting of the gonioscopy lens was permitted in an attempt to gain a view over the complexity of the iris. Time between measurement of index test and reference standard: same day
Statistical measures	AS-OCT ≥2 quadrants of the angle closed, all quadrants imaged Sensitivity 0.929 Specificity 0.520 AUC 0.724 (0.704-0.745)
Source of funding	SingHealth Foundation, Singapore and National Research Foundation
Limitations	Risk of bias: none Indirectness: none
Comments	

Reference	Narayanaswamy 2010[483]
Study type	Cross-sectional

Reference	Narayanaswamy 2010[483]
Study methodology	Data source: participants in a study evaluating the usefulness of new imaging devices for detecting narrow angles among Singaporeans attending a government-run polyclinic for general medical problems, systematically sampled (every fifth registered participant) Recruitment: 2,047 recruited, 515 were excluded because of scleral spur, 28 due to poor image quality, 39 due to software delineation errors
Number of participants	n=1,462
Participant characteristics	Age: Mean (SD) 62.7±7.7, range 50-93 Gender (male to female ratio): 46:54 Family origin: 90% Chinese, 1.8% Malaysian, 7% Indian Setting: government-run polyclinic for general medical problems Country: Singapore Inclusion criteria: ≥50 years old Exclusion criteria: history of intraocular surgery, any evidence of aphakia or pseudophakia, penetrating trauma in the eye, previous anterior segment laser treatment, history of glaucoma, corneal disorders such as endothelial dystrophy, corneal opacity, or pterygium
Target condition(s)	Angle closure
Index test(s) and reference standard	Index test(s) AS-OCT (Visante) Image acquisition rate 8 frames per second, with a transverse resolution of 60 micrometres and an axial resolution of 10-20 micrometres. After acquisition, the images were processed by customised software. A single ophthalmologist, who was masked to the other test results, examined the seated participants. Reference standard Gonioscopy by a trained ophthalmologist Static and dynamic gonioscopy. Performed in the dark by a single examiner masked to AS-OCT findings with extensive experience in performing gonioscopy in a research setting. Time between measurement of index test and reference standard: AS-OCT then gonioscopy performed on same day

Reference	Narayanaswamy 2010[483]
Statistical measures	AS-OCT (parameter AOD500 ≤191 micrometres, temporal quadrant) Sensitivity 0.889 (0.854-0.923) Specificity 0.746 (0.721-0.771) AUC 0.82 (0.79-0.84) 10% prevalence, PPV 0.279 (0.238-0.32) 10% prevalence, NPV 0.983 (0.976-0.991) 20% prevalence, PPV 0.466 (0.425-0.507) 20% prevalence, NPV 0.964 (0.951-0.976) AS-OCT – AOD500, nasal Sensitivity0.851 (0.811-0.890) specificity 0.761 (0.737-0.786) AUC0.81 (0.78-0.83) AS-OCT – TISA500 temporal Sensitivity0.882 (0.854-0.923) specificity 0.591 (0.563-0.620) AUC0.74 (0.71-0.76) AS-OCT – TISA500 nasal Sensitivity0.733 (0.684-0.782) specificity 0.752 (0.727-0.777) AUC0.74 (0.71-0.77)
Source of funding	SingHealth, Singapore; National Medical Research Council, Singapore; National Research Foundation, Singapore
Limitations	Risk of bias: none Indirectness: none
Comments	

H.2.2 Accuracy of IOP tests

Reference	Atkinson 1992[34]
Study type	Prospective randomised
Study methodology	Data source: People from the general ophthalmology outpatient departments and glaucoma clinics from St Paul's Eye Hospital, Liverpool and Queen's Medical Centre, Nottingham Recruitment: Randomly drawn from the above populations
Number of patients	n=403 eyes
Patient characteristics	Age: Mean (SD): Not reported Gender (male to female ratio): Not reported Family origin: Not reported Setting: General ophthalmology outpatient departments and glaucoma clinics from St Paul's Eye Hospital (machines A and B), Liverpool and Queen's Medical Centre, Nottingham (machine C) Country: United Kingdom Inclusion criteria: Not reported Exclusion criteria: Uncooperative people or those with scarred corneas
Target condition(s)	Detection of IOP ≥21mmHg
Index test(s) and reference standard	Index test(s) Pulsair non-contact tonometry Reference standard Goldmann applanation tonometry Time between measurement of index test and reference standard: Measurements were made with GAT within 3 minutes of the NCT measurements

Reference	Atkinson 1992[34]		
Statistical measures	Machine A (64 eyes) Sensitivity: 81% Specificity: 93% PPV: 85% NPV: 93% PLR: 12.47 NLR: 0.16 AUC: Not reported	Machine B (223 eyes) Sensitivity: 40% Specificity: 95% PPV: 84% NPV: 71% PLR: 8.1 NLR: 0.63 AUC: Not reported	Machine C (116 eyes) Sensitivity: 48% Specificity: 94% PPV: 63% NPV: 89% PLR: 7.54 NLR: 0.56 AUC: Not reported
Source of funding	Not reported		
Limitations	Risk of bias: No risk of bias Indirectness: No indirectness		
Comments			

Reference	Billy 2015[70]
Study type	Prospective cross-sectional
Study methodology	Data source: People of all ethnicities attending the ophthalmology clinic at the Eric Williams Medical Sciences Complex for a routine visit Recruitment: Not reported
Number of patients	n=100 participants, 198 IOP readings
Patient characteristics	Age: Mean (SD): 21-50 years: 33% 51-70 years: 51% >71 years: 26% Gender (male to female ratio): 39:61

Reference	Billy 2015[70]			
	Family origin: Indo-Trinidadian: 55% African-Trinidadian: 36% Mixed: 8% White: 1% Setting: Unit of Public Health and Primary Care at the University of the West Indies St Augustine Country: Trinidad and Tobago Inclusion criteria: People of all ethnicities attending the ophthalmology clinic at the Eric Williams Medical Sciences Complex for a routine visit were eligible Exclusion criteria: People aged under 18 years, people who had diminished mental capacity, people who were non-English speakers or people who were pregnant			
Target condition(s)	Detection of IOP ≥21mmHg			
Index test(s) and reference standard	Index test Reichert Tono-Pen AVIA carried out by trained medical students Reference standard Goldmann applanation tonometry carried out by a consultant or resident ophthalmologist Time between measurement of index test and reference standard: Not reported			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	9	4	13
	Index test -	7	178	185
	Total	16	182	198

Reference	Billy 2015[70]
Statistical measures	Sensitivity: 56.3% (33.2%, 76.9%) Specificity: 97.8% (94.5%, 99.1%) PPV: 69.2% (42.4%, 87.3%) NPV: 96.2% (92.4%, 98.2%) PLR: 25.6 (8.6, 73.9) NLR: Not reported AUC: Not reported
Source of funding	Not reported
Limitations	Risk of bias: No risk of bias Indirectness: No indirectness
Comments	

Reference	Catagay 2014[95]
Study type	Prospective randomised
Study methodology	Data source: Adults from ophthalmology departments in Turkey Recruitment: Randomised
Number of patients	n=40 right eyes of 40 participants
Patient characteristics	Age: Mean (SD): 35.73 ± 12.97 years Gender (male to female ratio): Not reported Family origin: Not reported Setting: Ophthalmology departments

Reference	Catagay 2014[95]			
	Country: Turkey Inclusion criteria: Adults who had no ocular pathology other than having myopia of 6 dioptres or over Exclusion criteria: Presence of any ocular pathology other than high myopia and ocular hypertension			
Target condition(s)	Detection of IOP above or below 21mmHg			
Index test(s) and reference standard	Index test Icare rebound tonometer Reference standard Goldmann applanation tonometry Time between measurement of index test and reference standard: 15 minute interval between readings			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	5	1	6
	Index test -	1	33	34
	Total	6	34	40
Statistical measures	Sensitivity: 83.3% Specificity: 97.1% PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: Not reported			
Source of funding	Not reported			
Limitations	Risk of bias: No risk of bias Indirectness: Serious indirectness			

Reference	Catagay 2014[95]
Comments	

Reference	Moreno-Montanes 2015[462]
Study type	Prospective cross-sectional
Study methodology	Data source: 2 ophthalmology departments Recruitment: Consecutive
Number of patients	n=150 eyes of 150 participants
Patient characteristics	Age: Mean (SD): 57.0 ± 18.13 years Gender (male to female ratio): 55 (36.7%)/95 (63.3%) Family origin: Not reported Setting: Ophthalmology departments Country: Spain Inclusion criteria: People with IOPs and no glaucoma and those with ocular hypertension or glaucoma. All eyes had healthy corneas and no history of ocular trauma. Only people with best-corrected visual acuity (VA) of 10/20 or better were included Exclusion criteria: Not reported
Target condition(s)	Detection of IOP ≥21mmHg
Index test(s) and reference standard	Index test(s) Icare rebound tonometry PRO Reference standard Goldmann applanation tonometry

Reference	Moreno-Montanes 2015[462]
	Time between measurement of index test and reference standard: Not reported
Statistical measures	Sensitivity: 79.5% Specificity: 74.6% PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: Not reported
Source of funding	Not reported
Limitations	Risk of bias: No risk of bias Indirectness: No indirectness
Comments	

H.2.3 Central corneal thickness measurement evidence

None.

H.2.4 Visual field evidence

None.

H.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]
Study type	Comparative diagnostic evaluation – Glaucoma Automated Tests Evaluation (GATE) study
Study	Data source: Prospective between April 2011 and July 2013

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]
methodology	Recruitment: Consecutive eligible people referred from community optometrists to hospital eye services with a glaucoma-related finding were identified at the time of referral. People identified from their referral letter as being referred with a possible glaucoma diagnosis or glaucoma-related finding, including high IOP, possible abnormalities in the optic disc or visual field tests, and possible narrow anterior chamber angle.
Number of patients	n=932
Patient characteristics	Age: Mean (SD) 60.5 (13.8) years Gender: female 482 (51.1%) Family origin: Black 4.7%, Asian 2.8%, Mixed 0.1%, White 89.2%, other 3.1% Setting: Five NHS hospital eye services in the UK. Three academic units of different sizes and 2 district general hospitals. Country: UK Inclusion criteria: Adults referred from community optometrists or general practitioners to hospital eye services with glaucoma-related findings, including those with OHT Exclusion criteria: People referred to hospital eye services because of ocular disease; people under age18; people who could not give informed consent; people who had already been diagnosed with glaucoma; and people referred from secondary care. n=955 recruited, n=12 imaging index tests not implemented correctly, n=11 no reference standard collected. No result categories excluded in default diagnostic analysis: test performed and imaging report produced but quality lower than manufacturer cut-off; no overall classification generated by machine; no clear imaging artefact on the report; no imaging acquired from the person's eyes, missing imaging output (study-related or data-collection related).
Target condition(s)	Glaucoma Evidence of glaucomatous optic neuropathy (from optic disc or RNFL structural abnormalities, diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles; documented, progressive thinning of the neuroretinal rim with associated increase in cupping of the optic disc; diffuse or localised abnormalities of the peripapillary RNFL, especially at the interior and superior poles; disc rim or

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]
	peripapillary RNFL haemorrhages; optic disc neural rim asymmetry of the 2 eyes consistent with loss of the neural tissue) and a characteristic VF loss (damage consistent with RNFL damage [nasal step, accurate field defect or paracentral depression in the cluster of test sites]. VF loss in 1 hemifield that is different from the other hemifield and that is across the horizontal midline [in early or moderate cases]. Absence of other known explanations). Severe: MD worse than or equal to -12.01 dB Moderate: MD between -6.01 dB and -12 dB Mild: MD better than or equal to -6 dB The 'worse' eye of each participant, as defined by the clinical reference standard, was used in the analyses. If the 2 eyes had a similar spectrum of disease, then a random eye was chosen.
Index test(s) and reference standard	Index test(s) HRT-III confocal laser scanning imaging technology. Topographic image derived from multiple optical sections at the consecutive focal depth planes. Images given a quality index (the mean topography standard deviation), for which the manufacturer recommends less than 40 micrometres. Two different classification tools. HRT-MRA: requires the user to draw a contour line to define the optic disc boundary. This produces an overall (global) classification as well as by 6segments (temporal, temporal superior, temporal inferior, nasal, nasal superior, and nasal inferior). Each was classified as within normal limits, borderline, or outside normal limits. The final classification was based on the most abnormal of any of the 7 classifications. HRT-GPS: glaucoma probability score that is fully automated and independent of the operator. The default final classification is based on applying a cut-off to the overall and 6 segment probabilities (<0.28 is within normal limits; ≥0.28 and <0.65 is borderline; ≥0.65 is outside normal limits). Spectral Domain-OCT Optical imaging technique capable of high resolution, cross-sectional imaging of the retina in a fashion analogous to B-scan ultrasonography but using light instead of sound. Software produces an average RNFL thickness value for the global and 6 segments that were automatically compared with a normative database. Produces an overall classification of within normal limits, borderline, or outside normal limits. Images were given a quality figure. The manufacturer recommendation was >15. Imaging always performed ahead of the reference standard. Imaging technicians and participants masked to the person's underlying condition at the time of testing. A positive test result defined under the imaging assessment was a result 'outside the normal limits'. Borderline cases were classified as negative. Reference standard

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]			
	An ophthalmologist with glaucoma expertise who was masked to the imaging results assessed participants. The reference standard represents current clinical practice in the UK. Clinical examination (biomicroscopy) of the appearance of the optic nerve head and evaluation of the visual field with standard automated perimetry (SITA). In addition, the clinician measured the IOP and examined the anterior chamber angle. Time between the measurement of the index test and the reference standard: All tests were conducted on the same day in 2 to 3 centres; the clinician assessment was on a separate day within 2 weeks of imaging.			
2x2 table HRT-MRA		Reference standard +	Reference standard -	Total
	Index test +	120	256	376
	Index test -	18	453	471
	Total	138	709	847
2x2 table HRT-GPS		Reference standard +	Reference standard -	Total
	Index test +	110	229	339
	Index test -	25	481	506
	Total	135	710	845
2x2 table SD-OCT		Reference standard +	Reference standard -	Total
	Index test +	113	158	271
	Index test -	34	578	612
	Total	147	736	883
2x2 table Combination HRT-MRA plus HRT-GPS		Reference standard +	Reference standard -	Total
	Index test +	122	329	451
	Index test -	12	367	379
	Total	134	696	830
2x2 table		Reference standard +	Reference standard -	Total

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]			
Combination HRT-MRA plus SD-OCT	Index test +	122	319	441
	Index test -	11	371	382
	Total	133	690	823
Statistical measures	HRT-MRA Sensitivity: 87% (80.2, 92.1) Specificity: 63.9% (60.2, 67.4) PLR: 2.41 NLR: 0.20 Diagnostic odds ratio: 11.80 (7.02, 19.81) AUC: 0.7873 (no CI reported) HRT-GPS Sensitivity: 81.5% (73.9, 87.6) Specificity: 67.7% (64.2, 71.2) PLR: 2.53 NLR: 0.27 Diagnostic odds ratio: 9.24 (5.82, 14.67) AUC: 0.8060 (no CI reported) OCT Sensitivity: 76.9% (69.2, 83.4) Specificity: 78.5% (75.4, 81.4) PLR: 3.58 NLR: 0.29 Diagnostic odds ratio: 12.16 (7.97, 18.54) AUC: 0.8394 (no CI reported) Combination: HRT-MRA + HRT-GPS			

Reference	Azuara-Blanco 2016[39] and Banister 2016[51]
	Sensitivity: 91.0% (84.9, 95.3) Specificity: 52.7% (48.9, 56.5) PLR: 1.93 NLR: 0.17 Diagnostic odds ratio: 11.34 (6.15, 20.90) Combination: HRT-MRA + OCT Sensitivity: 91.7% (85.7, 95.8) Specificity: 53.8% (50.0, 57.5) PLR: 1.98 NLR: 0.15 Diagnostic odds ratio: 12.90 (6.84, 24.34)
Source of funding	National Institute for Health Research (NIHR), Health Technology Assessment (HTA) program. The Health Services Research Unit is core funded by the Chief Scientist Office of the Scottish National Government Health and Social Care Directorates.
Limitations	Risk of bias: No concerns about risk of bias. Missing people from analysis clearly explained and explored through sensitivity analyses. Indirectness: No concerns about applicability
Comments	

Reference	Kamdeu Fansi 2011[311]
Study type	Cross-sectional
Study methodology	Data source: Subjects enrolled during the 6 months from August 2003 to February 2004 Recruitment: Population-based sample examined as part of the mobile glaucoma screening clinic project (MGSCP)
Number of patients	n=232 (LEFT EYES)
Patient characteristics	Age: Mean (SD) 61 (11) years

Reference	Kamdeu Fansi 2011[311]
	Gender (F/M): 151/81 Family origin: 54 African-Caribbean, 178 White Setting: Multiple Centres throughout Montreal but connected through a university hospital. Country: Canada Inclusion criteria: Focused on groups at 'high risk' for development of open-angle glaucoma, defined as one or more of the following: 1) Caribbean or African descent, 2) older than 50 years, 3) positive family history for open-angle glaucoma (immediate relative). Exclusion criteria: None reported. n=70 excluded for quality of HRT3 unknown or poor quality, or no clinical ophthalmologic test results, or no FDT screening performed, or optic nerves atypical and unclassifiable by the GPS algorithm. n=221 with both HRT and clinical classification results (n=70 excluded from 291 original identified as participants)
Target condition(s)	Definitive glaucoma Final diagnostic classifications were based on optic disc appearance and frequency-doubling technology (FDT) perimetry screening results. All eyes classified into 4 diagnostic groups including normal, possible glaucoma, probable glaucoma or definitive glaucoma. Glaucomatous optic nerve damage was documented using the vertical cup or disc ratio and the Disc Damage Likelihood Scale. Based on the results of the examination of the optic nerve and the retinal nerve fibre layer in each participant, individual eyes were classified as being not glaucoma(DDLS 0-1), glaucoma suspect (DDLS 2-3), or glaucoma (DDLS 4-7). An abnormal FDT perimetry screening was defined as at least 2 adjacent points of mild relative loss in the C-20-5 algorithm. Diagnostic classifications based on the clinical examination and FDT results: Not glaucoma: Ophthalmic exam normal + FDT result normal (n=129) Possible glaucoma: Ophthalmic exam normal + FDT abnormal; or ophthalmic exam glaucoma suspect + FDT normal (n=71) Probable glaucoma: Ophthalmic exam glaucoma suspect + abnormal FDT; or Ophthalmic exam glaucoma + normal FDT (n=17)

Reference	Kamdeu Fansi 2011[311]			
	Definitive glaucoma: Ophthalmic exam glaucoma + abnormal FDT (n=4)			
Index test(s) and reference standard	Index test(s) HRT-II confocal scanning laser ophthalmoscopy. All participants underwent HRTII testing. All HRTII images were reprocessed with HRT3. The parameters evaluated were HRTII/MRA, HRT3/MRA, HRT3/GPS, and combination HRT3/MRA/GPS. Subjects characterised as not glaucoma, borderline, and outside normal limits (no further details). Results shown for a positive test result defined as 'outside the normal limits'. Borderline cases classified as negative. Reference standard All underwent standard ophthalmologic examination including gonioscopy, IOP, slit-lamp examination, and observation of the optic disc, nerve fibre layer and retina after eye dilation. One of two glaucoma specialists masked to the results of the HRT-II performed the ophthalmic examination. Time between measurement of index test and reference standard: Unclear			
2x2 table HRTII-MRA		Reference standard +	Reference standard -	Total
	Index test +	3	12	15
	Index test -	1	205	206
	Total	4	217	221
2x2 table HRT3-MRA		Reference standard +	Reference standard -	Total
	Index test +	4	21	25
	Index test -	0	196	196
	Total	4	217	221
2x2 table		Reference standard +	Reference standard -	Total

Reference	Kamdeu Fansi 2011[311]			
HRT3-GPS	Index test +	3	40	43
	Index test -	1	177	178
	Total	4	217	221
2x2 table Combination HRT3-MRA - GPS		Reference standard +	Reference standard -	Total
	Index test +	4	58	62
	Index test -	0	159	159
	Total	4	217	221
Statistical measures	HRTII-MRA Sensitivity: 75% (21.9, 98.7) Specificity: 94.5% (90.4,97.0) PPV: 20 (5, 49) NPV: 99.5 (96.9, 99.9) PLR: 13.7 (6.2, 30.3) NLR: 0.26 (0.05, 1.44) HRT3-MRA Sensitivity: 100% (39.6, 100) Specificity: 90.4% (85.6, 93.8) PPV: 16 (5.2, 36.9) NPV: 100 (97.6, 100) PLR: 10.5 (6.9, 15.7) NLR: 0 (0, 0) HRT3-GPS Sensitivity: 75% (21.9, 98.7) Specificity: 81.7% (75.7, 86.5) PPV: 7.1 (1.8, 20.5)			

Reference	Kamdeu Fansi 2011[311]
	NPV: 99.4 (96.3, 99.9) PLR: 4.1 (2.2, 7.7) NLR: 0.3 (0.1, 1.7) Combination: HRT3-MRA + HRT3-GPS Sensitivity: 100% (39.6, 100) Specificity: 73.4% (66.8, 79.0) PPV: 6.6 (2.1, 16.7) NPV: 100 (97.0, 100) PLR: 3.7 (3.0, 4.7) NLR: 0 (0, 0)
Source of funding	Study funded by grants for the E Baker Foundation Canada and the international branches of the Lions Club, and the Glaucoma Research Society of Canada. The authors have no financial or other interest in the HRT3.
Limitations	Risk of bias: Very serious concerns about the risk of bias due to unclear patient selection. Unclear if the index tests completed were done so without knowledge of reference standard results. Unclear flow and timing between index tests and reference standard. Indirectness: No concerns about applicability
Comments	

Reference	Lee 2013[377]
Study type	Cross-sectional
Study methodology	Data source: unclear Recruitment: People referred to the glaucoma clinic of the hospital with borderline changes in morphology.
Number of patients	n=117
Patient characteristics	Age: Mean (SD) glaucoma 49.9 (12.8) years; no glaucoma 48.9 (11.2) years

Reference	Lee 2013[377]
	Gender: Not reported. Family origin: Not reported. Setting: Glaucoma clinic at a university hospital Country: Korea Inclusion criteria: People who had -6.0 to +6.0 dioptres (D) refractive error, no systemic disease, and no other significant ocular diseases were enrolled in the study. Exclusion criteria: Not reported All people who fit the profile were followed-up at 6-month intervals for 2 years using SITA.
Target condition(s)	Glaucoma Glaucoma characterised by the presence of a glaucomatous optic disc figure and a glaucomatous visual field with or without IOP ≥21 mmHg. The glaucomatous optic disc shapes included the presence of localised or diffuse neuroretinal rim thinning, notching associated with peripapillary atrophy, nerve fibre layer defects, and optic haemorrhage. Glaucomatous visual fields were confirmed by 2 consecutive abnormal visual field test results, which were defined as follows: 3 adjacent points depressed by 5 dB, with 1 of the points depressed by at least 10 dB; 2 adjacent points depressed by 10 dB; or A difference of 10 dB between 2 adjacent points across the nasal horizontal meridian.
Index test(s) and reference standard	HRT3 Software includes the calculation of GPS a new automated algorithm that evaluates both optic disc and the peripapillary retinal nerve fibre layer photography to estimate the probability of the presence of glaucoma. GPS uses horizontal and vertical RNFL curvature and optic nerve head shape parameters of cup size, cup depth, and rim steepness. The most representative outputs were considered horizontal and vertical RNFL curvature, cup size, rim steepness, cup depth, and GPS.

Reference	Lee 2013[377]			
	Cut-off values were arbitrarily selected to determine the best sensitivity and specificity relationship for each variable. Reference standard Comprehensive ophthalmologic examination including BCVA, slit-lamp biomicroscopy, IOP, gonioscopy, funduscopic examination with stereoscopic optic disc photography and monoscopic red-free digital fundus photography. Time between measurement of index test and reference standard: Unclear			
2x2 table HRT3-GPS Cut-off 0.78		Reference standard +	Reference standard -	Total
	Index test +	28	28	56
	Index test -	13	48	61
	Total	41	76	117
Statistical measures	HRT3-GPS Sensitivity: 69.2% (CI not reported) Specificity: 62.7% (CI reported) PPV: 41.9 NPV: 84.0 AUC: 0.619 (0.492, 0.745) HRT3 H-RNFL AUC: 0.601 (0.452, 0.728) HRT3 V-RNFL AUC: 0.595 (0.430, 0.694) HRT3 Cup size AUC: 0.553 (0418, 0.672)			

Reference	Lee 2013[377]
	HRT3 Rim steepness AUC: 0.568 (0.405, 0.648) HRT3 Cup depth AUC: 0.588 (0.439, 0.662)
Source of funding	Not reported.
Limitations	Risk of bias: There were very serious concerns about the risk of bias due to an unclear patient selection, and it was unclear if the index tests and reference standard results were interpreted without knowledge of each other. There was an unclear flow and timing between index tests and reference standard. Indirectness: No concerns about applicability
Comments	

Reference	Li 2010[393]
Study type	Cross-sectional
Study methodology	Data source: Community-based volunteers with risk factors for glaucoma enrolled between August 2003 and May 2008 Recruitment: recruited and examined consecutively at a Caribbean community church, an outdoor summer festival, a community park, a chronic care nursing centre, an eye clinic and the Glaucoma Institute (through advertisements placed in clinic waiting rooms, hospital circulars and local newspapers, or approaching those who have visited the Institute because they have family members who have glaucoma). Offered free glaucoma screening.
Number of patients	n=210 (RIGHT EYES)
Patient characteristics	Age: Mean (SD) 61.01 (8.73) years Gender (F/M): 157/53

Reference	Li 2010[393]
	Family origin: 7.14% Black, 91.43% White, 0.95% Hispanic, 0.48% other. Setting: Multiple community centres. Country: Canada Inclusion criteria: Focused on groups at 'high risk' for development of open-angle glaucoma, defined as one or more of the following: 1) Caribbean, African or Hispanic descent, 2) older than 50 years, 3) positive family history for open-angle glaucoma (immediate relative). Exclusion criteria: Inability to give informed consent and an inability to complete an ophthalmic examination or OCT scan. n=333 people enrolled. n=30 missing perimetry necessary for final diagnostic classifications or missing both RNFL and optic nerve head scans) n=100 poor quality RFNL or optic nerve head scans.
Target condition(s)	Definitive glaucoma Final diagnostic classifications were based on optic disc appearance and frequency-doubling technology (FDT) perimetry screening results. All eyes classified into 4 diagnostic groups including not glaucoma, possible glaucoma, probable glaucoma, or definitive glaucoma. Glaucomatous optic nerve damage was documented using the vertical cup and disc ratio and the Disc Damage Likelihood Scale. Based on the results of the examination of the optic nerve and the retinal nerve fibre layer in each participant, individual eyes were classified as being not glaucoma (DDLS 0-1), glaucoma suspect (DDLS 2-3), or glaucoma (DDLS 4-7). An abnormal FDT perimetry screening was defined as at least 2 adjacent points of mild relative loss in the C-20-5 algorithm. Diagnostic classifications based on the clinical examination and FDT results: Not glaucoma: Ophthalmic exam normal + FDT result normal (n=121) Possible glaucoma: Ophthalmic exam normal + FDT abnormal; or ophthalmic exam glaucoma suspect + FDT normal (n=71) Probable glaucoma: Ophthalmic exam glaucoma suspect + abnormal FDT; or Ophthalmic exam glaucoma + normal FDT (n=12) Definitive glaucoma: Ophthalmic exam glaucoma + abnormal FDT (n=6)

Reference	Li 2010[393]			
Index test(s) and reference standard	Index test(s) OCT (optical coherence tomography) scan A photographer masked to the results of the clinical and FDT examination performed non-dilated OCT scans. Scans with a signal strength of less than 6 were considered inadequate quality and were not analysed. Both the Fast RNFL and the Fast Optic Disc scan protocols of the Stratus were performed. Measurements were provided for clock-hour sectors, quadrant averages (superior, inferior, nasal, temporal), and overall averages of the circular scan. These measurements are compared with a normative database that is divided into percentiles. For Fast RNFL a scan was considered positive for glaucoma if at least 1 or more of the 3 parameters fell below the percentile cut-offs. For Fast Optic Disc scans, the 3 best performing parameters were identified by selecting those with the highest sensitivity-specificity combinations. Threshold values associated with the highest combinations for detection of definitive glaucoma were chosen as cut-offs. The 3 RNFL and 3 optic nerve head parameters were then combined to detect glaucoma where a positive test was considered when ≥1 of the 3 RNFL parameters and ≥1 of the 3 optic nerve parameters were below the cut-offs. Reference standard Ocular examination including pachymetry, gonioscopy, IOP, slit-lamp examination, and stereo examination of the optic nerve head, RNFL and retina. Completed eye examination by 1 or 2 glaucoma specialists who were masked to the results of the stratus scan and perimetry. Time between measurement of index test and reference standard: those examined in a mobile clinic were same day; those examined in hospital or the Glaucoma Institute were same day or within a month of their examination.			
2x2 table OCT – Fast RNFL parameters		Reference standard +	Reference standard -	Total
	Index test +	4	31	35
	Index test -	2	173	175
	Total	6	204	210
2x2 table OCT – FAST Optic Disc: Cup		Reference standard +	Reference standard -	Total
	Index test +	5	32	37
	Index test -	1	172	173

Reference	Li 2010[393]			
Diameter Cut-off ≥1.16	Total	6	204	210
2x2 table OCT – FAST Optic Disc: Cup/disc vertical ratio Cut-off ≥0.68		Reference standard +	Reference standard -	Total
	Index test +	5	37	42
	Index test -	1	167	168
	Total	6	204	210
2x2 table OCT – FAST Optic Disc: Cup area Cut-off ≥1.33		Reference standard +	Reference standard -	Total
	Index test +	5	38	43
	Index test -	1	166	167
	Total	6	204	210
2x2 table Combination OCT both RNFL and optic nerve head parameters		Reference standard +	Reference standard -	Total
	Index test +	4	8	12
	Index test -	2	196	198
	Total	6	204	210
Statistical measures	OCT – RFNL parameters – combined superior average, inferior average and overall RNFL thickness at 5th percentile cut-off Sensitivity: 67% (24, 94) Specificity: 85% (79, 90) PLR: 4.55 (2.12, 9.04) NLR: 0.39 (0.21, 1.16) OCT optic nerve head parameters Cup diameter Sensitivity: 83.33% Specificity: 84.39% AUC: 0.91 (0.82, 0.99)			

Reference	Li 2010[393]
	Cup or disc vertical ratio Sensitivity: 83.33% Specificity: 81.95 AUC: 0.88 (0.80, 0.95) Cup area Sensitivity: 83.33% Specificity: 81.46 AUC: 0.86 (0.78, 0.93) Combination: OCT – RNFL and optic nerve head parameters Sensitivity: 67% (22, 96) Specificity: 96% (93, 98) PLR: 17.10 (7.06, 41.40) NLR: 0.35 (0.11, 1.08)
Source of funding	Supported by Fonds de la recherché en santé du Quebec and Allergan
Limitations	Risk of bias: Concern about risk of bias due to not all people being included in the analysis. Indirectness: No concerns about applicability
Comments	

Reference	Pueyo 2009[547]
Study type	Cross-sectional
Study methodology	Data source: Unclear Recruitment: Unclear

Reference	Pueyo 2009[547]
Number of patients	n=140 eyes of 140 people
Patient characteristics	Age: Mean (SD) Not reported Gender: Not reported Family origin: Not reported. Setting: Single University Hospital Country: Spain Inclusion criteria: Aged between 18 and 80 years, best corrected visual acuity (BCVA) of at least 8/10 (Snellen scale), refractive error not exceeding 5 dioptres of sphere and 3 dioptres of cylinder, and transparent ocular media. Exclusion criteria: Subjects with any history of severe haematological, cardiovascular or neuro-ophthalmic disease, previous ocular surgery, angle anomalies, or any retinopathy
Target condition(s)	Glaucomatous eyes IOP ≥ 22mmHg or higher, repeated abnormal visual field defects and optic disc appearance consistent with glaucomatous optic neuropathy (diffuse or focal rim thinning, cupping, notching, haemorrhage, asymmetry of the vertical cup, or disc ratio > 0.2 or RNFL defects). Visual field losses in automated perimetry were defined by a pattern standard deviation outside 95% normal confidence limits, glaucoma hemifield test result outside normal limits or cluster of at least 3 points in the pattern deviation plot with sensitivity outside the 95% normal limits, repeated in 3 consecutive visual field tests.
Index test(s) and reference standard	Index test(s) HRT-2 confocal scanning laser ophthalmoscopy. For every subject, the instrument obtained 3 topographic images of each optic disc and the mean image was analysed. The parameters evaluated were disc area, cup area, rim area, cup or disc area ratio, rim or disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour, cup shape measure, mean RNFL thickness, RNFL cross-sectional area, horizontal cup or disc ratio, vertical cup or disc ratio, maximum contour elevation, maximum contour depression, contour line modulation temporal-superior, contour line modulation temporal-inferior,

Reference	Pueyo 2009[547]
	the 2 linear discriminant functions, from Mikelberg and Burk and the Moorfields Regression Analysis (MRA). OCT The OCT protocol performed was 3.4 mm circular scans to determine RNFL thickness in every location. Peripapillary RNFL evaluated were average thickness (360°), temporal quadrant thickness (316° to 45°), superior quadrant thickness (46° to 135°), nasal quadrant thickness (136° tp 225°), inferior quadrant thickness (226° to 315°) and thickness in the 12 clock-hour positions. RNFL parameters calculated in this study were superior maximum (Smax), inferior maximum (Imax), superior average (Savg), inferior average (Iavg), Imax/Smax, Smax/Imax, Imax/Tavg (temporal average thickness), Smax/Navg (nasal average thickness) and the difference between the thickest and thinnest points along the circle (Max-Min) No thresholds or cut-offs determined prior to assessment for definition of test positive or test negative. Reference standard Eyes were classified into 2 groups depending on the IOP levels, automated perimetry and optic disc appearance (slit lamp biomicroscopy and stereoscopic optic disc photography). Time between measurement of the index test and the reference standard: Unclear
Statistical measures	HRT-2 Fisher's linear discriminant function Sensitivity (with specificity fixed at 85%): 0.84 Sensitivity (with specificity fixed at 95%): 0.73 PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.90 (0.85-0.95) Vertical cup or disc ratio Sensitivity (with specificity fixed at 85%): 0.82

Reference	Pueyo 2009[547]
	Sensitivity (with specificity fixed at 95%): 0.74 PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.89 (0.84-0.95) Cup disc area ratio or rim disc area ratio Sensitivity (with specificity fixed at 85%): 0.87 Sensitivity (with specificity fixed at 95%): 0.76 PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.89 (0.84-0.95) SD-OCT RNFL thickness Average Sensitivity (with specificity fixed at 85%): 0.84 Sensitivity (with specificity fixed at 95%): 0.70 PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.93 (0.89-0.97) Inferior Sensitivity (with specificity fixed at 85%): 0.76 Sensitivity (with specificity fixed at 95%): 0.62

Reference	Pueyo 2009[547]
	PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.91 (0.86-0.95) Nasal Sensitivity (with specificity fixed at 85%): 0.66 Sensitivity (with specificity fixed at 95%): 0.49 PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.89 (0.83-0.94)
Source of funding	Not reported.
Limitations	Risk of bias: Very serious concerns about the risk of bias due to an unclear patient selection, unclear if the index tests and reference standard results were interpreted without knowledge of each other. Unclear flow and timing between index tests and reference standard. Indirectness: No concerns about applicability.
Comments	

Reference	Rolle 2016[577]
Study type	Prospective cross-sectional diagnostic evaluation
Study methodology	Data source: Prospective between September 2012 and October 2013 Recruitment: Consecutive enrolment from the Glaucoma Centre of the Eye Clinic at the University of Torino
Number of patients	n=113
Patient	Age Mean (SD): 62.1±14.53

Reference	Rolle 2016[577]
characteristics	Gender (male to female ratio): 61/52 Family origin: Not reported Setting: Glaucoma Centre of the Eye Clinic at the University of Torino Country: Italy Inclusion criteria: Not reported Exclusion criteria: Best corrected visual acuity <20/40; spherical equivalent refractive error >+3.00 or <-3.00 dioptres; age <20 and >80 years, diseases that could cause visual field loss (vascular and metabolic diseases) or diseases that could involve the macular thickness (epiretinal membrane, macular oedema, drusen) and previous intraocular surgery
Target condition(s)	Glaucoma Eyes with glaucomatous (abnormal) VF (PSD [p<0.05] or GHT [p<1%] outside normal limits; stages 1-5 of the GSS2) and ONH changes, such as optic rim notch or diffuse loss of optic rim tissue, vertical cup or disc diameter ratio asymmetry >0.2, disc haemorrhages.
Index test(s) and reference standard	Index test(s) SD-OCT images were acquired for the MRT measurement over the posterior pole by Spectralis SD-OCT. Posterior Pole Asymmetry Analysis combined mapping of the retinal thickness with asymmetry analysis between eyes and each eye hemisphere. An 8x8 grid was situated symmetrically to the fovea-disc axis. Only high quality scans were recorded. Images were correctly focused, and if necessary, illuminated as exposed by the reflectance. Reference standard VF test performed using Humphrey Field Analyser (Carl Zeiss Meditec, Jena, Germany) with Swedish Interactive Thresholding Algorithm standard strategy and biomicroscopic slit lamp examination. All subjects also underwent complete ophthalmic examination, including visual acuity, refraction, gonioscopy, Goldmann applanation tonometry, and ultrasound pachymetry. Time between measurement of the index test and the reference standard: SD-OCT images were acquired the same day as the visual field testing
Statistical measures	Spectralis SD-OCT

Reference	Rolle 2016[577]

Glaucoma Hemifield Test

	Total MRT	Superior MRT	Inferior MRT	Posterior pole asymmetry analysis (PPAA)			
				Superior temporal	Superior nasal	Inferior temporal	Inferior nasal
Sensitivity	70	71.25	75	72.73	78.79	69.70	75.76
Specificity	72.73	63.64	63.64	74.07	70.37	70.37	74.07
PPV	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
NPV	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
PLR	2.57	1.96	2.06	2.81	2.66	2.35	2.92
NLR	0.41	0.45	0.39	0.37	0.30	0.43	0.33
AROC	0.75 (0.63-0.80)	0.75 (0.63-0.80)	0.76 (0.66-0.83)	0.78 (0.69-0.86)	0.78 (0.69-0.86)	0.76 (0.66-0.84)	0.82 (0.72-0.89)

Glaucoma Staging System 2

	Total MRT	Superior MRT	Inferior MRT	Posterior pole asymmetry analysis (PPAA)			
				Superior temporal	Superior nasal	Inferior temporal	Inferior nasal
Sensitivity	61.11	74.44	70.0	72.86	75.71	72.86	74.29
Specificity	82.61	60.87	73.91	69.57	69.57	73.91	73.91
PPV	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
NPV	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
PLR	3.51	1.90	2.68	2.39	2.49	2.79	2.85
NLR	0.47	0.42	0.41	0.39	0.35	0.37	0.35
AROC	0.73 (0.63-0.82)	0.73 (0.63-0.82)	0.74 (0.64-0.82)	0.79 (0.70-0.90)	0.79 (0.70-0.90)	0.79 (0.69-0.87)	0.81 (0.71-0.89)

Source of	Not reported

Reference	Rolle 2016[577]
funding	
Limitations	Risk of bias: Very serious concerns about the risk of bias as unclear if the index tests and reference standard results were interpreted without knowledge of each other. Unclear flow and timing between index tests and reference standard Indirectness: No concerns about applicability
Comments	

Reference	Simavli 2015 [621]
Study type	Prospective cross-sectional diagnostic evaluation
Study methodology	Data source: Prospective between January 2009 and July 2013 Recruitment: Subjects recruited from the Glaucoma Service at the Massachusetts Eye and Ear Infirmary as part of the prospective Spectral Domain OCT in Glaucoma Study
Number of patients	n=156
Patient characteristics	Age: Mean (SD) Normal: 62.6 ± 11.6 POAG: 66.0 ± 10.6 Gender (male to female ratio): Not reported Family origin: Not reported Setting: Glaucoma Services in secondary care Country: USA Inclusion criteria: People with a spherical equivalent between -5.0 and +5.0 dioptres and a best-corrected visual acuity of 20/40 or better. Only people with reliable VF testing were included, with less than 33% fixation losses, less than 20% false-positive results, and less than 20% false-negative results. Only people with POAG were included.

	Exclusion criteria: People with discernible congenital anomalies of the anterior chamber, corneal scarring or opacities, diabetic proliferative or severe non-proliferative retinopathy, VF loss attributable to a non-glaucoma condition, or a dilated pupil diameter of less than 2mm When analysing OCA3, 38 of 156 subjects (23.7%) were excluded from the analysis because the 20x20 degree scan area did not fully cover the ringed area for OCA3.
Target condition(s)	Glaucoma Defined as characteristic changes of the ONH with corresponding abnormal VF defects. The VF was considered to be abnormal if 3 or more contiguous test locations in the pattern standard deviation plot were depressed significantly at the p<0.05 level with at least 1 at the p<0.01 level on the same side of the horizontal meridian and if the VF defect corresponded to the optic nerve appearance.
Index test(s) and reference standard	Index test(s) Spectralis OCT peripapillary retinal volume scan All imaging was performed after pupillary dilation. Scans with signal strength of less than 15 (range, 0-40) were excluded from the analysis. Criteria for determining adequate scan quality were a clear fundus image with good optic disc and scan circle visibility before and during image acquisition, overlay of volume scan visible and without interruptions, and a continuous scan pattern without missing or blank areas. Volume scans were performed with a 20x20 degree field centred on the ONH. One hundred ninety-three sections were taken with the high-speed rate and 3 frames for ART. All 193 B-scans for each subject were checked for algorithm artefacts and errors. Analysis of the volume scans was performed using the Heidelberg Eye Explorer version 1.7.0.0 (Heidelberg Engineering GmbH, Heidelberg, Germany). The scan area overlay was lowered to 0, and the circular grid pattern was centred on the ONH by one of the authors. The outer annulus for each of the grid-scan options was analysed because the inner circular region and inner annulus covered portions of the optic nerve. The outer annuli were further subdivided by quadrant: superior, temporal, inferior and nasal. For circumpapillary Annulus 1, circles of diameter 1.0mm and 2.0mm bound the inner area, and circles of diameters 2.0mm and 3.0mm (OCA1) bound the outer area. For OCA2, circles of diameters 1.0mm and 2.22mm bound the inner area, and circles of diameters 2.22mm and 3.45mm bound the outer area. For OCA3, circles of diameter 1.0mm and 3.0mm bound the inner area, and circles of diameters 3.0mm and 6.0mm bound the outer area. If parts of OCA1, OCA2 or OCA3 extended outside the 20x20 degree field, these areas were excluded from the final data analysis. Reference standard VF testing with the SITA 24-2 test of the Humphrey Visual Field Analyser (750i; Carl Zeiss Meditec, Inc.), stereo disc photography (Visucam Pro NM; Carl Zeiss Meditec, Inc.) and slit-lamp biomicroscopy. All subjects also underwent a complete eye examination by a glaucoma specialist, which included history, visual acuity testing, refraction, Goldmann applanation tonometry, gonioscopy, ultrasonic pachymetry, and dilated ophthalmoscopy

	Time between measurement of index test and reference standard: Not reported
Statistical measures	Peripapillary retinal thickness using SD-OCT 3D volume scan OCA1

	Superior	Temporal	Inferior	Nasal
Sensitivity	79.78 (69.9-87.6)	83.91 (74.5-90.9)	93.18 (85.7-97.5)	83.53 (73.9-90.7)
Specificity	85.07 (74.3-92.6)	76.12 (64.1-85.7)	88.06 (77.8-94.7)	65.67 (53.1-76.8)
PLR	5.34 (4.6-6.2)	3.51 (3.0-4.1)	7.8 (7.0-8.7)	2.43 (2.0-3.0)
NLR	0.24 (0.1-0.5)	0.21 (0.1-0.4)	0.077 (0.03-0.2)	0.25 (0.1-0.4)
PPV	87.7 (78.4-94.0)	82.0 (72.5-89.4)	91.1 (83.2-96.1)	75.5 (65.6-83.8)
NPV	76.0 (64.7-85.1)	78.5 (66.5-87.7)	90.8 (80.9-96.6)	75.9 (62.7-86.2)

OCA2

	Superior	**Temporal**	**Inferior**	**Nasal**
Sensitivity	85.39 (76.3-92.0)	83.53 (73.9-90.7)	88.64 (80.1-94.4)	77.65 (67.3-
Specificity	77.61 (65.8-86.9)	77.61 (65.8-86.9)	89.55 (79.7-95.7)	62.69 (50.0-
PLR	3.81 (3.3-4.5)	3.73 (3.2-4.4)	8.48 (7.6-9.5)	2.08 (1.7-2.6
NLR	0.19 (0.10-0.4)	0.21 (0.1-0.4)	0.13 (0.05-0.3)	0.36 (0.2-0.6
PPV	83.5 (74.2-90.5)	82.6 (72.8-89.9)	91.8 (83.7-96.6)	72.5 (62.1-8
NPV	80.0 (68.2-88.9)	78.8 (66.9-88.0)	85.7 (75.3-92.9)	68.9 (55.7-8

OCA3

	Superior	Temporal	Inferior	Nasal
Sensitivity	90.24 (81.7-95.7)	59.52 (48.3-70.1)	79.78 (69.9-87.6)	68.49 (56.6-78.9)
Specificity	63.64 (50.9-75.1)	77.61 (65.8-86.9)	85.07 (74.3-92.6)	71.67 (58.6-82.5)
PLR	2.48 (2.0-3.0)	2.66 (2.1-3.3)	5.34 (4.6-6.2)	2.42 (1.9-3.0)
NLR	0.15 (0.07-0.3)	0.52 (0.3-0.9)	0.24 (0.1-0.5)	0.44 (0.3-0.7)
PPV	75.5 (65.8-83.6)	76.9 (64.7-86.5)	87.7 (78.4-94.0)	74.6 (62.5-84.5)

	NPV	84.0 (70.7-92.9)	60.5 (49.3-70.8)	76.0 (64.7-85.1)	65.2 (52.4-76.5)
Source of funding	Massachusetts Lions Eye Fund, Harvard Catalyst Grant, National Institutes of Health, Agency for Healthcare Research and Quality, Fidelity Charitable Fund (Harvard University)				
Limitations	Risk of bias: Very serious concerns about the risk of bias due to an unclear patient selection. It was unclear if the index tests and reference standard results were interpreted without knowledge of each other. There was unclear flow and timing between index tests and reference standard. Indirectness: No concerns about applicability				
Comments					

Reference	**Wu 2012[695]**
Study type	Prospective cross-sectional diagnostic evaluation
Study methodology	Data source: Prospective between January 2009 and July 2009 Recruitment: People from the Glaucoma Service at the Massachusetts Eye and Ear Infirmary (MEEI)
Number of patients	n=146
Patient characteristics	Age: Mean (SD) Normal: 63.5±14.0 Glaucoma: 69.2±13.0

Reference	Wu 2012[695]
	Gender (female % total) Normal: 52.9 Glaucoma: 59.0% Family origin (White % total) Normal: 74.1 Glaucoma: 67.2 Setting: Glaucoma Service in secondary care setting Country: USA Inclusion criteria: People with a spherical equivalent between -5.0 dioptres and +5.0 dioptres and with a best-corrected visual acuity of 20/40 or better. The study only included people with reliable VF testing with less than 33% fixation losses, less than 20% false positives, and less than 20% false negatives. Exclusion criteria: People with discernible congenital anomalies of the anterior chamber, corneal scarring or opacities, diabetic proliferative or severe non-proliferative retinopathy, VF loss attributable to a non-glaucoma condition, or a dilated pupil diameter of less than 2 mm. People with all types of glaucoma were included, except for traumatic glaucoma. Primary open angle: 67.2% Normal tension: 9.8% Pseudoexfoliative: 9.8% Chronic angle closure:: 6.6% Inflammatory: 1.6% Pigmentary: 1.6% Juvenile open angle: 1.6% Iridocorneal endothelial syndrome with glaucoma: 1.6%
Target condition(s)	Glaucoma Defined as characteristic change of the optic nerve head with corresponding abnormal VF defects. The VF was considered to be abnormal if 3 or more

Reference	Wu 2012[695]
	contiguous test locations in the pattern standard deviation plot were depressed significantly at the p<5% level with at least 1 at the p<1% level on the same side of the horizontal meridian if the VF defect corresponded to the optic nerve appearance
Index test(s) and reference standard	Index test Spectralis OCT Peripapillary Nerve Fibre Layer Measurement: All imaging was performed after pupillary dilation; the circular scan pattern was used for peripapillary RNFL thickness measurement. Different operators acquired images on the same day as the VF examination. In this study, 16 frames were acquired per eye with Automatic Real-Time function. Scans with signal strength of less than 15 (range, 0-40) were excluded from the analysis. Criteria for determining adequate scan quality were a clear fundus image with good optic disc and scan circle visibility before and during image acquisition, RNFL visible and without interruptions, and a continuous scan pattern without missing or blank areas. 6 different diagnostic criteria were tested: Average overall globe RNFL thickness abnormal at the <5% level Average overall globe RNFL thickness abnormal at the <1% level 1 quadrants abnormal at the <5% level 1 quadrants abnormal at the <1% level 1 sector [TS,TI,NS and NI] abnormal at the <5% level 1 sectors [TS, TI, NS and NI] abnormal at the <1% level Reference standard VF testing with (SITA) 24-2 test of the Humphrey Visual Field Analyser 750i [Carl Zeiss Meditec, Dublin, CA], stereo disc photography [Visucam Pro NM (Carl Zeiss Meditec, Dublin, CA, USA)] and slit-lamp biomicroscopy. All subjects also underwent a complete eye examination by a glaucoma specialist, which included history, visual acuity testing, refraction, Goldmann applanation tonometry, gonioscopy, ultrasonic pachymetry and dilated ophthalmoscopy. Time between measurement of index test and reference standard: SD OCT images were acquired on the same day as VF examinations.
Statistical measures	SD OCT Overall global RNFL thickness abnormal at <5% level Sensitivity:80.3 (73.9-86.85) Specificity: 92.9 (88.8-97.1)

Reference	Wu 2012[695]
	PPV: 89.1 (84.0-94.1) NPV: 86.8 (81.3-92.3) PLR: 11.38 (6.59-29.88) NLR: 0.21 (0.14-0.29) AUC: Not reported Overall global RNFL thickness abnormal at <1% level Sensitivity: 67.2 (59.6-74.8) Specificity: 100 PPV: 100 NPV: 81.0 (74.6-87.3) PLR: +∞ NLR: 0.33 (0.25-0.40) AUC: Not reported 1 quadrants with RNFL thickness abnormal at <5% level Sensitivity: 96.7 (93.8-99.6) Specificity: 85.9 (80.2-91.5) PPV: 83.1 (77.0-89.2) NPV: 97.3 (94.7-99.9) PLR: 6.85 (4.75-11.76) NLR: 0.04 (0-0.08) AUC: Not reported 1 quadrants with RNFL thickness abnormal at <1% level Sensitivity: 88.5 (83.4-93.7) Specificity: 95.3 (91.9-98.7) PPV: 93.1 (89.0-97.2) NPV: 92.0 (87.7-96.4) PLR: 18.81 (10.24-73.73)

Reference	Wu 2012[695]
	NLR: 0.12 (0.06-0.18) AUC: Not reported 1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at <5% level Sensitivity: 98.4 (96.3-100) Specificity: 88.9 (84.0-94.0) PPV: 87.0 (81.5-92.4) NPV: 98.6 (96.7-100) PLR: 8.85 (5.94-16.70) NLR: 0.02 (0-0.04) AUC: Not reported 1 sectors of TS, TI, NS, NI with RNFL thickness abnormal at <1% level Sensitivity: 93.4 (89.4-97.5) Specificity: 95.3 (91.9-98.7) PPV: 93.4 (89.4-97.5) NPV: 95.3 (91.9-98.7) PLR: 19.86 (10.98-76.69) NLR: 0.07 (0.03-0.12) AUC: Not reported
Source of funding	Supported in part by the National Institutes of Health
Limitations	Risk of bias: Very serious concerns about the risk of bias due to an unclear patient selection. It was unclear if the index tests and reference standard results were interpreted without knowledge of each other. Indirectness: No concerns about applicability
Comments	

Reference	Zheng 2010[718]
Study type	Prospective cross-sectional diagnostic evaluation

Reference	Zheng 2010[718]
Study methodology	Data source: Prospective between August 2004 and June 2006 Recruitment: Singapore Ministry of Home Affairs provided a list of names of 16,069 Malaya persons living in 15 residential districts across the southwestern part of Singapore. An age-stratified, random sampling procedure was used to select a list of 5,600 names for the study (1,400 residents from each decade of 40-49, 50-59, 60-69, and 70-79 years).
Number of patients	n=308
Patient characteristics	Age: Mean (SD) Not reported, subjects ages ranged between 40-80 years Gender (male to female ratio): Not reported Family origin: 100% Malay Setting: Singapore Eye Research Institute Country: Malaysia Inclusion criteria: Not reported, proportion of people included had closed angle glaucoma, less than 8% of study population Exclusion criteria: People were considered ineligible if they had moved residential addresses, had not lived at their current residence in the past 6 months, or were deceased or terminally ill
Target condition(s)	Glaucoma Defined according to the International Society for Geographic and Epidemiological Ophthalmology criteria based on 3 categories. Category 1: Defined as glaucomatous optic disc abnormality (VCDR or VCDR asymmetry ≥ 97.5th percentile, or neuroretinal rim width between 11 and 1 o'clock or 5 and 7 o'clock <0.1 VCDR) with a corresponding visual field defect. Category 2: Defined as severely damaged optic disc (VCDR or VCDR asymmetry ≥ 99.5th percentile) in the absence of a visual field test.

Reference	Zheng 2010[718]
	In diagnosing category 1 or 2 glaucoma, the requirement was no other explanation for the VCDR finding (for example, dysplastic discs or marked anisometropia) or visual field defect (for example, retinal vascular disease, macular degeneration, or cerebrovascular disease). Category 3: Defined as subjects without visual field or optic disc data who were blind (corrected visual acuity, <3/60) and had previous glaucoma surgery or an IOP>99.5TH percentile
Index test(s) and reference standard	Index test(s) HRT II HRT cylinders were adjusted for subjects who had astigmatism ≥ 1.0 D. After the baseline image was captured, a trained ophthalmologist manually defined the optic disc margin. This critical step was accomplished by plotting a series of dots around the margin of the disc on the reflectance image, and the disc margin was defined as the inner edge of Elschnig's ring. Data were then analysed with version 2.02 software. The HRT II optic nerve head scan protocol was adopted, automatically repeated 3 times, and combined to produce a pseudo 3-dimensional image of the optic disc topography. Each image was coupled with a standard deviation to reflect the image quality. Reference standard Optic disc was evaluated using a +78 D lens at x16 magnification with a measuring graticule (Hagg-Streit). The margins of the optic cup were defined stereoscopically as the point of maximal inflection of vessels crossing the neuroretinal rim. The vertical cup diameter was measured as the vertical distance between the points of maximal centrifugal extension of the cup between 11 and 1 o'clock and 5 and 7 o'clock. The vertical cup-to-disc ratio was then calculated. For small optic discs with no visible cup, the measurement was taken as the diameter of the emerging retinal vessels. The optic disc grading was performed, according to a standardised protocol, by 1 experienced ophthalmologist. People without visual field or optic disc data who were blind also underwent a comprehensive interview and ophthalmologic examination including slit lamp examination, Goldmann applanation tonometry. Gonioscopy was performed with a Goldmann-type 2-mirror gonioscope on 3 groups of participants: (1) those with suspected glaucoma, (2) all participants with a shallow peripheral anterior chamber (van Herick ≤ grade 2), and (3) 1 in 5 randomly selected participants not meeting the first 2 criteria Time between measurement of index test and reference standard: Not reported
Statistical measures	Index text HRT II

Reference	Zheng 2010[718]
	H MRA 1 (cut-off point 'borderline' or more Sensitivity: 0.71 (0.62-0.79) Specificity: 0.86 (0.83-0.9) PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.79 (0.74-0.83) MRA 2 (cut-off point 'out' or more) Sensitivity: 0.44 (0.35-0.53) Specificity: 0.97 (0.95-0.99) PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.70 (0.66-0.75) LDF1 Sensitivity: 0.73 (0.64-0.80) Specificity: 0.78 (0.74-0.82) PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.75 (0.71-0.80) LDF2 Sensitivity: 0.66 (0.57-0.74)

Reference	Zheng 2010[718]
	Specificity: 0.85 (0.81-0.88) PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.75 (0.71-0.80) LDF3 Sensitivity: 0.67 (0.60-0.77) Specificity: 0.84 (0.80-0.87) PPV: Not reported NPV: Not reported PLR: Not reported NLR: Not reported AUC: 0.76 (0.72-0.81)
Source of funding	Supported by the National Medical Research Council Grant and Biomedical Research Council Grant
Limitations	Risk of bias: Very serious concerns about the risk of bias as it was unclear if the index tests and reference standard results were interpreted without knowledge of each other. There was an unclear flow and timing between index tests and reference standard. Indirectness: No concern about applicability.
Comments	

H.3 Reassessment intervals

H.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

No relevant clinical studies were identified.

H.3.2 Optimum intervals for chronic open-angle glaucoma

No relevant clinical studies were identified.

H.4 Overview of Treatment

Table 2: Any treatment vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kass et al., 2002[316] Ocular Hypertension Treatment Study (OHTS) **Study design:** RCT Single masked **Evidence level:** 1+	**Patient group:** OHT patients **Inclusion criteria:** Age between 40-80 years, a qualifying IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 32 mmHg in the other eye, gonioscopically open angles, 2 normal and reliable visual field tests per eye and normal optic discs **Exclusion criteria:** Visual acuity worse than 20/40 in either eye, previous intraocular surgery (other than uncomplicated cataract extraction with posterior chamber lens implantation), and diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration.	**Group 1** Topical ocular hypotensive medication. Treatment to achieve a target IOP of 24 mm Hg or less and a minimum 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomisation visit. Topical medication was changed and/or added until both of these goals were met or the participant was receiving maximum tolerated topical medical therapy. Medications were	**Patients developed POAG** (end points of visual field abnormality or optic disc deterioration)	**Group1:** 36/817 (4.4%) African American: 14/203 Other: 22/614 **Group 2:** 89/819 (10.9%) African American: 26/205 Other: 63/614	**Funding:** Study was supported by grants EY09341 and EY09307 from the National Eye Institute and the National Centre on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Md; Merck Research Laboratories, White House Station, NJ; and by an unrestricted grant from Research to Prevent Blindness, New York, NY. **Limitations:** Patient and clinician were not blinded to
			Cumulative probability of developing POAG	**Hazard Ratio:** 0.40 (95% CI: 0.27 to 0.59) **p value:** <0.0001	
			Cumulative probability of developing POAG at 60 months:	**Group1:** 4.4% **Group 2:** 9.5%	
			Cumulative probability of developing POAG	**African-American participants:** Hazard ratio: 0.54 (95% CI:0.28-	

2009

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		added and changed in one-eyed therapeutic trials.		1.03	randomisation during follow-up.
Duration of follow-up: Median follow-up for African American participants 72 months and 78 months for other participants.	**Setting**: 22 clinical centres, USA **<u>All patients</u>** **N:** 1636 **<u>Group 1</u>** **N:** 817 **N medication withdrawn**:40 **M/F:** 359/458 **Age categories:** 40 to ≤ 50 years: 291 (35.6%) >50 to ≤ 60 years: 270 (33.0%) >60 to ≤ 70 years: 202 (24.7%) >70 to 80 years: 64 (6.6%) **Previous use of OHT medication**: 35.0% **First-degree family history of glaucoma**: 34.0% **Myopia ≥1-diopter spherical equivalent**: 34.4% **Oral B-adrenergic antagonist**: 5.4% **Oral calcium channel blocker**: 12.8% **History of migraine**: 10.4% **History of diabetes**: 11.5% **History of hypertens**ion: 37.5% **History of low blood pressure**: 4.8% **History of cardiovascular disease**: 6.8% **History of stroke**:0.9% **Drop outs:** 115 (28 died) **<u>Group 2</u>**	Included all topical ocular hypotensive medications commercially available in the US. Follow-up visits every six months. **Group 2** No treatment		**Other participants:** Hazard ratio: 0.34 (95% CI:0.21-0.56 P=0.26	**Additional outcomes:** Cumulative probability of developing a reproducible visual field abnormality or an optic disc deteriorations due to POAG or a variety of other caused was reported. Estimated of the effect of treatment after adjusting. Treatment benefit for reproducible visual field abnormality attributed to POAG and for reproducible optic disc deterioration attributed to POAG reported. **Notes:**
			Change in IOP	**Group 1:** Baseline: 24.9±2.6 Reduction from baseline: -22.4%±9.9 **Group 2:** Baseline: 24.9±2.7 Reduction from baseline: -4.0%±11.6	
			Adverse effects:	**Ocular symptoms:** **Group1:** 57% **Group 2:** 47% **P value**: <0.001	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 819 **N medication initiated**:42 **M/F:** 346/473 **Age categories:** 40 to ≤ 50 years: 287 (35.0%) >50 to ≤ 60 years: 259 (31.6%) >60 to ≤ 70 years: 210 (25.6%) >70 to 80 years: 63 (7.7%) **Previous use of OHT medication**: 39.3% **First-degree family history of glaucoma**: 35.6% **Myopia ≥1-diopter spherical equivalent**: 33.7% **Oral B-adrenergic antagonist**: 4.6% **Oral calcium channel blocker**: 14.0% **History of migraine**: 11.7% **History of diabetes**: 12.1% **History of hypertension**: 38.1% **History of low blood pressure**: 4.0% **History of cardiovascular disease**: 6.5% **History of stroke**: 1.6% **Drop outs:** 113 (29 died)			**Symptoms affecting skin, hair or nails:** **Group1:** 23% **Group 2:** 18% **P value**: <0.001	Randomisation method was adequate and primary outcome assessment was masked. 3328 screened but 1636 entered into study (1692 not eligible for various reasons).
			Difference between groups total hospitalisations	**P=0.56**	
			Difference between groups worsening of pre-existing conditions	**P=0.28**	
			Difference between groups mortality rates	**P=0.70**	
			Other adverse events (≥10%) **Tearing/watering** **Itching** **Blurry or dim vision** **Feels like object in eye** **Poor night vision** **Difficulty Sleeping**	**Medication (%) Observation (%)** **12.6 13.2** **11.4 11.8** **11.4 11.6** **10.1 10.6** **12.2 11.8** **17.2 16.8** **10.7 11.8** **11.2 12.6** **13.9 16.3**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Headache **Loss of libido** **Numbness/tingling arms**		

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Heijl et al., 2002[267] Early Manifest Glaucoma Trial (EMGT) **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** At least 6 years. Open label	**Patient group:** patients with chronic open angle glaucoma **Inclusion criteria:** Men and women with newly diagnosed, previously untreated COAG (POAG, NTG or PEX) with repeatable visual field defects in at least one eye measured using Humphrey 24-2 full programme. Age between 50 and 80 years **Exclusion criteria:** • Advanced visual field defects (MD-16dB or threat to fixation) • Visual acuity < 0.5 • Mean IOP >30 mmHg • Lens opacities exceeding N1, C1 or P1 in Lens Opacities Classification System • Patients with glaucomatous visual field defects in both eyes eligible if MD = -10 dB or better in one eye and -16 dB in other eye. **Setting**: 2 clinical centres (1 reading and 1 co-ordinating), Sweden **<u>All patients</u>**	**Group 1** Betaxolol 5 mg/ml 2/day and argon laser trabeculoplasty (ALT) 360 degrees performed 1 week after inclusion. If eligible eye achieved 25 mmHg in 2 consecutive visits or other eye was 35 mmHg in 1 visit then latanoprost 50 µm/day. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for visual acuity, Goldmann tonometry, Humphrey 30-2 Full threshold visual field testing,	**Glaucoma progression (visual or optic disc changed*) after follow up of 48 months** Data from Rolim et al., 2007[575]	**Group 1**: 39/129 (30%) **Group 2**: 62/126 (49%) **p value**: 0.002 (calculated by NCC-AC Chi-squared test)	**Funding:** Study was supported by grants U10EY10260 and U10EY10261 from the National Eye Institute, Bethesda, USA and K2002-74X-10426-10A from the Swedish Research Council, Stockholm **Limitations:** **Additional outcomes:** Health-related quality of life scores **Notes:**
			Glaucoma progression (visual field and optic disc) after 6 years (range 51-102 months	**Group 1**: 58/129 (45%) **Group 2**: 78/126 (62%) **p value**: 0.07	
			Visual field progression alone after 6 years (range 51-102 months	**Group 1**: 57/129 (44%) **Group 2**: 78/126 (62%) **p value**: 0.005 (calculated by NCC-AC Chi-squared test)	
			Ocular side effects (reduction in visual acuity, floaters or conjunctivitis)	**Group 1**: 21/129 (16%) **Group 2**: 16/126 (13%) **p value**: 0.43 (calculated by NCC-AC Chi-squared test)	
			Systemic side effects	**Group 1**: 6/129 (4.6%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
design but outcome measurement was masked	**N:** 255 **Group 1** **N:** 129 **Both eyes eligible**: 34 (26%) **One eye eligible**: 95 (74%) **Age ± SD:** 68.2 ± 4.8 (range 58-78) **M/F:** 47/82 **Mean Baseline IOP mmHg ± SD**: 20.6 ± 4.1 **Patients with IOP < 21 mmHg**: 69 **Mean Visual Acuity**: ± SD: 0.9 ± 0.1 **Mean deviation ± SD**: -5.0 ± 3.7 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 147 **Myopia ≤1-diopter spherical equivalent**: 19(12%) **Exfoliation Syndrome**: 9 (6%) Disease History: **Family history of glaucoma**: 26 (20%) 34.4% **Cardiovascular disease**: 19 (15%) **Stoke/low blood pressure**: 12 (9%) **General arteriosclerosis**: 4 (3%) **Peripheral vasospasms and migraine**: 21 (16%) **Pulmonary disease**: 3 (2%) **Diabetes**: 3 (2%) Medication use: **Antihypertensives**: 31 (24%) **Corticosteroids**: 0 **Insulin or oestrogen**: 57 (44%) **Drop outs:** 24 (3 lost to follow up, 15 died, 6 received ALT but discontinued medications) **Group 2**	ophthalmoscopy, slit lamp examination and optic disc photographs every 6 months. *Visual field progression defined as worsening of 3 consecutive points in the Glaucoma Change Probability map, confirmed by 3 consecutive visual fields. *Optic disc progression detected from baseline line and follow up photographs by a masked reader using flicker chronoscopy and	**(asthma, bradycardia, depression)**	**Group 2**: 1/126 (0.8%) **p value**: 0.12 (calculated by NCC-AC Fishers exact test)	Randomised using computer generated sequence. Computerised visual field and optic disc photographs read by masked observers. IOP evaluation also masked. An Intention to Treat analysis was used. Patients and clinicians were not masked to treatment allocation

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 126 **Both eyes eligible**: 27 (21%) **One eye eligible**: 99 (79%) **Age ± SD:** 68.0 ± 5.0 (range 50-79) **M/F:** 39/87 **Mean Baseline IOP mmHg ± SD**: 20.9 ± 4.1 **Patients with IOP < 21 mmHg**: 63 **Mean Visual Acuity**: ± SD: 1.0 ± 0.1 **Mean deviation ± SD**: -4.4 ± 3.3 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 138 **Myopia ≤1-diopter spherical equivalent**: 23(15%) **Exfoliation Syndrome**: 16 (10%) Disease History: **Family history of glaucoma**: 24 (19%) 34.4% **Cardiovascular disease**: 14 (11%) **Stoke/low blood pressure**: 5 (4%) **General atheriosclerosis**: 5 (4%) **Peripheral vasospasms and migraine**: 26 (21%) **Pulmonary disease**: 0 **Diabetes**: 6 (5%) Medication use: **Antihypertensives**: 31 (25%) **Corticosteroids**: 4 (3%) **Insulin or oestrogen**: 55 (44%) **Drop outs:** 10 (3 lost to follow up, 7 died)				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Collaborative Normal-Tension Glaucoma Study Group, 1998[137] Collaborative Normal-Tension Glaucoma Study (CNTGS) **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:**	**Patient Group:** Normal tension glaucoma **Inclusion criteria:** Unilateral or bilateral normal tension glaucoma with optic disc abnormalities and visual field defects and IOP ≤ 24 mmHg in either eye. Age 20 to 90 years. After 4 week washout patients required to have a median of 10 IOP readings of ≤ 20 mmHg and 3 good baseline visual fields. **Exclusion criteria:** • Patients on systemic beta-blockers or clonidine. • Patients unable to perform visual field test • Eyes with previous laser treatment, ocular surgery • Eyes with traumatic VF defects • Narrow angles • Best correct visual acuity of < 20/30 • Baseline visual fields too damaged to record further progression **Setting**: 24 clinical centres, international	**Group 1** Achieved 30% change in IOP using medical or surgical interventions except for beta-blockers or adrenergic agonists. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for first year and every 6 months thereafter. Tests performed for visual acuity, visual field using Humphrey and appearance of optic disc and optic disc photographs every year.	**Glaucoma progression (optic disc or visual field progression*)** Data from Sycha et al., 2003[648]	**Group 1**: 22/61 (31%) **Group 2**: 31/79 (39%) **p value**: 0.7 (calculated by NCC-AC Chi-squared test)	**Funding:** Glaucoma research Foundation with grants from Oxnard Foundation and Edward J Daly Foundation, San Francisco, USA **Limitations:** Allocation concealment and masking of outcome assessment was not clearly reported **Additional outcomes:** **Notes:** Randomisation using block randomisation scheme occurred after selected eye
			Visual Field Progression*	**Group 1**: 11/61 (18%) **Group 2**: 24/79 (30%) **p value**: 0.09 (calculated by NCC-AC Chi-squared test)	
			Cataract Formation	**Group 1**: 23/61 (38%) **Group 2**: 11/79 (14%) **p value**: 0.011 (calculated by NCC-AC Chi-squared test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
5 years.	**<u>All patients</u>** **N:** 145 **<u>Group 1</u>** **N:** 79 **Age ± SD:** 65.5 ± 9.6 **M/F:** 30/49 **Mean IOP at randomisation mmHg ± SD**: 16.1 ± 2.3 **Visual Acuity**: 0.89 ± 2.86 **Mean deviation at randomisation ± SD**: -7.54 ± 4.31 dB **Refraction**: -0.66 ± 2.86 Ethnicity **Asian**: 9 **Black**: 2 **Hispanic**: 2 **White**: 65 **Drop outs:** 5 **<u>Group 2</u>** **N:** 61 **Age ± SD:** 66.3 ± 10.3 **M/F:** 17/44 **Mean IOP at randomisation mmHg ± SD**: 16.9 ± 2.1 **Visual Acuity**: 0.89 ± 0.15 **Mean deviation at randomisation ± SD**: -8.38 ± 5.26 dB **Refraction**: -1.09 ± 3.3 Ethnicity	Visual field progression was defined by deepening of existing scotoma, expansion of an existing scotoma or new or expanded threat to fixation (cluster of 3 points) or fresh scotoma in previously normal part of visual field. *Visual field progression was confirmed by 4/5 consecutive follow up visits showed progression relative to baseline. Optic disc damage was independently assesses by masked observers using stereo photographs and agreed.			had a visual field defect that threatened fixation. Intention to treat analysis was performed The study was carried out before the introduction of topical carbonic anhydrase inhibitors and prostaglandin analogues.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Asian: 3 **Black**: 5 **Hispanic**: 1 **White**: 51 **Drop outs:**				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

H.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

H.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Alm 1995[13] Study design: RCT Double masked Evidence level: 1+ Duration of follow-up:	People group: COAG and OHT Setting: multi-centre across 13 Scandinavian eye clinics Inclusion criteria: Age ≥ 40 years old Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. Completion of adequate washout period for sympathomimetics, CAI and miotics. Exclusion criteria: People on topical beta-blockers within 6 months of study	Group 1 Latanoprost 0.005% in the morning followed by placebo in the evening for the first 3 months, then the regimen was reversed for the next 3 months Group 2 Latanoprost 0.005% in the evening preceded by placebo in the morning for the first 3 months, then the regimen was reversed for the next 3 months	Mean ± SD* baseline diurnal IOP mmHg	Group 1: 24.8 ± 3.77 Group 2: 25.5 ± 2.91 Group 3: 24.6 ± 2.75	Funding: Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost. Limitations: Allocation concealment was not reported. Not known if the statistical calculations were done on an ITT basis.
			Mean ± SD* end point diurnal IOP (6 months) mmHg	Group 1: 16.2 ± 2.83 Group 2: 17.7 ± 2.91 Group 3: 17.9 ± 2.75	
			Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 8.6 ± 4.06** Group 2: 7.8 ± 3.51** Group 3: 6.7 ± 2.99**	
			IOP reduction in Group 1 versus Group 3 at 6 months	Group 1: 8.6 ± 4.06** Group 3: 6.7 ± 2.99** p value: <0.001 (using ANCOVA)	
			% people at 6 months reaching ≤ 17 mmHg	Group 1: 58/84 (69%) Group 2: 27/79 (34%)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
6 months	Angle-closure glaucoma history Ocular trauma Previous filtration or laser surgery for glaucoma within 6 months of study Dry eye syndrome Ocular inflammation or infection within 3 months of study People who wear contact lenses Those with contraindications for beta-blockers People who would not benefit from monotherapy All participants n=267 Age (mean): 67 (40-85) M/F: 116/151 Dropouts: 15 Family origin: Not reported Group 1 n=89 Age (mean): 67 (40-84) M/F: 39/50 Dropouts: 5 OHT: 43	Group 3 Timolol 0.5% 2 –per day for 6 months Examination methods: IOP measured by Goldmann Applanation Tonometry – 3 readings taken in each eye (0.800, 12.00 and 16.00hrs) and mean used for statistical analysis. (Average of 2 eyes used for bilateral people) Visual acuity readings, slit lamp examination and blood and urine samples taken throughout study. Photographs of iris taken and classified by independent evaluator Visual fields examined using Humphrey 24:2 or Octopus		p value: <0.001 (Chi-squared test)	Number of people remaining at the end of the study does not add up to figures in table listing reasons for withdrawal Additional outcomes: Detailed analysis of conjunctival hyperaemia Notes: *SD=SE*√n **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426](bimatoprost) Computer-generated randomisation
			Apparent deterioration or visual field	Groups 1 and 2: 0 Group 3: 1	
			Disc haemorrhage	Groups 1 and 2: 3 Group 3: 3	
			Total number of local ocular side effects by group	Groups 1 and 2: 86 Group 3: 41 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	Groups 1 and 2: 7 Group 3: 0	
			Total number of cardiovascular systemic side effects by group	Groups 1 and 2: 20 Group 3: 18 Includes upper respiratory tract infection, angina, thrombophlebitis	
			Reasons for withdrawals (dropouts)	Groups1 and 2: Inadequate IOP control=1 Repeated corneal erosions=1 Retinal arterial embolus=1 Retinal vein thrombosis=1 Increase in iris pigmentation=1 Information about iris changes=2 Decrease in visual acuity due to diabetes=1 Burning sensation on tongue=1 Cancer metastasis=1 Unknown reason for exit=4	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	COAG: 46 Group 2 n=94 Age (mean): 67 (44-85) M/F: 43/51 Dropouts: 9 OHT: 44 COAG: 50 Group 3 n=84 Age (mean): 66 (42-84) M/F: 34/50 Dropouts: 5 OHT: 36 COAG: 48			Group 2: Inadequate IOP control=1 Information about iris changes=3 Headaches=1	sequence.

Study	Ang 2008[20]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=Travoprost: 54; Placebo: 34)
Countries and setting	Conducted in United Kingdom; Setting: Norfolk and Norwich University Hospital glaucoma clinic
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Glaucomatous optic disc changes and visual field defects characteristic of glaucoma (as defined by the CNTGS) present in one or both eyes that were reliable (15% false positives, <20% false negatives and <15% fixation losses); open drainage angles at gonioscopy; IOP≤22mmHg in both eyes during daytime IOP phasing, 1 spike of up to 24mmHg being allowed
Exclusion criteria	Exclusion criteria included fixation-threatening or symptomatic visual field defects, previous intraocular surgery, use of systemic medications with potential effects on visual field, and a previous history of systemic or ocular pathology that may have affected the optic disc, visual field or IOP. People on systemic beta-blockers were not excluded if treatment started before enrolment in the study, and the dosage remained stable throughout the study duration.
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Travoprost: 67.3 (13.1); no treatment: 67.6 (9.6). Gender (M:F): not reported; Family origin: White: Travoprost: 53 (96%); Placebo: 33 (97%)
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: Prostaglandin analogues - Travoprost. Travoprost 0.004%. Duration 6 months. Concurrent medication or care: Not applicable (n=34) Intervention 2: No treatment. Not applicable. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRAVOPROST versus NO TREATMENT

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 2/47, Group 2: 0/34

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 2

Protocol outcome 2: Intraocular pressure
- Actual outcome: Final IOP at 6 months; Group 1: mean 12.5 mmHg (SD 2.21); n=42, Group 2: mean 14.5 mmHg (SD 2.63); n=34

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 2

Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Treatment adherence; Quality of life (validated score)

Study	**Aung 2014[35]**
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=BBFC: 193; Brinzolamide: 191; Brimonidine: 175)
Countries and setting	Conducted in multiple countries; Setting: 63 centres in the Asia-Pacific region, European Union, Latin America, Caribbean nations, and the United States of America
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Not reported
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): BBFC: 64.9 (12.2); Brinzolamide: 64.1 (11.2); Brimonidine: 64.3 (11.6). Gender (M:F): BBFC: 87/106; Brinzolamide: 90/101; Brimonidine: 73/102. Family origin: White: BBFC - 133; Brinzolamide - 138; Brimonidine – 123; Black or African-American: BBFC - 20; Brinzolamide - 14; Brimonidine - 14 Asian: BBFC - 16; Brinzolamide - 16; Brimonidine - 14 Multiracial: BBFC - 4; Brinzolamide - 2; Brimonidine - 3 Other: BBFC - 20; Brinzolamide - 21; Brimonidine - 21
Indirectness of population	No indirectness
Interventions	(n=193) Intervention 1: Fixed combination solutions - Carbonic anhydrase inhibitors with sympathomimetics. Brinzolamide 1% and brimonidine 0.2% twice per day. Duration 6 months. Concurrent medication or care: Not

	applicable (n=191) Intervention 2: Carbonic anhydrase inhibitors. Brinzolamide 1% twice per day. Duration 6 months. Concurrent medication or care: Not applicable (n=175) Intervention 3: Sympathomimetics - Brimonidine tartrate. Brimonidine 0.2% twice per day. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Other (Funded by Alcon)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS WITH SYMPATHOMIMETICS versus CARBONIC ANHYDRASE INHIBITORS

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 11/193, Group 2: 1/191

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 2
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 3/193, Group 2: 0/191

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 13

Protocol outcome 2: Intraocular pressure
- Actual outcome: Mean change in IOP from baseline (%) at 09.00hrs at 6 months; Group 1 (SE): -27.7 (0.95); Group 2 (SE): -25.6 (1.03)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 13
- Actual outcome: Mean change in IOP from baseline (%) at 11.00hrs at 6 months; Group 1 (SE): -35.0 (0.89); Group 2 (SE): -27.9 (1.06)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean change in IOP from baseline (%) at 16.00hrs at 6 months; Group 1 (SE): -28.8 (1.01); Group 2 (SE): -25.8 (1.14)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Treatment adherence
- Actual outcome: Treatment discontinuation due to adverse events at 6 months; Group 1: 20/193, Group 2: 1/191

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS WITH SYMPATHOMIMETICS versus BRIMONIDINE TARTRATE

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 11/193, Group 2: 8/175
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 3/193, Group 2: 2/175
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 30

Protocol outcome 2: Intraocular pressure
- Actual outcome: Mean change in IOP from baseline (%) at 09.00hrs at 6 months; Group 1 (SE): -27.7 (0.95); Group 2 (SE): -23.6 (1.14)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 30
- Actual outcome: Mean change in IOP from baseline (%) at 11.00hrs at 6 months; Group 1 (SE): -35.0 (0.89); Group 2 (SE): -30.0 (1.16)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: Mean change in IOP from baseline (%) at 16.00hrs at 6 months; Group 1 (SE): -28.8 (1.01); Group 2 (SE): -23.6 (1.23)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1

Protocol outcome 3: Treatment adherence
- Actual outcome: Treatment discontinuation due to adverse events at 6 months; Group 1: 20/193, Group 2: 13/175
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 33; Group 2 Number missing: 30

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS versus BRIMONIDINE TARTRATE

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 1/191, Group 2: 8/175
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 30

- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 0/191, Group 2: 2/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 12; Group 2 Number missing: 30 Protocol outcome 2: Intraocular pressure - Actual outcome: Mean change in IOP from baseline (%) at 09.00hrs at 6 months; Group 1 (SE): -25.6 (1.03); Group 2 (SE): -23.6 (1.14) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Mean change in IOP from baseline (%) at 11.00hrs at 6 months; Group 1 (SE): -27.9 (1.06); Group 2 (SE): -30.0 (1.16) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Mean change in IOP from baseline (%) at 16.00hrs at 6 months; Group 1 (SE): -25.8 (1.14); Group 2 (SE): -23.6 (1.23) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1 Protocol outcome 3: Treatment adherence - Actual outcome: Treatment discontinuation due to adverse events at 6 months; Group 1: 1/191, Group 2: 13/175 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 30	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Quality of life (validated score)

Study	**Barnebey 2016[53]**
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in the USA; Setting: 2 sites in the USA (Seattle, WA, and Baltimore, MD) between March 2007 and January 2010
Line of therapy	Not applicable
Duration of study	Intervention and follow-up: 12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People 18 or older diagnosed with open-angle glaucoma (including open-angle glaucoma with pigment dispersion and pseudoexfoliation) or ocular hypertension. Additional inclusion criteria were discontinuation of all IOP-lowering medications for the appropriate minimum washout period, determined by ocular hypotensive class, and mean post-washout IOP ≥21mmHg in at least 1 eye and mean IOP ≤36mmHg in both eyes. The study eye was the qualifying eye (IOP ≥21mmHg) at the eligibility visit.
Exclusion criteria	Any form of glaucoma other than open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation) or ocular hypertension; and condition that precluded safe administration of a prostaglandin analogue or beta-blocker; history of chronic or recurrent severe inflammatory disease, or severe ocular pathology; history of ocular trauma or intraocular surgery ≤6 months before screening; ocular laser surgery or ocular infection or inflammation ≤3 months before screening; best-corrected visual acuity worse than 0.60 LogMAR in either eye; severe central visual field loss; and pregnancy, potential of becoming pregnant during the study, or breastfeeding. People using non-IOP lowering medications that may have affected IOP (for example, systemic beta-blockers) were required to have a stable dosing regimen for ≥30 days before screening and throughout the study.
Recruitment/selection of people	Sequential randomisation using a set of randomisation numbers developed to ensure a 1:1 assignment ratio.
Age, gender and family origin	Age - Mean (SD): FC: 58.7 (10.2); Non-FC: 61.5 (9.3). Gender (M:F): FC: 28/13; Non-FC: 26/14. Family origin: FC: White: 35 (85.4%); Black or African-American: 4 (9.8%); Native Hawaiian or Pacific Islander: 1 (2.4%); Other: 1 (2.4%) Non-FC: White: 37 (92.5%); Black or African-American: 3 (7.5%); Native Hawaiian or Pacific Islander: 0; Other: 0
Indirectness of population	No indirectness
Interventions	(n=41) Intervention 1: Fixed combination solutions - Prostaglandin analogue with beta-blockers. 0.004% travoprost/0.5% Timolol (DuoTrav; Alcon Laboratories, Inc., Fort Worth, TX, USA. Duration 12 months. Concurrent medication or care: Not applicable (n=40) Intervention 2: Prostaglandin analogues – Timolol with travoprost. Unfixed travoprost 0.004% (Alcon Laboratories, Inc.) and Timolol 0.5% (Falcon Pharmaceuticals, Ltd). Duration 12 months. Concurrent medication or care: Not applicable
Funding	Study funded by industry (Alcon Research, Ltd)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROSTAGLANDIN ANALOGUE WITH BETA-BLOCKERS versus TIMOLOL WITH TRAVOPROST	

Protocol outcome 1: Adverse events of pharmacological treatments - Actual outcome: Ocular hyperaemia at 12 months; Group 1: 3/41, Group 2: 3/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5 Protocol outcome 2: Treatment adherence - Actual outcome: Cumulative % of days that people were adherent with dosing at 12 months; Group 1: mean 60 % (SD 28); n=41, Group 2: mean 43 % (SD 27); n=40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Intraocular pressure; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Bucci, 1999[86] Study design: RCT Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG Setting: Multi-centre, Italy Inclusion criteria: Diagnosis of unilateral or bilateral POAG or Pseudoexfoliation glaucoma (PEX) Uncontrolled IOP on current beta-blocker therapy Age >18 years Exclusion criteria: Current therapies other than beta adrenergic agonists Closed-anterior angle glaucoma Severe trauma Previous ocular inflammation in last 3 months	Group 1 Latanoprost 0.005% 1 per day and Timolol 0.5% 2 per day Group 2 Latanoprost 0.005% 1 per day Examination methods: IOP measured at baseline, 2 weeks, 3 months and 6 months using a Goldmann tonometer. 3 (09.00, 12.00, and 16.00hrs) measurements were taken in each eye and	Mean ± SD baseline diurnal IOP mmHg	Group 1: Not reported Group 2: Not reported	Funding: Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata Limitations: Randomisation method not described. Open label design Masking of outcome assessment not mentioned No washout period for latanoprost monotherapy. People were selected for inadequate IOP
			Mean ± SD end point diurnal IOP at 6 months	Group 1: Not reported Group 2: Not reported	
			Mean ± SD reduction in IOP mmHg at 6months (baseline – end point) SD=SE*√n	Group 1: 6.1 ± 2.10 Group 2: 5.5 ± 2.12 P between arm difference=not significant (using ANCOVA)**	
			% people achieving an acceptable 30% reduction in IOP <20% reduction from baseline (~21 mmHg) is approximately <18 mmHg	Group 1: 30/45 (not ITT) Group 2: 32/46 (not ITT)	
			Total number of local ocular side effects by group	Group 1: 21 Group 2: 17 Includes itching, stinging,	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Any condition affecting IOP measurement Pregnant, nursing or people considering pregnancy All participants n=99 Group 1 n=49 Age (mean ± SD): 63 ± 12 M/F: 21/28 POAG: 43 PEX: 6 Dropouts: 4 Group 2 n=50 Age (mean ± SD): 59 ± 13 M/F: 28/22 POAG: 50 PEX: 1* Dropouts: 4 * person had different diagnosis in each eye	mean value used in statistical analysis.		conjunctivitis, vision disturbance and conjunctival hyperaemia	control on various medications including Timolol and clonidine and Timolol and dipivefrine **Significance testing between arms does not appear to be on an ITT basis. Additional outcomes: Timolol and pilocarpine study arm Notes: If 2 eyes used in study, mean IOP was taken.
			Total number of systemic side effects by group	Group 1: 1 Group 2: 4	
			Total number of people with hyperaemia	Group 1: 8/49 Group 2: 4/50	
			Reasons for withdrawals	Group 1: Inadequate IOP control=1 Conjunctivitis=1 Hyperaemia=1 Self-withdrawal=1 Group 2: Conjunctivitis=1 Hyperaemia=1 Self-withdrawal=2	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Camras, 1996[97] Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG and OHT Setting: multi-centre – 17 centres across the USA Inclusion criteria: Age ≥ 40 years old Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg with no more than 1 current topical medication Expectation that participants' IOP would be controlled for 6 months without VF degeneration Completion of adequate washout period for sympathomimetics, CAI and miotics. Exclusion criteria: Use of any ocular medications other than for glaucoma People with advanced glaucoma that would be at risk during washout period Angle-closure glaucoma history Ocular trauma Previous filtration or laser surgery for glaucoma within 6 months of study Allergies to trial medications Ocular inflammation or infection within 3 months of study People who wear contact lenses	Group 1 Latanoprost 0.005% in evening preceded by placebo in morning for 6 months Group 2 Timolol 0.5% 2 per day for 6 months Examination methods: IOP measured using Goldmann tonometer taking 3 replicate measurements on same calibrated machine per people for each visit at 08.00, 12.00 and 16.00hrs VF measured on Humphrey or Octopus 4 weeks before start of study at 6 month stage.	Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 6.7 ± 3.4 Group 2: 4.9 ± 2.9 p value: <0.001 (using 2 tailed unpaired t-test)	Funding: Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost Limitations: Allocation concealment with sealed envelopes was not reported. Lack of reliable ITT data in original study. Assumption that later study figures were reliable Additional outcomes: Study reported in detail on conjunctival hyperaemia Notes: For people with 2 eyes eligible – mean IOP value was used for all calculations Computer-generated
			Apparent deterioration or visual field	Group 1: 1 Group 2: 1	
			Number of people with local ocular side effects	Group 1: 71 Group 2: 101 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	Group 1: 1 Group 2: 0	
			Number of people with cardiovascular systemic side effects	Group 1: 26 Group 2: 33 Includes upper respiratory tract infection, palpitations, shortness of breath, syncope	
			Reasons for withdrawals (dropouts)	Group 1: Local side effects=2 (including allergic blepharoconjunctivitis Systemic effects=4 (including palpitations, peptic ulcer symptoms and 2 people with a maculopapular rash) Non-medical reasons=4 (including left area, lost to follow-up, time constraints)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Those with contraindications for beta-blockers Pregnant women, women of childbearing potential and nursing mothers History of non-compliance All participants n=268 M/F: 114/154 Dropouts: 20 OHT: 44 COAG: 50 Black: 65 Non-black: 203 Group 1 n=128 Age (mean): 61 ± 12 (30-89) M/F: 58/70 Dropouts: 10 OHT: 80 COAG: 48 Black: 27 Non-black: 101 Group 2 n=140 Age (mean): 63 ± 11 (33-90)			Group 2: Inadequate IOP control=4 Local side effects=2 (including swelling of eyelids and allergic conjunctivitis) Systemic effects=4 (including palpitations, shortness of breath followed by bypass surgery, post mastectomy) Non-medical reasons=1 people left study without explanation	randomisation sequence. People and examiners were kept masked to treatment allocation.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	M/F: 56/84 Dropouts: 10 OHT: 90 COAG: 50 Black: 38 Non-black: 102				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Camras et al., 2005[98] Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 6 months	People group: POAG and OHT people Setting: Multi-centre – 23 centres in the USA Inclusion criteria: ≥ 18 years Naïve to glaucoma therapy or on topical monotherapy Best-corrected visual acuity ≥ 20/80 IOP ≥ 22 mmHg Exclusion criteria: Closed or barely opened anterior chamber angle or history of acute angle closure No history of Argon laser	Group 1 Latanoprost 0.005% once daily (08.00hrs) for 6 months Group 2 Brimonidine 0.2% twice daily 08.00 and 20.00hrs) for 6 months All Washout period completed as appropriate 6 visits: Screening Baseline Week 2 3 months	Mean diurnal (08.00, 12.00 and 16.00hrs) IOP at 6 months (mmHg)	Group 1: 18.8 ± 0.3 (± SEM) Group 2: 21.5 ± 0.3 (± SEM) p value: p < 0.001 (significantly lower than corresponding baseline values)	Funding: Supported in part by Pharmacia corporation, a Pfizer company (New York City, NY, USA), which manufactures latanoprost and an unrestricted grant from (University of Nebraska Medical Centre, Omaha, NE, USA) from Research to Prevent Blindness Inc. (New York City, NY, USA). Limitations: Open label Use of adjusted and unadjusted means
			Differences in mean diurnal IOP reduction between groups: baseline to 6 months	Mean: 2.5 ± 0.3 (± SEM) 95% CI: 1.9- 3.2 p value: p < 0.001 in favour of group 1 (latanoprost)	
			Adjusted mean diurnal IOP reduction from baseline to 6 months	Group 1: 5.7 ± 0.3 (± SEM) Group 2: 3.1 ± 0.3 (± SEM) p value: p < 0.001	
			Differences in mean diurnal IOP reduction between groups: baseline to 6 months (Post hoc analyses including 10.00hrs reading).	Group 1: 5.5 ± 0.3 (± SEM) Group 2 : 3.6 ± 0.3 (± SEM) Difference in mean: 2.0 ± 0.4 95% CI: 1.3- 2.6 p value: p < 0.001 in favour of group 1 (latanoprost)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	trabeculoplasty (ALT) or any ocular surgery, inflammation or infection within the 3 months prior to pre-study visit All participants n=303 Mean IOP: Dropouts: 57 (19%) Group 1 (reported as ITT group) n=151 Age (mean ± SEM): 62 ± 1.0 M/F: 70/81 Family origin: White: 104; African-American: 36; Other: 11 Mean IOP ± SEM: 24.6 ± 0.3 Dropouts: 21 (14% including 4 adverse events, 8 IOP not controlled, 2 lost to follow-up and 2 protocol violations) Group 2 (reported as ITT group) n=150 Age (mean ± SEM): 64 ± 1.0 M/F: 77/73 Family origin: White: 103; African-American: 39;	6 months Follow-up Goldmann applanation tonometer to record IOP reading (08.00, 10.00, 12.00 and 16.00hrs except week 2 visit only 08.00hrs)	Mean % reduction on diurnal IOP at month 6	Group 1: 22.6% Group 2: 12.8% 95% CI: Not reported p value: p < 0.001	was very confusing. High dropout rate >20% in Brimonidine group Additional outcomes: Percentage of people achieving pre-specified IOP levels (for example, ≥ 40%, ≥ 30%, ≥ 10%) after 6 months of treatment Notes: Originally 303 people (152/151) but 2 excluded and not considered in the ITT analysis (terminated after baseline and before instillation of treatment. Computer-generated randomisation using allocation. Study reported that outcome assessment was masked.
			Adverse events resulting in withdrawal from study	Any adverse event Group 1: 4/151 (3%) Group 2: 23/152 (15%) p value: p < 0.001 (Fisher's exact test) External ocular Group 1: 2/151 (1%) Group 2: 15/152 (10%) p value: p=0.06 (Fisher's exact test) Central nervous system Group 1: 0 Group 2: 5/152 (3%) p value: p < 0.001 (Fisher's exact test) Dry mouth: Group 1: 0 Group 2: 1/152 (1%) Other (including palpitations, reduced visual acuity, blurred vision, increased lacrimation, diplopia) Group 1: 2/151 (2%) Group 2: 2/152 (1%)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Other: 8 Mean IOP ± SEM: 24.8 ± 0.2 Dropouts: 36 (24% including 23 adverse events, 10 IOP not controlled, 2 lost to follow-up, 1 protocol violation).				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Fellman 2002[202] Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG and OHT Setting: Multi-centre (44 sites) USA Inclusion criteria: Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT Age ≥ 21 IOP 24-36 mmHg in same eye on 2 separate eligibility visits Women post-menopausal or surgically sterilised Exclusion criteria: People who wear contact lenses Women of childbearing potential IOP >36mmHg Visual acuity worse than 0.60 LogMAR Cup or disc ratio > 0.80 Chronic or recurrent inflammatory eye disease	Group 1 Travoprost 0.004% in the evening, placebo in the morning Group 2 Timolol 0.5% 2 per day Examination methods: 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by the same observer throughout the study by looking at photographs depicting ocular	Mean baseline diurnal IOP ± SD	Group 1: 25.9 ± Not reported Group 2: 26.2 ± Not reported	Funding: Alcon Research Ltd. (Houston, TX, USA), which manufactures travoprost. Dr Fellman has no proprietary interest in any of the medications Limitations: Additional outcomes: Detailed analysis of conjunctival hyperaemia
			Mean IOP reductions from baseline at 6 months	Group 1: 7.1 (08.00), 6.6 (10.00), 6.5 (16.00) Group 2: 6.8 (08.00), 6.3 (10.00), 5.2 (16.00)	
			Mean IOP reductions from baseline mmHg at 6 months (end point – baseline	Group 1: 6.73 ± 6.87** Group 2: 6.1 ± 4.83** (IOP calculated as mean across 3 times)	
			% people achieving target of >25% reduction in IOP over all visits (ITT) – average of 3 time points	Group 1: 113/197 (57%) Group 2: 79/199 (40%) People numbers rounded up.	
			Changes in visual field (baseline visit compared to exit visit)	Study reported no significant differences between treatment groups – actual data Not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Ocular trauma in last 6 months Recent ocular infection or inflammation Ocular pathology preventing beta-blockers or PGAs Recent ocular surgery Contraindications for beta-blockers – respiratory, cardiovascular, hepatic, renal People on adjunctive IOP lowering therapies, glucocorticoids or NSAIDS People with hypersensitivities to the medications All participants n=396 (excludes nonstarters – those who did not attend treatment visits and travoprost 0.00015% not given at this concentration) Group 1 n=197 Age (mean ±SD): 64.4 ± 10.2 M/F: 94/103 OHT: 61 COAG: 136 Black: 17 Non-Black: 180 Dropouts: 9/201 (4.48%)* see notes Group 3	hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey or Octopus	Number of people with local ocular adverse events	Group 1: 152 Group 2: 58 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	Notes: *withdrawals due to adverse effect of treatment includes nonstarters randomised to treatment third arm of travoprost 0.001% not reported here ** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[97], Martin 2007[426] and Mastropasqua 1999[432] Computer-generated randomisation sequence. Participants and examiners were masked to treatment allocation.
			Increase in iris pigmentation and Eyelash changes	Group 1=104 Group 2=4	
			Number of people with cardiovascular systemic side effects	Group 1=Not reported Group 2=Not reported	
			Reasons for withdrawals (dropouts)	Group 1 9 includes local ocular effects and systemic effects including arrhythmia and Group 2 1 dizziness, asthenia and ocular discomfort 1 bradycardia, hypotension and dizziness	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	n=199 Age (mean ±SD): 63.9 ± 11.2 M/F: 64/105 OHT: 71 COAG: 128 Black: 23 Non-Black: 176 Dropouts: 2/202 (0.99%)* see notes				

Study	Frezzotti 2014[210]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	First line
Duration of study	12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First POAG or OH diagnosis requiring bilateral treatment to reduce intra-ocular pressure.
Exclusion criteria	History of inflammatory or infective eye disease, previous eye surgery or trauma, allergic mucosal pathology, chronic use of eye drops and contact lenses in the last 6 months, systemic diseases for which beta-blockers were contraindicated, IOP>30mmHg, any systemic treatment affecting tear production.
Recruitment or selection of people	Not reported

Age, gender and family origin	Age - Mean (SD): PF group: 60.25 (8.9); BAK group: 61.5 (13.2). Gender (M:F): male: 19; female: 21. Family origin: Not reported
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Preservative. 0.01% Benzalkonium chloride preserved 0.5% Timolol maleate (Merck Sharp Dohme Corp., Rome, Italy). Duration 12 months. Concurrent medication or care: Not applicable (n=20) Intervention 2: Preservative - Preservative free. 0.1% preservative-free Timolol maleate gel (Timogel; Farmilia-Thea Farmaceutici S.p.A, Verone, Italy). Duration 12 months. Concurrent medication or care: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BAK PRESERVED TIMOLOL versus PRESERVATIVE-FREE TIMOLOL Protocol outcome 1: Intraocular pressure - Actual outcome: Mean intraocular pressure at 12 months; Group 1: mean 16.6 mmHg (SD 1.5); n=20, Group 2: mean 16.2 mmHg (SD 1.8); n=20 Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Major adverse events at 12 months; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Adverse events of pharmacological treatments; Treatment adherence; Quality of life (validated score)

Study	**Fuchsjager-mayrl 2010[213]**
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=Dorzolamide: 57; Timolol: 83)
Countries and setting	Conducted in Austria; Setting: Department of Clinical Pharmacology and the Department of Ophthalmology, Allgemeines Krankenhaus, Vienna
Line of therapy	Not applicable

Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with either POAG or OHT with an untreated IOP ≥ 21 mmHg (documented on at least 3 different occasions) in at least 1 eye were included.
Exclusion criteria	People with exfoliation glaucoma, pigmentary glaucoma, history of acute-angle closure, mean-deviation of visual field testing ≥ -10, intraocular surgery or Argon laser trabeculoplasty within the previous 6 months, ocular inflammation or infection within the previous 3 months, bradycardia (heart rate ≤50 bpm), second- and third-degree heart block, asthma bronchiale, COPD, congestive heart failure, severe renal impairment (creatinine clearance ≤ 1.8 L/h), history of hypersensitivity to 1 of the study medicines or a medicine with a similar chemical structure, history of non-IOP responder to topical beta-blockers or topical carbonic anhydrase inhibitors, and pregnancy.
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): POAG: 63 (13.%); OHT: 61.2 (13.3). Gender (M:F): POAG: 19/30; OHT: 48/43. Family origin: Not reported
Extra comments	Data for change in IOP from baseline presented for POAG people only
Indirectness of population	No indirectness
Interventions	(n=57) Intervention 1: Carbonic anhydrase inhibitors. Dorzolamide 3 times per day. Duration 6 months. Concurrent medication or care: Not applicable (n=83) Intervention 2: Beta-blockers - Timolol maleate. Timpotic (MSD) twice per day. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Other (Supported by an unrestricted grant from Merck Sharpe and Dohme, Hoddesdon, UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS versus TIMOLOL MALEATE

Protocol outcome 1: Intraocular pressure (POAG)
- Actual outcome: Mean change in IOP from baseline (%) at 6 months (people with POAG); Group 1: mean -18.7 % (SD 12.3); n=20, Group 2: mean -21.5 % (SD 12.3); n=29

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0 ; Group 2 Number missing: 0 Protocol outcome 1: Intraocular pressure (OHT) - Actual outcome: Mean change in IOP from baseline (%) at 6 months (people with OHT); Group 1: mean -20.8 % (SD 12.6); n=37, Group 2: mean -23.5 % (SD 12.8); n=54; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Adverse events of pharmacological treatments; Treatment adherence; Quality of life (validated score)

Study	**United Kingdom Glaucoma Treatment Study (UKGTS) trial: Garway-heath 2015[228]**
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=516)
Countries and setting	Conducted in United Kingdom; Setting: 10 tertiary referral centres, teaching hospitals, and district general hospitals throughout the UK.
Line of therapy	Not applicable
Duration of study	Intervention time: 24 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with newly diagnosed, untreated open-angle glaucoma defined as the presence of glaucomatous visual field defects in at least 1 eye with corresponding damage to the optic nerve head and an open iridocorneal drainage angle on gonioscopy.
Exclusion criteria	Advanced glaucoma (visual field mean deviation worse than -10 dB in the better eye or -16 dB in the worse eye), mean baseline intraocular pressure of 30 mmHg or higher, Snellen visual acuity worse than 6/12, and poor image quality (>40micrometres mean pixel height standard deviation) with the Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany)

Recruitment or selection of people	Consecutive recruitment, random allocation (1:1) to either latanoprost or placebo. People were assigned the next available study ID number and randomised in permuted blocks of varying sizes (blocks ranging from 4 to 10) and stratified by participating centre.
Age, gender and family origin	Age - Mean (SD): Placebo: 66 (10); Latanoprost: 65 (11). Gender (M:F): male: 273; female: 243 (number randomised not analysed). Family origin: not reported
Indirectness of population	No indirectness
Interventions	(n=231) Intervention 1: Prostaglandin analogues - Latanoprost. Latanoprost 0.005%. Duration 24 months. Concurrent medication or care: Not applicable (n=230) Intervention 2: No treatment - Placebo. Latanoprost vehicle eye drops (placebo). Duration 24 months. Concurrent medication or care: Not applicable
Funding	Study funded by industry (Pfizer, UK National Institute for Health Research Biomedical Research Centre, London, UK)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LATANOPROST versus PLACEBO
Protocol outcome 1: Visual field defect
- Actual outcome: Time to confirmed visual field deterioration (visual field deterioration defined as at least 3 visual field locations worse than baseline at the 5% levels in 2 consecutive reliable visual fields and at least 3 visual field locations worse than baseline at the 5% levels in the 2 subsequent consecutive reliable visual fields) at 24 months; HR 0.44 (95%CI 0.28 to 0.69)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Did not attend any post-baseline study visits, or did not meet eligibility criteria; Group 2 Number missing: 28, Reason: Did not attend any post-baseline study visits, or reached IOP endpoint

- Actual outcome: Number of people reaching deterioration endpoint at 24 months (visual field deterioration defined as at least 3 visual field locations worse than baseline at the 5% levels in 2 consecutive reliable visual fields and at least 3 visual field locations worse than baseline at the 5% levels in the 2 subsequent consecutive reliable visual fields) at 24 months; Group 1: 35/231, Group 2: 59/230

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Did not attend any post-baseline study visits, or did not meet eligibility criteria; Group 2 Number missing: 28, Reason: Did not attend any post-baseline study visits, or reached IOP endpoint

Protocol outcome 2: Adverse events of pharmacological treatments
- Actual outcome: Myocardial infarction at 24 months; Group 1: 1/231, Group 2: 2/230

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Did not attend any post-baseline study visits, or did not meet eligibility criteria; Group 2

Number missing: 28, Reason: Did not attend any post-baseline study visits, or reached IOP endpoint Protocol outcome 3: Intraocular pressure - Actual outcome: Mean intraocular pressure reduction from baseline at 24 months; Group 1: mean 4 mmHg (SD 3.4); n=231, Group 2: mean 1.3 mmHg (SD 3.6); n=230; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27, Reason: Did not attend any post-baseline study visits, or did not meet eligibility criteria; Group 2 Number missing: 28, Reason: Did not attend any post-baseline study visits, or reached IOP endpoint	
Protocol outcomes not reported by the study	Optic nerve damage; Vision loss; Treatment adherence; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Goldberg 2001[235] Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 9 months	People group: COAG and OHT Setting: multi-centre 64 sites. Europe and Australia Inclusion criteria: Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT Age ≥ 21 IOP 24-36 mmHg in same eye on 2 separate eligibility visits Women post-menopausal or surgically sterilised Exclusion criteria: Women of childbearing potential Visual acuity worse than 0.60 log MAR Cup or disc ratio > 0.80 Abnormalities preventing applanation tonometry	Group 1 Travoprost 0.004% 1 per day in the evening, placebo in the morning Group 2 Timolol 0.5% 2 per day Examination methods: IOP measurements made at 09.00, 11.00 and 16.00hrs using Goldmann applanation tonometry. Photographs were taken to record iris pigmentation or	Mean IOP at baseline (data requested from author)	Group 1: 27.4 ± 2.85 (09.00), 26.4 ± 3.04 (11.00), 25.5 ± 3.18 (16.00) Group 2: 27.1 ± 2.88 (09.00), 26.2 ± 2.91 (11.00), 25.1 ± 2.67 (16.00)	Funding: Alcon Research Ltd, which manufactures travoprost Limitations: Reasons for dropouts not reported Notes: **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426](bimatoprost)
			Mean IOP at baseline (using 11.00hrs reading)	Group 1: 26.4 ± 3.04 Group 2: 26.2 ± 2.91 (calculated as mean across 3 times)	
			Mean IOP at end point (9 months; data requested from author)	Group 1: 18.9 ± 3.59 (09.00), 18.0 ± 3.30 (11.00), 17.6 ± 3.05 (16.00) Group 2: 19.4 ± 3.56 (09.00), 18.8 ± 3.42 (11.00), 18.7 ± 3.67 (16.00)	
			Mean IOP at end point (9 months; using 11.00hrs reading)	Group 1: 18.0 ± 3.30 Group 2: 18.8 ± 3.42 (calculated as mean across 3 times)	
			Mean IOP reductions from baseline at 9 months	Group 1: 8.5 (09.00), 8.4 (11.00), 8.0 (16.00) Group 2: 7.6 (09.00), 7.4 (11.00), 6.4 (16.00) p value using least-square mean is	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Severe central field loss: sensitivity <10dB Chronic or recurrent inflammatory eye disease Ocular trauma in last 6 months Recent ocular infection or inflammation Ocular pathology preventing beta-blockers or PGAs Recent ocular surgery within 3 months Contraindications for beta-blockers – respiratory, cardiovascular, hepatic, renal People on adjunctive IOP lowering therapies, glucocorticoids People with hypersensitivities to the medications People that could not be safely discontinued from current ocular hypertensive medications All participants n=382 Group 1 n=197 Age (mean ± SD): 63.0 ± 10.3 M/F: 96/101 OHT: 74	eyelash characteristics and assessed by 2 independent analysts, with a third to resolve differences. VF evaluation using Humphrey or Octopus Hyperaemia assessed by visual inspection using scale. Aqueous flare and inflammatory cells assessed using slit-lamp		<0.0001 at all time points	Computer-generated randomisation sequence. People and examiners were masked to treatment allocation
			Mean IOP reductions from baseline mmHg at 9 months (end point – baseline; using 11.00hrs reading)	Group 1: 8.4 ± 3.84** Group 2: 7.4 ± 3.46**	
			% people achieving target IOP ≤ 20mmHg (not ITT data)	Group 1: 85 – 95.7% Group 2: 76.1 – 86.8% Per protocol dataset	
			Number of people with local ocular adverse events reported at incidence of >1%	Group 1: 107 Group 2: 22 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation and eyelash changes	Group 1:=10 Group 2:=0	
			Number of people with cardiovascular systemic side effects	Group 1:=Not reported Group 2:=Not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	COAG: 123 Black/non-black: 2/195 Dropouts: 9 Group 2 n=185 Age (mean ±SD): 62.5 ± 10.6 M/F: 96/89 OHT: 73 COAG: 112 Black/non-black: 2/183 Dropouts: 3				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Higginbotham 2002[270] Study design: RCT Double masked Evidence level: 1+ Duration of	People group: COAG or OHT Setting: multi-centre (38 eye clinics) USA Inclusion criteria: Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT Aged 18 or older Best-corrected visual acuity measuring 20/200 Pre-study IOP >30mmHg without IOP reducing medication OR >25mmHg with prior treatment	Group 1 Fixed combination of Latanoprost 0.005% and Timolol 0.5% 08.00 AND placebo 20.00hrs Group 2 Latanoprost 0.005% 08.00 AND placebo 20.00hrs	Mean ± SD baseline diurnal IOP mmHg	Group 1: 23.1 ± 3.8 Group 2: 22.9 ± 4.1 Group 3: 23.7 ± 4.1	Funding: Pharmacia and Upjohn Inc.; Research to Prevent Blindness Inc. Limitations: Run in period 2-4 weeks with Timolol 0.5 % 2 per day prior to starting the study Notes: *Differences in the mean diurnal reduction in IOP between groups estimated
			Mean ± SD diurnal IOP at 6 months mmHg	Group 1: 19.9 ± 3.4 Group 2: 20.8 ± 4.6 Group 3: 23.4 ± 5.4	
			Mean ± SD reduction in diurnal IOP mmHg at 6 months §	Group 1 to Group 3: -2.9 (95% CI: -3.5 to -2.3, p<0.001) Group 1 to Group 2: -1.0 (95% CI: -1.7 to -0.3, p=0.005)	
			Mean ± SD reduction in diurnal IOP mmHg at 6	Group 2: 2.1 ± 5.27**	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
follow-up: 6 months (double masked RCT part of study) Study continued for a further 6 months as an open-label study with everyone receiving the fixed combination treatment.	Previous latanoprost or Timolol therapy permitted Exclusion criteria: History of acute angle-closure or occludable angles Use of contact lenses Ocular surgery, Argon laser trabeculoplasty, or ocular inflammation or infection within 3 months of the pre-study visit Hypersensitivity to benzalkonium chloride Any other abnormal ocular condition or symptom that investigator determined precluded study enrolment Presence of concomitant diseases that contraindicate adrenergic antagonist Nursing mothers, pregnant women and women who were of childbearing potential not using adequate contraception for at least the previous 3 months People who could not adhere to treatment or the visit plan People who had participated in another clinical study within 1 month of previous visit All participants	Group 3 Timolol 0.5% 0.8.00 AND 20.00hrs Examination methods: IOP measured by calibrated Goldmann applanation tonometer. Each measurement taken in triplicate in each eye. Measurements taken at 08.00, 10.00 and 16.00hrs at baseline and weeks 2, 13, 26 and 52. Automated visual field examination performed at baseline and weeks 13, 26 and 52. Visual acuity assessed and eye-	months	Group 3: 0.3 ± 5.27**	(least square mean difference) using a repeated-measures analysis of covariance with baseline IOP as a covariate; people, treatment, visit and centre as main factors; and treatment group-by-visit and treatment group-by-centre interaction factors. § values not reported for group 2 or group 3 † side effects include blepharitis, hypertrichosis, irritation, meibomianitis, seborrhoea, eye hyperaemia, chemosis, conjunctival discolouration, corneal disorder, keratitis, keratopathy, cataract, optic atrophy, errors of refraction, increased IOP, vision decreased, visual field defect, conjunctivitis, epiphora, eye pain, photophobia, vision blurred Intention to treat analysis for the first 6 months included all people who received at least 1 drop of medication. For IOP measurements, the last
			Percent of people reaching IOP <15mmHg as of 6 months §	Group 1: 6 /130 Group 2: 4/128 Group 3: 1/129 p value (group 1 to 3): 0.06 p value (group 1 to 2): 0.56	
			Percent of people reaching IOP <18mmHg as of 6 months §	Group 1: 28/130 Group 2: 30/128 Group 3: 8/129 p value (group 1 to 3) =0. 01 p value (group 1 to 2) =0. 65	
			Percent of people reaching IOP <21mmHg as of 6 months §	Group 1: 68/130 Group 2: 63/128 Group 3: 39/129 p value (group 1 to 3) <0.001 p value (group 1 to 2) =0.36	
			Number of ocular side effects †	Group 1: 86 Group 2: 86 Group 3: 59	
			Visual field defects	Group 1: 7/130 Group 3: 4/128	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	n=418 Age (mean): Not reported M/F: 215/203 Dropouts: 73 Family origin: White: 276; Black: 110; Hispanic: 27; Other: 5 Diagnosis: POAG: 278; psuedoexfoliative glaucoma: 9; pigmentary glaucoma: 13; OHT: 109; mixed (different diagnosis in each eye): 8; none listed: 1 IOP reducing medication in last 3 months: 351/418 Group 1 n=138 Age (mean): 61 +12 M/F: 67/71 Dropouts: 13 Family origin: White: 90; Black: 38; Hispanic: 7; Other: 3 Diagnosis: POAG: 94; psuedoexfoliative glaucoma: 2; pigmentary glaucoma: 4; OHT: 36; mixed 2; none listed: 0 IOP reducing medication in last 3 months: 117/138 Group 2 n=140	lid slit lamp biomicroscopy performed at each visit. Ophthalmoscopy performed at pre-study visit and weeks 26 and 52.			available IOP measurement was carried forward. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426] (bimatoprost) Computer-generated randomisation sequence. People and examiners were masked to treatment allocation

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 63 +13 M/F: 80/60 Dropouts: 36 Family origin: White: 90; Black: 35; Hispanic: 14; Other: 1 Diagnosis: POAG: 95, psuedoexfoliative glaucoma: 4; pigmentary glaucoma: 5; OHT: 33; mixed: 3; none listed: 0 IOP reducing medication in last 3 months: 117/140 Group 3 n=140 Age (mean): 63 +12 M/F: 68/72 Dropouts: 24 Family origin: White: 96; Black: 37; Hispanic: 6; Other: 1 Diagnosis: POAG: 89; exfoliative glaucoma: 3; pigmentary glaucoma: 4; OHT: 40; mixed: 3; none listed: 1 IOP reducing medication in last 3 months: 117/140				

Study	Hollo 2014[278]
Study type	RCT (People randomised; Parallel)

Number of studies (number of participants)	1 (n=FC: 201; NFC: 199)
Countries and setting	Conducted in Multiple countries; Setting: 35 centres in 7 countries of the European Union
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria comprised best-corrected visual acuity not worse than +0.6 logarithm of minimal resolution in both eyes, a clinical need for an additional IOP-lowering medication based on the investigators opinion, IOP in at least 1 eye ≥23mmHg at 08.00hrs at baseline, and ≤36mmHg in both eyes at any time point at the screening and baseline visits.
Exclusion criteria	Pregnancy and planned pregnancy for the study period, breast feeding, corneal abnormalities preventing reliable applanation tonometry; prior refractive corneal surgery, hypersensitivity or contraindication to tafluprost or Timolol, prior filtration surgery, or any other ocular surgery, including intraocular laser procedures within 6 months before screening in the eye(s) to be treated, advanced visual field defects in either eye, anticipated progression during study period, risk for angle closure (≤2 grades anterior chamber angle width according to Schaffer's classification), use of contact lenses at screening or during the study, and lack of ability to safely discontinue the use of ocular hypotensive medications during the washout period.
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): FC: 63.5 (10.6); NFC: 64 (10.6). Gender (M:F): FC: 75/126; NFC: 77/122. Family origin: FC White: 100% NFC White: 99%; Black: 0.5%; Hispanic: 0.5%
Indirectness of population	No indirectness
Interventions	(n=199) Intervention 1: Prostaglandin analogues - Tafluprost. NFC: preservative-free tafluprost 0.0015% at 08.10hrs and

	preservative-free Timolol 0.5% at 08.00 and 20.00hrs. Duration 6 months. Concurrent medication or care: Not applicable (n=201) Intervention 2: Fixed combination solutions – Prostaglandin analogue with beta-blockers. FC: preservative-free fixed combination of tafluprost 0.0015% or Timolol 0.5% administered at 08.10hrs and preservative-free vehicle (placebo) at 08.00 and 20.00. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Study funded by industry (Santen Oy, Tampere, Finland. The sponsor participated in the design of the study, conducting the study, data collection, data management, data analysis, data interpretation, and the preparation, review and approval of the article.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROSTAGLANDIN ANALOGUE WITH BETA-BLOCKERS FIXED COMBINATION versus TAFLUPROST AND TIMOLOL Protocol outcome 1: Adverse events of pharmacological treatments - Actual outcome: Adverse events including: Conjunctival hyperaemia, eye irritation, eye pain and eye pruritus at 6 months; Group 1: 24/201, Group 2: 18/199 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Intraocular pressure - Actual outcome: IOP reduction of ≥ 35% from baseline at 6 months; Group 1: 73/201, Group 2: 85/199 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: IOP reduction of ≥ 30% from baseline at 6 months; Group 1: 117/201, Group 2: 133/199 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: IOP reduction at 6 months; Group 1: mean 8 mmHg (SD 2.87); n=201, Group 2: mean 8.3 mmHg (SD 2.86); n=199 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Mean IOP of ≤ 18mmHg at 6 months at 6 months; Group 1: 138/201, Group 2: 135/199 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Treatment adherence; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Kampik [313] European latanoprost study group Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 6 months	People group: POAG and OHT people Setting: Multi-centre – 30 eye clinics in Germany, UK, Spain and Finland Inclusion criteria: Age ≥ 18 years Unilateral or bilateral POAG or exfoliation glaucoma or OHT with IOP of ≥ 21mmHg with current monotherapy or dual therapy Exclusion criteria: Previous treatment with latanoprost or brimonidine or ongoing treatment with α-adrenoceptor agonists Closed or barely open anterior chamber angle or history of acute angle closure Argon laser trabeculoplasty, filtering surgery or other ocular surgery within the last 3 months Current use of contact lenses Ocular inflammation or infection within the last 3 months Known hypersensitivity to any of the eye drop components All participants n=379	Group 1 Latanoprost 0.005% once daily (22.00hrs) for 6 months Group 2 Brimonidine 0.2% twice daily (08.00 and 22.00hrs) for 6 months. All At least 4 weeks washout period 4 visits during 6 month study: Baseline 2 weeks 3 months 6 months ○ 3 IOP measurements in each eye using Goldmann applanation tonometer taken at: 10.00	Mean ± SD diurnal IOP at baseline (mmHg)	Group 1: 25.1 ± 3.7 Group 2: 24.9 ± 3.0	Funding: Supported by a research grant from Pharmacia Corporation (Peapack-Gladstone, NJ, USA) manufacturers of latanoprost Limitations: Open label Randomisation method and allocation concealment were not reported. Significantly higher number of OHT people in group 1 compared to group 2 (p=0.027) Additional outcomes: Percentage of people achieving pre-specified IOP levels (for example, ≤21, ≤20, ≤15) after 6 months of treatment
			Mean ± SD diurnal IOP at 6 months (mmHg)	Group 1: 18.0 ± 2.9 Group 2: 19.8 ± 3.1	
			Mean ± SD diurnal IOP reduction from baseline at 6 months (mmHg)	Group 1: 7.1 ± 3.3 p value: p < 0.001 (ANCOVA) Group 2: 5.2 ± 3.5 p value: p < 0.001 (ANCOVA)	
			% reduction in mean IOP from baseline	Group 1: 28% Group 2: 21% p value: p < 0.001 (ANCOVA) favouring latanoprost	
			Mean ± SD IOP at 10.00 and 17.00hrs at 6 months (mmHg)	IOP 10.00: Group 1: 18.1 ± 2.9 Group 2: 19.5 ± 3.2 P value: p < 0.001 (ANCOVA) in favour of latanoprost IOP 17.00: Group 1 : 17.8 ± 3.0 Group 2: 19.8 ± 3.4 p value: p < 0.001 (ANCOVA) in favour of latanoprost	
			Number of people with systemic adverse	Group 1: 23 (including 4 respiratory) Group 2: 56 (including 4 respiratory, 1	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean): M/F: 154/225 Mean IOP: Not reported Dropouts: 52 (13.3%) Group 1 n=187 Age (mean): 64 ± 11 M/F: 77/110 Mean IOP: 25.1 ± 3.7 This group had significantly (p=0.027) more OHT people than group 2. Dropouts: 5 (including IOP not controlled, ocular irritation, Argon laser trabeculoplasty and corneal oedema) Group 2 n=192 Age (mean): 65 ± 12 M/F: 77/115 Mean IOP: 24.9 ± 3.0 Dropouts: 47 (including 4 before instillation of treatment. Other reasons for withdrawing included 14 ocular allergic reactions, 13 IOP not controlled, withdrawal of consent and Argon laser trabeculoplasty).	○ and 17.00hrs at baseline, 3 months and 6 months ○ only before 12.00hrs at 2 weeks The mean of the 3 measurements was taken, and if both eyes were study-eyes, the mean of the 2 eyes was used.	events* Number of people with ocular adverse events**	serious) p value: p < 0.005 Fisher exact test (this was for all systemic side effects as defined in the paper). 95% CI: Not reported Group 1: 62 Group 2: 95 p value: Not significant except for significantly more ocular allergic reactions (p < 0.001 Fisher exact test) in the brimonidine group. 95% CI: Not reported	Notes: Statistical analysis does not include the 4 people randomised to receive brimonidine who withdrew consent. *includes respiratory, dry mouth, headaches, fatigue and infection **includes ocular irritation, ocular allergic reaction, increased iris pigmentation, disturbed vision and conjunctival disorders Study reported that outcome assessment was masked.

Study	Low-pressure Glaucoma Treatment Study trial: Krupin 2011[356]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=178; brimonidine: 99; Timolol: 79)
Countries and setting	Conducted in the USA; Setting: 13 clinical centres
Line of therapy	Not applicable
Duration of study	Intervention time: 48 months mean follow-up (SE) 30 (1.2) months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women, ≥30 years of age, with previously diagnosed LPG. Untreated LPG with Goldmann applanation IOP ≤ 21 mmHg on a diurnal (08.00, 10.00, 12.00, 16.00hrs) curve before medication randomisation
Exclusion criteria	History of untreated IOP >21 mmHg, or a >4-mmHg difference in IOP between the eyes. Advanced visual field loss (mean deviation, >15 dB) or threat to fixation. Corrected visual acuity <20/40 in either eye. Pigmentary or exfoliative glaucoma. History of angle-closure or an occludable angle by gonioscopy. Prior filtration surgery or laser iridotomy. Cataract surgery with posterior chamber lens implant performed less than 1 year before enrolment. Argon laser trabeculoplasty performed less than 6 months previously or for an untreated IOP >21 mmHg. History or signs of inflammatory eye disease, ocular trauma, or potentially progressive retinal disease. History of allergy or intolerance to topical Timolol, brimonidine, or to any components of these medications. Resting pulse rate <50 beats per minute. Severe, unstable, or uncontrolled cardiovascular, renal, or pulmonary disease. Women pregnant, nursing, or contemplating pregnancy.
Recruitment/selection of people	People were enrolled if all known and study baseline untreated diurnal IOPs were ≤21 mmHg and glaucomatous optic disc cupping was consistent with the visual field damage. Participants were assigned to 1 of 2 treatment groups, brimonidine tartrate 0.2% or Timolol maleate 0.5% (both medications used throughout the study), according to a computer-generated randomisation list stratified by the centre. To allow for higher people attrition in the brimonidine group because of an expected 15% allergy rate in a long-term study, randomisation was in groups of 7:4 to brimonidine and 3 to Timolol. Coded medications were dispensed in identical opaque bottles with instructions for twice-daily administration to both eyes, including the morning before each protocol visit. Intraocular pressure-lowering agents, other than the study medication, were not allowed.
Age, gender and family origin	Age - Mean (SD): Brimonidine: 64.3 (10.9); Timolol: 65.7 (10.4). Gender (M:F): Define. Family origin: White: 137 (72.1%); Black: 26 (13.7%); Hispanic: 14 (7.4%); Asian: 13 (6.8%)

Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Sympathomimetics – Brimonidine tartrate. Brimonidine tartrate 0.2% twice per day. Duration 48 months. Concurrent medication or care: Not applicable (n=79) Intervention 2: Beta-blockers – Timolol maleate. Timolol 0.5% twice per day. Duration 48 months. Concurrent medication or care: Not applicable
Funding	Equipment or medicine provided by industry (Study medications were provided by Allergan and an unrestricted study grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BRIMONIDINE TARTRATE versus TIMOLOL MALEATE Protocol outcome 1: Visual field defect - Actual outcome: Visual field progression at 48 months; Group 1: 9/99, Group 2: 31/79 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 18 Protocol outcome 2: Treatment adherence - Actual outcome: Discontinuation prior to 1 year at 12 months; Group 1: 36/99, Group 2: 8/79 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 18 - Actual outcome: Discontinuation > 1 year at 12 months; Group 1: 18/99, Group 2: 15/79 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 18 Protocol outcome 3: Intraocular pressure - Actual outcome: Final value IOP at 48 months mean (SD); Group 1: 14 (2.6), Group 2: 14.2 (1.9) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 18	
Protocol outcomes not reported by the study	Optic nerve damage; Vision loss; Adverse events of pharmacological treatments; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Le Blanc, 1998[372] Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 12 months	People group: POAG and OHT Setting: multi-centre, Canada and USA Inclusion criteria: Diagnosis of POAG or OHT and on no more than 2 glaucoma medicine Best-corrected visual acuity of 20/80 or better in each eye Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other Washout of current medications Exclusion criteria: Active ocular disease Severe dry eye Corneal abnormalities Advanced glaucoma (C/D≥ 0.8) People who wear contact lenses Use of other ocular medications Surgery or laser surgery within 6 months Uncontrolled hypertension or diabetes Women with childbearing potential	Group 1 Brimonidine 0.2% 2 per day Group 2 Timolol 0.5% 2 per day Examination methods: IOP was measured at trough – 12 hours after instillation of evening medication and at peak – 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup-to-disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	Mean and 95% CI reduction in peak IOP mmHg (averaged over all time points to 12 months)	Group 1: 6.8 CI (7.2 - 6.4) Group 2: 5.9 CI (6.4 - 5.4) Group 1 was significantly better at reducing pressure than group 2 p value < 0.001 at weeks 1 and 2 and month 12 using paired t-test	Funding: Allergan Inc. Manufacturers of brimonidine Limitations: Very high dropout rate for brimonidine group 47% Additional outcomes: Mean heart rate Notes: Computer-generated randomisation sequence by allocation and allocation concealment. People and examiners were masked to treatment assignment. Uneven randomisation. 3:2 Schuman 1996[597]reported
			Mean and 95% CI reduction in trough IOP mmHg (averaged over all time points to 12 months)	Group 1: 3.9 CI (4.2 - 3.6) Group 2: 6.0 CI (6.4 - 5.6) Group 2 was significantly better at reducing pressure than group 1 p value < 0.001 at all time points using paired t-test	
			Mean ± SD reduction in diurnal IOP mmHg (averaged over all time points to 12 months)	Group 1: 5.4 ± Not reported Group 2: 5.9 ± Not reported	
			Possible worsening of visual field (increase >5dB for Mean Deviation)	Group 1: 5 Group 2: 6 No significant between group differences in VF observed	
			*Reasons for withdrawals (dropouts)	Group 1: Inadequate IOP control=30 All adverse events=76 Ocular Adverse events =43 Systemic =16 (includes fatigue or drowsiness, headache, dry mouth) Other reasons (including cataract) surgery)=31 Group 2:	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Contraindications to beta-blockers or α adrenergic agonists Hypersensitivity to treatment medications Those who have participated in previous trial within 30 days start of study. All participants n=463 Age (mean): Not reported M/F: 234/229 Group 1 n=280 Age (mean): 63 (28.5-86.4) M/F: 138/142 Dropouts: 137/292* POAG: 157 OHT: 112 1 eye OHT/1 eye POAG: 11 Black/ non-black: 32/260 Dropouts: 137/292* (47%) Group 2 n=183 Age (mean): 61 (32.8-83)			Inadequate IOP control=10 All adverse events=9 (3 for fatigue or drowsiness) Other reasons (including cataract surgery)=21	intermediate results of Le Blanc 1998[372] (6 months of data) and Schuman 1997 *Dropout figures include those who were eligible for study but did not begin protocol.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	M/F: 96/87 Dropouts: 40/191* POAG: 98 OHT: 78 1 eye OHT/1 eye POAG: 7 Black/non-black: 15/ 168 Dropouts: 40/191 (21%)*				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Manni 2004[417] Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG Setting: Single centre, Italy Inclusion criteria: COAG At least 6 months current treatment with Timolol 0.5% 2 per day Age >18 years Best-corrected visual acuity 20/80 or better IOP ≥ 21 mmHg in at least 1 eye but at least 20% lower than before any IOP lowering treatment. Repeatable VF defect in same eye	Group 1 Latanoprost 0.005% (evening) 1 per day and Timolol 0.5% (morning) 1 per day Group 2 Bimatoprost 0.03% 1 per day evening Examination methods: IOP measured at baseline, 2 weeks and every month using a Goldmann tonometer. 3 times per day (08.00, 12.00 and 16.00hrs) measurements were	Mean ± SD baseline diurnal IOP mmHg	Group 1: 24.1 ± 4.6 Group 2: 23.5 ± 3.2	Funding: Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata Limitations: No washout period for bimatoprost monotherapy. People were selected for inadequate IOP control on Timolol 0.5% *Significance testing between arms does not appear to be on an ITT basis – only 28 people counted per
			Mean ± SD end point diurnal IOP at 6 months	Group 1: 16.8 ± 1.4 Group 2: 17.0 ± 2.1	
			Mean ± SD reduction in IOP mmHg at 6mths (baseline – end point)	Group 1: 7.3 ± 5.59** Group 2: 6.5 ± 3.98** p=not significant*	
			Total number of people reporting ocular side effects	Group 1: Not reported Group 2: Not reported	
			Total number of cardiovascular systemic side effects by group	Group 1: Not reported Group 2: Not reported 6 people in group 1 reported a headache	
			Reasons for	Group 1:	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Exclusion criteria: Uncontrolled systemic diseases Allergy to treatment medications Severe trauma Previous ocular surgery in last 6 months Any condition affecting IOP measurement such as corneal abnormalities Pregnant, nursing or people considering pregnancy All participants n=61 Age (mean ± SD): 59.4 ± 14.1 Group 1 n=30 Age (mean ± SD): 59.7 ± 13.5 M/F: 16/14 Dropouts: 4 Group 2 n=31 Age (mean ± SD): 59.2 ± 14.7 M/F: 14/17 Dropouts: 7	taken in each eye and the mean value was used in the statistical analysis. Photographs of lids and periocular area were taken at baseline to compare to end point.	withdrawals	Inadequate IOP control=2 Ocular allergy=2 Group 2: Inadequate IOP control=2 Ocular allergy=3 Self-withdrawal=2	group Additional outcomes: Occurrence of hyperaemia and eyelash growth Notes: Investigators were masked to treatment allocation. Computer-generated randomisation sequence. **Standard deviations were estimated using the precise p values reported in the study following the method detailed in the Cochrane Handbook
			Hyperaemia at baseline	Group 1: 10/30 Group 2: 9/31 p value: 0.20	
			Hyperaemia at 90 days	Group 1: 24/30 Group 2: 14/31 p value: 0.004	
			Hyperaemia at 180 days	Group 1: 19/30 Group 2: 14/31 p value: 0.08	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
March 2000[425] The Brinzolamide Long-Term Therapy Study Group Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 18 months	People group: COAG or OHT Setting: multi-centre (18 sites) USA Inclusion criteria: Diagnosis of psuedoexfoliative glaucoma, POAG, pigmentary glaucoma or OHT ≥21 years old Post-menopausal or sterilised women only IOP 22 – 36 mmHg after washout period Exclusion criteria: People with corrected visual acuity of worse than 20/80 Pregnant or nursing women People with history of hypersensitivity to test medications Previous intraocular surgery Ocular trauma Recent ocular inflammation or infection Photophobia or diplopia Contraindications to beta-blockers, CAI Use of medications causing dry eye Concomitant use of systemic CAIs	Group 1 Brinzolamide 1% 2 per day (and placebo for afternoon dose) Group 2 Brinzolamide 1% 3 per day Group 3 Timolol 0.5% 2 per day (and placebo for afternoon dose) Examination Methods: At each visit, the IOP was measured before the morning dose using a Goldmann tonometer. Automated perimetry was performed at month 12 and on completion.	Mean ± SD baseline IOP mmHg (average of both eyes 08.00)	Group 1: 25.1 ± Not reported Group 2: 26.1 ± Not reported Group 3: 25.4 ± Not reported	Funding: Alcon laboratories. Manufacturer of brinzolamide Limitations: Randomisation method and allocation concealment not reported. Although study states that it was a double-masked design, it was not clear whether examiners were masked SDs missing from IOP outcome data High dropout rate. Results presented were per protocol not ITT Additional outcomes: Corneal thickness and corneal endothelial cell density
			Mean ± SD reduction in IOP mmHg at 18 months (baseline – end point)	Group 1: 3.3 ± Not reported Group 2: 3.2 ± Not reported Group 3: 5.3 ± Not reported p is < 0.002 comparing Timolol versus brinzolamide 2 or 3 per day	
			Number of people reporting local ocular side effects	Group 1: 45 Group 2: 47 Group 3: 19 Includes itching, stinging, vision disturbance, eyelid discomfort, hyperaemia	
			Number of people reporting bitter taste	Group 1: 5 Group 2: 12 Group 3: 0	
			Number of people with cardiovascular systemic side effects	Group 1: Not reported Group 2: Not reported Group 3: Not reported	
			Reasons for withdrawals (dropouts)	Group 1: Inadequate IOP control=9 Adverse events=21 Other (includes self-withdrawal, lost to follow-up, non-compliance)=14 Group 2: Inadequate IOP control=13 Adverse events=17	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	All participants n=378 Group 1 n=150 Age (mean ± SD): 63.0 ± 11.6 M/F: 68/82 Black/non-black: 27/123 OHT/COAG: 59/91 Dropouts: 44 (29%) Group 2 n=153 Age (mean ± SD): 60.3 ± 12.9 M/F: 76/77 Black/non-black: 33/120 OHT/COAG: 57/96 Dropouts: 63 (41%) Group 3 n=75 Age (mean ± SD): 59.9 ± 13.2 M/F: 28/47 Black/non-black: 14/61 OHT/COAG: 25/50 Dropouts: 27 (36%)			Other (includes self-withdrawal, lost to follow-up, non-compliance)=33 Group 3: Inadequate IOP control=1 Adverse events=8 Other (includes self-withdrawal, lost to follow-up, non-compliance)=18	Notes: Randomisation 2:2:1 Dropout figures due to other reasons include proportion of people withdrawing from study at 12 months. People were masked to treatment assignment

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Martin 2007[426] Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG and OHT Setting: single centre, Spain Inclusion criteria: Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT in at least 1 eye Age > 18 IOP ≥ 22 mmHg at enrolment and between 24-34 mmHg after washout. Visual acuity ≥ 0.1 in study eye Completion of adequate washout period for Sympathomimetics, CAI and miotics. Exclusion criteria: Infection or inflammation of the eye Any anomaly impeding tonometry History of contraindications for any treatments Macular or retinal pathologies Diabetes Women of childbearing potential not using contraception Requirement for other chronic eye medication during the study Eye surgery 6 months previously Laser treatment 3 months previously	Group 1 Bimatoprost 0.03% 1 per day at 21.00 Group 2 Timolol 0.5% 2 per day Examination methods: Applanation tonometry Macular tomography using OCT 3000 Anterior flare determination using laser flare meter	Mean ± SD baseline diurnal IOP mmHg	Group 1: 24.1 ± 3.2 Group 2: 24.1 ± 1.7	Funding: Partly financed by the Instituto de Salud Carlos III. Authors declared no commercial interests. Limitations: Author reported that the study was not sponsored, so allocation concealment and masking of people were not possible. This might have affected the self-reporting of adverse events, but an ophthalmologist masked to treatment allocation performed the outcome assessment. Baseline data not reported Additional outcomes: Inter or intra group differences in macular
			Mean ± SD end point diurnal IOP (6 months) mmHg	Group 1: 13.5 ± 3.1 Group 2: 16.6 ± 2.4 p value compares difference in end point IOPs between groups, p is 0.003 using ANOVA for repeated measures	
			Mean ± SE reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 10.7 ± 3.8 Group 2: 7.6 ± 2.3	
			Proportion of people reaching target of ≤30mmHg	Figures were only reported graphically but study reported the number for bimatoprost as significantly greater than Timolol	
			Conjunctival hyperaemia	Group 1: 4 Group 2: 0	
			Increase in iris pigmentation and Eyelash changes	Group 1: 3 Group 2: 0	
			Number of people with cardiovascular systemic side effects	Group 1:=Not reported Group 2:=Not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	All participants n=60 Age (mean): Not reported M/F: Not reported Dropouts: 0 Group 1 n=30 Age (mean): Not reported M/F: Not reported Dropouts: 0 Group 2 n=30 Age (mean): Not reported M/F: Not reported Dropouts: 0				thickness not significant Inter or intra group differences in anterior chamber flare not significant Notes: No people discontinued study due to adverse events Computer-generated randomisation sequence. Outcome assessment was masked.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Mastropasqua 1999[432] Study design: RCT Double	People group: Pigmentary Glaucoma Setting: single centre, Italy Inclusion criteria: Untreated IOP > 21 mmHg Evidence of optic nerve head	Group 1 Latanoprost 0.005% 1 per day 20.00hrs with morning placebo Group 2 Timolol 0.5% 2 per day	Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 6.0 ± 4.5 Group 2: 4.8 ± 3.0	Funding: Funding details not clear but study conducted at Institute of Ophthalmology, University 'G D'Annunzio', Chieti,
			Mean ± SD reduction in diurnal IOP mmHg at 12 months	Group 1: 5.9 ± 4.6 Group 2: 4.6 ± 3.1	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
masked Evidence level: 1+ Duration of follow-up: 12 months	change and VF changes Best-corrected visual acuity ≥ 15/20 – no media opacities Refractive errors not exceeding -8 or +6D MD Humphrey not exceeding -12.0dB Discontinuation of previous glaucoma treatments of 4 weeks Exclusion criteria: History of ocular, rhinological, neurologic or systemic disorders accounting for optic nerve head damage History of haemodynamic crisis Previous surgery or laser treatment in either eye All participants n=36 Age (mean): Not reported M/F: 21/15 Dropouts: 2 Family origin: Not reported Family history: 9 Group 1 n=18	Examination methods: Goldmann applanation tonometer used to measure IOP. Average of 3 readings taken at each time interval: 08.00, 12.00, 16.00 and20.00. Outflow facility measured with a Scholtz electronic tonometer at baseline and at end point of study.	(baseline – end point) Total number of ocular side effects experienced at least once in 1 year* Increase in iris pigmentation Reasons for withdrawals (dropouts)	Group 1: 24 Group 2: 35 Includes itching, stinging, conjunctival hyperaemia and dry eye Group 1: 3 Group 2: 0 Group 1: moved away=1 Group 2: inadequate IOP control=1	Italy Limitations: Small study. Additional outcomes: Aqueous outflow facility (C) measured at baseline and after 1 year. Microliters per minute per mmHg Detailed analysis of conjunctival hyperaemia Notes: Computer-generated randomisation sequence. Participants and examiners were masked to treatment allocation.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean ± SD): 46.1 ± 9.9 M/F: 10/8 Family history: 4 Dropouts: 1 Group 2 n=18 Age (mean ± SD): 45.8 ± 10.5 M/F: 11/7 Family history: 5 Dropouts: 1				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Miglior 2005[453] European Glaucoma Prevention Study (EGPS) Group. Study design: RCT Double	People group: Consecutive people from clinic population with ocular hypertension (aged over 30). Setting: People from 18 centres in 4 European countries. Inclusion: IOP (22-29mmHg), two normal and reliable visual fields and normal optic discs, PEX allowed (below 2%), normal optic discs in both eyes, open angle, PEX and PDS allowed. Exclusion: Visual acuity below 20/40, previous intraocular surgery, previous	Group 1 Dorzolamide 2% (CAI) – 3 times daily. Group 2 Placebo – 3 times daily.	Development of reproducible visual field defects:	Group 1: 26/536 (4.9%) Group 2: 38/541 (7.0%) OR: 0.68 (95% CI: 0.41-1.12)	Funding: Supported by The European Commission (BIOMED II program, contract no.: BMH4-CT-96-1598), and Merck (Whitehouse Station, NJ). Limitations: High dropouts (30.1%). A comparative analysis of the mean IOP between people still
			Dropouts due to adverse events:	Group 1: 116/536 (21.7%) Group 2: 51/541 (9.4%) OR: 2.54 (95% CI: 1.83-3.53)	
			Development of reproducible VF defect or glaucomatous change of optic disc:	Group 1: 46/536 Group 2: 60/541 OR: 0.86 (95% CI: 0.58-1.26) p value: 0.45	
			Mean % reduction from baseline in observed cases:	6 Months Group 1: 14.5% Group 2: 9.3%	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
masked Evidence level: 1+ Duration of follow-up: Median 55.3 months.	laser trabeculoplasty within 3 months, secondary causes of elevated IOP. All participants n=1,077 Age (mean): 57.03±10.3 Family origin: White: 1,075; African European: 1; Asian: 1 Mean IOP: 23.6±1.6 Group 1 n=536 Age (mean): 56.42±10.32 M/F: 232/304 Mean IOP: 23.4 Dropouts: 191 (116 adverse events) Group 2 n=541 Age (mean): 57.63±10.30 M/F: 259/282 Mean IOP: 23.5 Dropouts: 134 (51 adverse events)			5 years: Group 1: 22.1% Group 2: 18.7%	in the study and those who voluntarily withdrew revealed a higher IOP level in the group of withdrawn people. Additional outcomes: Notes: Computer-generated randomisation by allocation sequence and allocation concealment. People and examiners were masked to treatment assignment. Initially 1,081 enrolled and randomised but 4 excluded as had glaucoma so not included in intention to treat analysis.
			Mean % reduction IOP from baseline in last observation carried forward analysis: (5 years)	Group 1: 17.9% (SD 14.1%) Group 2: 13.7% (SD 15.9%)	
			Safety endpoint (IOP 35mmHg or greater):	Group 1: 1/536 (0.2%) Group 2: 12/541 (2.2%)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Mills 1983[455]	People group: people with chronic open-angle glaucoma	Group 1	Mean ± SD diurnal IOP at	Group 1: 26.9± 5.1(RE), 26.8± 5.5 (LE)	Funding: Not reported

Study details	Participants	Interventions	Outcome measures	Effect size		Comments
Study design: RCT Evidence level: 1+ Duration of follow-up: 12 months	Setting: Not reported Inclusion criteria People with optic nerve head and visual field changes of open-angle glaucoma, either controlled on topical glaucoma medication or presenting as new people. Exclusion criteria: People with a history of cardiovascular disease or bronchospasm or who were receiving concomitant medication for a cardiovascular disease. All participants n=30 Age (mean ± SD): 70 ± 8.8 M/F: 16/14 Mean IOP: Not reported Dropouts: 9 Group 1 n=15 Age (mean): 71 M/F: 9/6 Mean IOP: 26.9 ± 5.1 (RE), 26.8 ± 5.5 (LE) Dropouts: 4 in total. 3 required additional treatment as pressure not adequately controlled by Timolol alone) and 1 had elevated IOP immediately after instillation of treatment, which was therefore discontinued) Group 2 n=15 Age (mean): 69		Timolol 0.25% twice daily Group 2 Timolol 0.5% twice daily All 7 day washout period for people on topical glaucoma therapy Each person had a day curve of IOP at 09.00, 12.00, 16.00 and 20.00) measured by Goldmann applanation tonometry and Haag-Streit slit lamp. A mean of the day curve pressures was calculated. People were reviewed at 1, 3, 6, 9 and 12 months.	baseline (mmHg)	Group 2: 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) 95% CI: Not reported p value: Not reported	Limitations: 8 people (group 1: 3 and group 2: 5) required further treatment to control their IOP and were given pilocarpine. These people were not included in the final analysis. Additional outcomes: Side effects were few. One person complained of occasional hallucinations and 2 of tinnitus, which was temporary
			Mean ± SD diurnal IOP at 6 months (mmHg)	Group 1: 20.5 ± 4.3 (RE), 20.1 ± 3.2 (LE) Group 2: 20.1 ± 4.2 (RE), 21.2 ± 3.9 (LE) 95% CI: Not reported p value: 0.8 (RE); 0.4 (LE)		
			Mean ± SD diurnal IOP reduction from baseline at 6 months (mmHg)	Group 1: 6.4 ± 4.3 (RE), 6.7 ± 3.2 (LE) Group 2: 4.1 ± 4.2 (RE), 4.2 ±3.9 (LE) 95% CI: Not reported p value: 0.14 (RE); 0.04 (LE)		
			Mean ± SD diurnal IOP at 9 months (mmHg)	Group 1: 18.4 ± 4.4 (RE), 18.6 ± 2.9 (LE) Group 2: 17.5 ± 3.8 (RE), 19.1± 4.3 (LE) 95% CI: Not reported p value: 0.55 (RE); 0.71 (LE)		
			Mean ± SD diurnal IOP reduction from baseline at 9 months	Group 1: 8.5 ± 4.4(RE), 8.2 ± 2.9 (LE) Group 2: 6.7 ± 3.8 (RE), 6.3 ±4.3 (LE) 95% CI: Not reported		

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	M/F: 6/9 Mean IOP: 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) Dropouts: 5 (additional treatment was needed as pressure not adequately controlled by Timolol alone)		(mmHg)	p value: 0.22 (RE); 0.16 (LE)	
			Mean ± SD diurnal IOP at 12 months (mmHg)	Group 1: 20.0 ± 2.5 (RE), 20.8 ± 2.1 (LE) Group 2: 19.4 ± 2.3 (RE), 20.2 ± 3.6 (LE) 95% CI: Not reported p value: 0.49 (RE); 0.58 (LE)	
			Mean ± SD diurnal IOP reduction from baseline at 12 months (mmHg)	Group 1: 6.9 ± 2.5 (RE), 6.0 ± 2.1 (LE) Group 2: 4.8 ± 2.3 (RE), 5.1 ± 3.6 (LE) 95% CI: Not reported p value: 0.02 (RE); 0.40 (LE)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Netland 2001[489] Study design: RCT Double masked	People group: COAG and OHT Setting: Multi-centre USA Inclusion criteria: Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT IOP 24 – 36mmHg in same eye on 2 separate eligibility visits Women post-menopausal or	Group 1 Travoprost 0.004% in the evening, placebo in the morning Group 2 Timolol 0.5% 2 per day	Mean baseline diurnal IOP ± SD	Group 1: 25.5 ± Not reported Group 2: 25.7 ± Not reported Group 3: 25.7 ± Not reported	Funding: Alcon Research Ltd, which manufactures Travoprost. Limitations: Study provides detailed baseline data on 585 people but excludes
			Mean IOP reductions from baseline at 12 months	Group 1: 5.8 (08.00), 7.3 (10.00), 7.6 (16.00) Group 2: 5.0 (08.00), 5.8 (10.00), 5.8 (16.00) Group 3: 6.3 (08.00), 7.6 (10.00), 7.1 (16.00)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Evidence level: 1+ Duration of follow-up: 12 months	surgically sterilised Exclusion criteria: People who wear contact lenses Women of childbearing potential IOP >36mmHg Visual acuity worse than 0.60 LogMAR Chronic or recurrent inflammatory eye disease Ocular trauma in last 6 months Recent ocular infection or inflammation Ocular pathology preventing beta-blockers or PGAs Cup or Disc ratio >0.80 Recent ocular surgery Contraindications for beta-blockers – respiratory, cardiovascular, hepatic, renal People on adjunctive IOP lowering therapies All participants n=585 Group 1 n=197 Age (mean ±SD): 64 ± 13.3 M/F: 100/97	Group 3 Latanoprost 0.005% evening, placebo in morning Examination methods: 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by the same observer throughout the study by looking at photographs depicting ocular hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey	Mean IOP reductions from baseline mmHg at 12 months (end point –baseline	Group 1: 6.9 ± 6.87** Group 2: 5.53 ± 4.83** Group 3: 7.0 ± 6.87** (calculated as mean across 3 times)	those who were randomised but never started trial. However, adverse events % includes people who never started trial Additional outcomes: Detailed analysis of conjunctival hyperaemia Notes: *No discontinuations due to adverse events were reported but dropout numbers refer to those who were randomised into the trial but failed to start treatment. ** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[97], Martin 2007[426]and Mastropasqua 1999[432] Computer-generated randomisation
		Mean diurnal IOP reductions from baseline mmHg (expressed as a range)	Group 1: 6.6 – 8.1 Group 2: 4.7 – 7.1 Group 3: 6.2 – 8.1 p value compares difference between travoprost 0.004% and Timolol using ANOVA for repeated measures. p is <0.01 at all time points	
		Proportion of people reaching target of >30% reduction from baseline or ≤17 mmHg	Group 1: 54.7% Group 2: 39.0% Group 3: 49.6% not clear what people numbers were used	
		Total number of people with local ocular adverse events reported at incidence of >3%	Group 1: 219 Group 2: 93 Group 3: 121 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eyes and conjunctival hyperaemia	
		Increase in iris pigmentation and Eyelash changes	Group 1: 118 Group 2: 6 Group 3: 60	
		Number of people with cardiovascular	Group 1: 13	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	OHT: 67 COAG: 130 Black/non-black: 49/ 148 Dropouts: 3 *see notes Group 2 n=195 Age (mean ±SD): 64.8 ± 11.6 M/F: 107/88 OHT: 55 COAG: 140 Black/non-black: 40/155 Dropouts: 5 *see notes Group 3 n=193 Age (mean ±SD): 64.5 ± 11.6 M/F: 89/104 OHT: 59 COAG: 134 Black/non-black: 43/150 Dropouts: 3 * see notes		systemic side effects reported at incidence of >3%	Group 2: 9 Group 3: 7 Includes hypertension	sequence. People and examiners were masked to treatment allocation.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Orengo-Nania 2001[514]	People group: COAG or OHT Setting: Multi-centre	Group 1 Travoprost 0.004% 1 per day	Mean ± SD baseline diurnal IOP (mmHg)	Group 1: 25.0 ± Not reported Group 2: 25.2 ± Not reported	Funding: Alcon Research Ltd, manufacturers of

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Study design: RCT, masked (subjects, investigators and study staff) Evidence level: 1+ Duration of follow-up: 6 months	Inclusion criteria: Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma (PG), pseudoexfoliation glaucoma (PEX) or OHT Completed 3 weeks Timolol 0.05% 2times per day IOP in at least 1 eye of 24-36mmHg at 08.00 AND 21-36mmHg at 10.00 and 16.00hrs; all 3 measurements on 2 eligibility days Exclusion criteria: Best-corrected visual acuity worse than 0.6 LogMAR chronic or recurrent severe inflammatory eye disease ocular trauma in past 6 months ocular infection or ocular inflammation in past 3 months clinically significant progressive retinal disease inability to undergo applanation tonometry ocular disease precluding the use of beta-blockers or prostaglandins cup to disc ratio >0.8 in either eye severe central visual field loss intraocular surgery in past 6 months laser surgery in past 3 months severe hypersensitivity to study medications or 'vehicle'	and Timolol 0.5% 2 per day* Group 2 Placebo 1 per day and Timolol 0.5% 2 per day* Examination methods: Mean IOP measured by calibrated Goldmann applanation tonometer at 08.00, 10.00 and 16.00hrs for the people's eye with the highest reading. Hyperaemia measured by comparing photographs of subjects' eyes with a standard set of photographs depicting ocular hyperaemia.		p value: not significant	travoprost Limitations: Reporting of discontinuations was not clear for each group. 24 discontinued due to inadequate IOP control 21 in Timolol group and 3 across both travoprost groups. *Timolol was open label Additional outcomes: Data for travoprost 0.0015% not included in study (dosage not in BNF) Eyelash changes were mentioned; no one stopped treatment due to these. No reported iris pigmentation changes or clinical visible cystoid
			Mean IOP at end point (6 months)	Group 1: 19.6 (08.00), 18.3 (10.00), 18.9 (16.00) Group 2: 23.8 (08.00), 23.0 (10.00), 23.1 (16.00)	
			Mean diurnal IOP at end point (6 months)	Group 1: 18.9 ± Not reported Group 2: 23.3 ± Not reported (calculated as mean across 3 times)	
			Mean IOP reductions from baseline mmHg at 6 months (end point – baseline	Group 1: 6.1 ± Not reported Group 2: 1.9 ± Not reported p=0.0001 (ANOVA – repeated measures)	
			Percent of people with >6mmHg decrease in IOP OR <20mmHg at 6 months	Group 1: 73.0–86.9% Group 2: 23.1-43.3% (per protocol data)	
			Percent of people with acceptable decrease >30% in IOP OR <17mmHg at 6 months	Group 1: 55/114 (47.8%) Group 2: 11/112 (9.9%) p value groups 1 to 2: <0.0001 (per protocol data)	
			Number of ocular adverse events by group seen in >2% of any treatment group (Please note that some people may have had more than 1 adverse event)	Group 1: 78 Group 2: 34 Includes: aqueous flare, anterior chamber cells, blurred vision, discomfort, dry eye, foreign body sensation, hyperaemia, keratitis, lid disorder, pain, photophobia, pruritus, tearing, visual acuity decreased	
			Number of non-ocular adverse events by group	Group 1: 19	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	severe, unstable or uncontrolled cardiovascular, hepatic or renal disease in which the use of beta-blockers is contraindicated bronchial asthma or COPD Starting any medication that might affect IOP <1 month prior to study entry, glucocorticosteroid use during eligibility phase, current use of NSAIDs Glaucoma other than open angle or ocular hypertension Anterior chamber angle grade < 2 inability to use medication in both eyes Women who were not 1 year post-menopausal or had not been surgical sterilised 3 months before study All participants n=271 Group 1 n=145 Age (mean): 63.9 +11.1 M/F: 65/72 Dropouts: 8 Black/Non-black: 35/105 COAG/OHT: 123/14 Group 2	Hyperaemia and iris and eyelash changes were assessed by masked ophthalmologists.	seen in >2% of any treatment group (Please note that some people may have had more than 1 adverse event)	Group 2: 13 Includes: cold syndrome, infection, sinusitis, surgical or medical procedure, urinary tract infection.	macular oedema reported. Notes: All subjects who qualified stopped any ocular hypotensive medication (other than Timolol) and were placed on Timolol 0.05% 2 per day for 3 weeks. Run-in phase Computer-generated randomisation sequence. Allocation concealment was sealed but not in necessarily opaque envelopes.
			Number of people with hyperaemia (assessed on a scale. 1=none, 2=mild, 3=moderate, 4=severe. Mean hyperaemia score in all groups <0.50)	Group 1: 52/145 Group 2: 13/139 p value groups 1 to 2: <0.001	
			Reasons for withdrawals	Group 1: Not reported Group 2: Inadequate IOP control=21	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	n=139 Age (mean): 63.3 +11.3 M/F: 56/78 Dropouts: 5 Black/Non-black: 32/102 COAG/OHT: 121/13				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Ozturk 2007[518] Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 6 months	People group: COAG or OHT Setting: Ophthalmology clinic, Turkey Inclusion criteria: IOP >21mmHg without medication Washout period for topical medications prior to baseline visit (CAI – 1 week, beta-blockers – 4 weeks, prostaglandins – 6 weeks) Exclusion criteria: IOP >35mmHg History of chronic or recurrent inflammatory eye disease Ocular trauma Ocular infection Severe retinal disease	Group 1 Fixed combination of dorzolamide and Timolol (COSOPT, Merck, USA) 2 per day (concentrations not reported) Group 2 Bimatoprost 0.03% 1 per day Examination methods: IOP measured by calibrated Goldmann applanation tonometer. Mean	Mean ± SD baseline diurnal IOP mmHg	Group 1: 24.1 ± 2.1 (n=29) Group 2: 23.7 ± 2.0 (n=34) p value: 0.38	Funding: not reported Limitations: Adverse events poorly reported. Additional outcomes: Also reported IOP taken at 12.00hrs on day 15, and months 1 and 3. Notes: Investigators assessing IOP masked to treatments. † Reported adverse
			Mean ± SD diurnal IOP at 6 months mmHg	Group 1: 17.6 ± 2.9 (n=29) Group 2: 17.5 ± 2.3 (n=34) p value: 0.89	
			Mean reduction in IOP at 6 months	Group 1: 6.5 ± 2.3 (n=29) Group 2: 6.2 ± 1.8 (n=34) p value: 0.89	
			Number of ocular and systemic adverse events by group (some people had more than 1 ocular events)	Group 1: 11 Group 2: 28	
			Number of people with conjunctival hyperaemia	Group 1: 2/29 Group 2: 18/34 p value: 0.02	
			Number of people with breathlessness	Group 1: 0/29	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Previous intraocular or laser surgery Any condition preventing reliable applanation tonometry Use of any systemic medication that might affect IOP Unstable cardiopulmonary disease All participants n=65 Group 1 n=30 Age (mean): 64.9 (48-78) M/F: 15/14 Dropouts: 1 Family origin: Not reported Diagnosis: POAG: 22; ocular hypertension: 7 Group 2 n=35 Age (mean): 61.9 (48-75) M/F: 13/21 Dropouts: 1 Family origin: Not reported Diagnosis: POAG: 26; ocular hypertension: 8	of 3 consecutive measurements used. Bilateral POAG or OHT people had eye with higher IOP selected; if eyes had equal IOP, then right eye was selected. Measurements for baseline and 6-month visits taken at 08.00, 12.00 and 16.00hrs.		Group 2: 1/34 p value: 0.47	events: burning or stinging, conjunctival hyperaemia, bitter taste, dry eye, eyelid eczema, breathlessness
			Total number of dropouts	Group 1: 1/30 Group 2: 1/35 p value: 0.71	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Pfeiffer 2002[540] European Latanoprost Fixed Combination Study Group Study design: RCT Evidence level: 1+ Duration of follow-up: 6 months Plus a 6-month, open-label study with all people using the fixed combination of latanoprost and Timolol	People group: COAG or OHT Setting: multicentre study involving 37 centres Inclusion criteria: Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT Aged 18 or older IOP >25mmHg with prior therapy IOP >30mmHg without prior therapy Exclusion criteria: History of angle-closure glaucoma Previous ocular surgery, Argon laser trabeculoplasty, ocular inflammation or infection 3 months prior to pre-study visit People with a known hypersensitivity or contraindication to any component of study medicine All participants n=436 Age (mean): Not reported M/F: 196/240 Dropouts: 72 Family origin: Not reported Diagnosis: POAG: 336; pseudoexfoliative glaucoma: 22;	Group 1 Fixed combination of latanoprost 0.005% and Timolol 0.5% in the morning, placebo at night Group 2 Latanoprost 0.005% in the morning, placebo at night Group 3 Timolol 0.5% 2 per day Examination methods: IOP measured by calibrated Goldmann applanation tonometer at pre-study visit. Method of measurement for other visits not stated. Each	Mean ± SD baseline diurnal IOP mmHg	Group 1: 21.6 +3.8 (n=140) Group 2: 22.5 +4.0 (n=147) Group 3: 22.5 +4.1 (n=149)	Funding: Pharmacia Inc. Limitations: Adverse events poorly reported. Additional outcomes: Also reported mean diurnal IOP at week 2 and 13; number of people switching to open-label trial on fixed combination. Notes: † Reported ocular adverse events: eye irritation, visual field change (suspected), hypertrichosis, hyperaemia, vision decreased, increased iris pigmentation, corneal disorder, cataract, optic atrophy, conjunctivitis, iritis,
			Mean ± SD diurnal IOP at 6 months mmHg	Group 1: 19.0 +3.5 (n=140) Group 2: 20.4 +4.9 (n=147) Group 3: 21.4 +5.4 (n=149) p values 1 versus 2: 0.006 p values 1 versus 3: <0.001 p values 2 versus 3: 0.096	
			Mean change in diurnal IOP at 6 months mmHg	Group 1 to Group 2: -1.2 (95% CI: -1.8 to -0.5, p<0.001) Group 1 to Group 3: -1.9 (95% CI: -2.5 to -1.2, p<0.001)	
			Number of people reaching IOP <15mmHg at 6 months or up to treatment failure	Group 1: 14/140 (10.0%) Group 2: 8/147 (5.4%) Group 3: 7/149 (4.7%) p values 1 versus 2: 0.11 p values 1 versus 3: 0.07 p values 2 versus 3: 0.49	
			Number of people reaching IOP <18mmHg at 6 months or up to treatment failure	Group 1: 54/140 (38.6%) Group 2: 48/147 (32.7%) Group 3: 37/149 (24.8%) p values 1 versus 2: 0.17 p values 1 versus 3: 0.008 p values 2 versus 3: 0.09	
			Number of people reaching IOP <21mmHg at 6 months or up to	Group 1: 110/140 (78.6%) Group 2: 101/147 (68.7%)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	pigmentary glaucoma: 8; ocular hypertension: 64; mixed (different diagnosis in the two eyes): 6 Previous IOP reducing medication: 401 Group 1 n=140 Age (mean): 64 +13 M/F: 67/73 Dropouts: 12 Family origin: Not reported Diagnosis: POAG: 106; pseudoexfoliative glaucoma: 2; pigmentary glaucoma: 3; ocular hypertension: 27; mixed (different diagnosis in the two eyes): 2 Previous IOP reducing medication: Not reported Group 2 n=147 Age (mean): 63 +12 M/F: 77/70 Dropouts: 28 Family origin: Not reported Diagnosis: POAG: 112; pseudoexfoliative glaucoma: 13; pigmentary glaucoma: 4; ocular hypertension: 16; mixed (different	measurement taken 3 times in each eye. Measurements for each visit taken at 08.00, 10.00 and 16.00hrs. Also determined at each visit: best-corrected visual acuity and slit lamp examination. Refraction recorded, ophthalmoscopy performed and Colour Polaroid photographs taken at 6 months.	treatment failure	Group 3: 83/149 (55.7%) p values 1 versus 2: 0.21 p values 1 versus 3: <0.001 p values 2 versus 3: 0.01	change in refraction, blepharitis. Gives number of people for each adverse event. § Reported non-ocular adverse events: Cardiovascular disorder, influenza-like symptoms, metabolic disorders, respiratory disorders, cerebrovascular disorders, vertigo, sleep disorders, headache, liver/biliary disorders * People switched medications to the fixed combination used in for group 1 if treatment failure occurred. Treatment failure defined as increased IOP >10%
			Number of ocular adverse events by group seen in >1% of any treatment group (some people had more than 1 ocular events) §	Group 1: 34 Group 2: 41 Group 3: 21	
			Number of non-ocular adverse events by group seen in >1% of any treatment group (some people had more than 1 ocular events) §	Group 1: 22 Group 2: 18 Group 3: 19	
			Number of people with cardiovascular side effects	Group 1: 5/140 Group 2: 1/147 Group 3: 2/149 p value group 1 to 2: =0.24 p value group 1 to 3: =0.13 p value group 2 to 3: =0.58	
			Number of people with respiratory side effects	Group 1: 3/140 Group 2: 6/147 Group 3: 7/149 p value group 1 to 2: =0.36 p value group 1 to 3: =0.25 p value group 2 to 3: =0.80	
			Number of people not completing 6 months in	Group 1: 12/140 Group 2: 28/147	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	diagnosis in the two eyes): 2 Previous IOP reducing medication in last: Not reported Group 3 n=149 Age (mean): 64 +10 M/F: 52/97 Dropouts: 32 Family origin: Not reported Diagnosis: POAG: 118; pseudoexfoliative glaucoma: 7; pigmentary glaucoma: 1; ocular hypertension: 21; mixed (different diagnosis in each eye): 2 Previous IOP reducing medication in last: Not reported		randomised group *	Group 3: 32/149 p value group 1 to 2: =0.006 p value group 1 to 3: =0.001 p value group 2 to 3: =0.10	of the mean IOP from baseline and an IOP of >23mmHg on 2 examinations within 2 weeks. Study reported numbers by group. If treatment still did not work, participants were withdrawn.
			Number of people not completing 6 months in randomised group OR in open label trial	Group 1: 10/140 Group 2: 14/147 Group 3: 16/149 p values: not significant	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Polo 2005[544] Study design: RCT Evidence level:	People group: COAG Setting: Single centre Inclusion criteria: POAG and Psuedoexfoliative Glaucoma (PEX) People on monotherapy with beta=blocker Age >18 years	Group 1 Dorzolamide 2% 2 per day and Timolol 0.5% 2 per day Group 2 Latanoprost 0.005% 1 per day	Mean ± SD baseline diurnal IOP mmHg	Group 1: 23.8 ± 2.3 Group 2: 23.9 ± Not reported	Funding: Not reported. Conducted at Department of Ophthalmology, Hospital Universitario Miguel Servet, Zaragoza, Spain
			Mean ± SD end point diurnal IOP at 24 months	Group 1: 18.4 ± 1.9 Group 2: 15.9 ± 2.04	
			Mean ± SD reduction in IOP	Group 1: 5.4 ± 2.53**	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
1 + Duration of follow-up: 24 months	IOP ≥ 22 mmHg Optic nerve head showing signs of glaucomatous damage Exclusion criteria: Previous treatment of dorzolamide or latanoprost Ocular infection or inflammatory disease in the last 3 months Allergy to treatment medications or preservative Closed-angle glaucoma Previous ocular surgery or laser treatment in last 3 months Cardiovascular or bronchial disease Pregnant, nursing or people considering pregnancy All participants n=61 Group 1 n=30 Age (mean ± SD): 67.9 ± 11.2 M/F: 60%/40% eyes 1 eye/2 eyes: 2/28 Family history: 24% eyes POAG/PEX: 23/8 Dropouts: 26/58 eyes (45%) Group 2	Examination methods: At eligibility testing, automated perimetry (Humphrey 30-II STATPAC 2) was used to measure visual field, stereo photographs used to assess glaucomatous damage (including neuroretinal rim loss and haemorrhage), visual acuity, refraction, slit lamp examination also performed and IOP measurement technique was not specified. Examination schedule was at baseline, 2 weeks and every 3 months.	mmHg at 24 months (baseline – end point)	Group 2: 8.0 ± 1.94** p <0.05	Limitations: Randomisation method not explained and no allocation concealment Unmasked study, no placebo. 3 week run-in period on Timolol No dropout figures reported for people Not ITT analysis Additional outcomes: Notes: Data analyses use data per eye rather than people. ** Standard deviations (SD) for fixed versus monotherapy calculated using the Cochrane method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[518]
			Eyes reaching acceptable IOP of ≥ 20% reduction from baseline after 24 months (<21 mmHg) Figures estimated from Kaplan-Meier graph	Group 1: 17/30 (56%) Group 2: 37/45 (82%)	
			Total number of people reporting ocular side effects	Group 1: Not reported Group 2: Not reported	
			Total number of people reporting cardiovascular systemic side effects	Group 1: Not reported Group 2: Not reported	
			Reasons for withdrawals	Group 1: Not reported Group 2: Not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	n=31 Age (mean ± SD): 64.6 ± 19.1 M/F: 64%/36% eyes 1 eye/2 eyes: 3/28 Family history: 29% eyes POAG/PEX: 25/5 Dropouts: 14/59 eyes (24%)				(CAI and BB versus PGA)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Rismanchian 2008[572] Study design: RCT Observer masked Evidence level: 1+ Duration of follow-up: 6 months	People group: Newly diagnosed bilateral POAG Setting: single centre, ophthalmology department, Isfahan University of Medical Science, Feiz Hospital, Isfahan, Iran Inclusion criteria: Diagnosis of unilateral or bilateral POAG with either visual field defects or optic nerve damage and elevated IOP ≥ 22 mmHg Aged 18 or older No previous treatment Exclusion criteria: History of acute angle closure or occludable angles Contraindication to beta-blockers Ocular surgery or Argon laser trabeculoplasty History of asthma, COPD, cardiac failure, sinus	Group 1 Fixed combination of dorzolamide 2% and Timolol maleate 0.5% 2 per day. Group 2 Latanoprost 0.005% 1per day Examination methods: At baseline, best-corrected visual acuity, refraction, visual field testing, ophthalmoscopy, IOP measurement and slit lamp examination were performed. Goldmann applanation tonometry was used to measure IOP at 1, 3 and 6	Mean ± SD IOP at 6 months mmHg	Group 1: 22.9 ± 5.81 Group 2: 22.4 ± 5.42	Funding: Not reported Limitations: Randomisation method and allocation concealment not reported Dropouts were not reported, so it was unclear if all people completed the study. Notes: If both eyes qualified for the
			Mean ± SD change in IOP from baseline at 6 months mmHg	Group 1: 7.4 ± 2.32 Group 2: 7.1 ± 2.71 p value: 0.52 (calculated by NCC-AC team using t-test with equal variances and ITT analysis)	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	bradycardia, second or third degree atrioventricular block. Severe renal impairment and hyperchloremic acidosis Pregnant or breastfeeding women History of non-compliance or hypersensitivity to study medicine Use of systemic medications affecting IOP All participants N: 120 Age (mean ± SD): 57.3 ± 13.15 (range 21-80) M/F: 60/60 Dropouts: Not reported Group 1 n=60 Age (mean ± SD): 54.8 ± 15.49 (range 21-80) M/F: 28/32 Dropouts: Not reported Mean Cup disc ratio ± SD: 0.60 ± 0.15 Mean baseline IOP ± SD mmHg: 30.4 ± 6.58 Group 2 n=60 Age (mean ± SD): 52.7 ± 10.84 (range 35-80) M/F: 32/28 Dropouts: 0	months by same masked observer			study, the worse eye was used. No serious adverse events were observed.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Mean Cup disc ratio ± SD: 0.60 ± 0.08 Mean baseline IOP ± SD mmHg: 29.6 ± 5.81				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Schuman, 1997[599] Study design: RCT Evidence level: 1+ Double masked Duration of follow-up: 12 months	People group: POAG and OHT Setting: multi-centre, USA Inclusion criteria: Diagnosis of POAG or OHT and on no more than 2 glaucoma medicines Best-corrected visual acuity of 20/80 or better in each eye Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other Exclusion criteria: Active ocular disease Severe dry eye Corneal abnormalities Advanced glaucoma (C/D≥ 0.8) People who wear contact lenses Use of other ocular medications Surgery or laser surgery within 6 months	Group 1 Brimonidine 0.2% 2 per day Group 2 Timolol 0.5% 2 per day Examination methods: IOP was measured at trough – 12 hours after instillation of evening medication and at peak – 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup-to-disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each	Mean ± SD reduction in peak IOP mmHg (averaged over all time points to 12 months)	Group 1: 6.5 ± Not reported Group 2: 6.1 ± Not reported No significant difference between groups	Funding: Allergan Inc. Manufacturers of brimonidine Limitations: Study says it was a double-blind randomised trial (1:1), but the randomisation method is not stated. No mention of evaluators being masked in methods. Study reported that people were given medication in a masked fashion but no further details were available *Dropout rates were reported as % some as <1.0%, so it was difficult to calculate the numbers. In the context of adverse events, the study was biased towards Timolol as most people had already been taking Timolol and therefore
			Mean ± SD reduction in trough IOP mmHg (averaged over all time points to 12 months)	Group 1: 4.3 ± Not reported Group 2: 6.3 ± Not reported P is significant	
			Possible worsening of visual field (subset of people)	Group 1: 17/77 (22.1%) Group 2: 23/111 (20.7%)	
			Number of people reporting local ocular adverse events	Group 1: 325 Group 2: 238 Including stinging, blurring and allergic reactions, hyperaemia, photophobia, pruritus	
			Number of people reporting systemic adverse events	Group 1: 159 Group 2: 125 Includes dry mouth, fatigue or drowsiness and headache	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Uncontrolled hypertension or diabetes Women with childbearing potential Contraindications to beta-blockers or α adrenergic agonists Hypersensitivity to treatment medications Those who had participated in a previous trial within 30 days of the start of this study. All participants n=374 Age (mean ± SD): 63 ± 11 M/F: 50:50 Dropouts: Not reported* Group 1 n=186 Age (mean): Not reported M/F: Not reported Dropouts: 35 Group 2 n=188 Age (mean): Not reported M/F: Not reported Dropouts: 4	visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	*Reasons for withdrawals (dropouts) Data taken from Vass 2007[672] systematic review which reported dropout rates for study	Group 1: Local adverse events=25 Systemic adverse events=10 Group 2: Local adverse events=2 Systemic adverse events=2	tolerated the treatment much better than brimonidine. Additional outcomes: Schirmer tear test – significant changes from baseline for both grouped but no significant differences between groups Cup or Disc ratio – no significant changes from baseline or between groups Notes: Schuman 1996[597] reported intermediate results of Le Blanc 1998[372] (6 months of data) and Schuman 1997

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Sherwood2006[612] Study design: RCT Evidence level: 1+ Duration of follow-up: 12 months	People group: Bilateral COAG or OHT Setting: ophthalmology centre Inclusion criteria: Baseline IOP (after washout) between 24 and 34 mmHg in each eye with no more than 5 mmHg difference between eyes Best -corrected visual acuity of 20/100 Aged 18 and over Continuation of long-term systemic therapy that could affect IOP was allowed as long as doses were constant throughout the trial Exclusion criteria: Active ocular disease Functionally significant or progressive visual field loss in the previous year Abnormally low or high blood pressure or pulse rate Contraindications or sensitivity to any component of the study treatments Use of other topical medications or other therapies that might have a substantial effect on IOP Ocular surgery in previous 3 months Women not using 'effective means of contraception' or who were pregnant	Group 1 Fixed combination of brimonidine 0.2% and Timolol 0.5% 2 per day and placebo for third administration Group 2 Brimonidine 0.2% 3 per day* Group 3 Timolol 0.5% 2 per day and placebo for third administration Washout periods for previous medications: CAI and parasympathomimetic 4 days, sympathomimetics 2 weeks, beta-blockers and prostaglandins 4 weeks	Mean baseline diurnal IOP mmHg (08.00, 10.00, 15.00 and 17.00hrs)	Group 1: 24.7, 23.3, 22.1, 21.8 (n=385) Group 2: 24.9, 23.5, 22.5, 22.2 (n=382) Group 3: 25.0, 23.5, 22.5, 22.4 (n=392) p value: not significant	Funding: Allergan Inc. provided funding, had a primary role in study design, management and analysis of the data, and in the preparation of the manuscript. Limitations: No measurements given for IOP or IOP change throughout the study, only graphs shown. Additional outcomes: Notes: * Brimonidine 3 per day used to see whether the added dose of brimonidine provided additional IOP lowering effects. † Reported adverse
			Total number of people with treatment-related adverse events with an incidence of >5% in any group and a statistically significant between group difference †	Group 1: 204/385 Group 2: 240/382 Group 3: 160/392 p value group 1 to 2: =0.006 p value group 1 to 3: <0.001 p value group 2 to 3: <0.001	
			Total number of dropouts	Group 1: 99/385 Group 2: 169/382 Group 3: 58/392 p value group 1 to 2: <0.001 p value group 1 to 3: <0.001 p value group 2 to 3: <0.001	
			Number of dropouts due to adverse events	Group 1: 55/385 Group 2: 117/382 Group 3: 20/392 p value group 1 to 2: <0.001 p value group 1 to 3: <0.001 p value group 2 to 3: <0.001	
			'Treatment-related, serious' adverse events	Group 1: 0/385 Group 2: 0/382 Group 3: 2/392 (respiratory distress	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	or nursing All participants n=1,159 Age (mean): 62.6 (23-89) M/F: 518/641 Dropouts: 326 Family origin: White: 879; African-American: 187; Hispanic: 78; Asian: 11; Other 4 Diagnosis: POAG: 762; ocular hypertension: 384; mixed (different diagnosis in the two eyes): 13 Number of people requiring washout due to previous medication: 795 Group 1 n=385 Age (mean): 62.0 +12.2 M/F: 181/204 Dropouts: 99 Group 2 n=382 Age (mean): 63.8 +11.8 M/F: 151/231 Dropouts: 169 Group 3 n=392	Examination methods: IOP measured by calibrated Goldmann applanation tonometer. The mean of 2consecutive measurements were used for each eye. The median of 3 measurements for each eye was used if the first 2 measurements differed by >2mmHG. Each measurement of IOP was taken 4 times in each eye at 08.00, 10.00, 15.00 and 17.00hrs. Adverse events measured using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)		secondary to emphysema and tachycardia, sweating and nausea) p value: not significant	events: Conjunctival hyperaemia, ocular stinging, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, oral dryness, conjunctival allergy or inflammation (includes any combination of conjunctival hyperaemia, eye pruritus, follicular conjunctivitis, allergic conjunctivitis, conjunctivitis, chemical conjunctivitis, conjunctival oedema and blepharoconjunctivitis. Gives number of people for each adverse event. Significantly more events with fixed combination of brimonidine-Timolol than with
			Mortality	Group 1: 2/385 Group 2: 2/382 Group 3: 1/392 value: not significant	
			Total number of dropouts	Group 1: 99/385 Group 2: 169/382 Group 3: 58/392 p value group 1 to 2: <0.001 p value group 1 to 3: <0.001 p value group 2 to 3: <0.001	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 62.0 +12.3 M/F: 186/206 Dropouts: 58				Timolol alone for conjunctival allergy or inflammation adverse events.

Study	Siesky 2010[619]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=24)
Countries and setting	Conducted in USA; Setting: Indiana University, Bloomington, IN
Line of therapy	Not applicable
Duration of study	Intervention time: 8 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary open-angle glaucoma
Exclusion criteria	Not reported
Recruitment/selection of people	Not reported
Age, gender and family origin	Age – Mean (SD): POAG: 64 (10.3); Control: 49 (6.4). Gender (M:F): Not reported. Family origin: White: 16; Black: 5;

	Asian: 1
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: Beta-blockers – Timolol maleate. 0.5% twice daily. Duration 8 months. Concurrent medication or care: Not applicable (n=12) Intervention 2: Carbonic anhydrase inhibitors. Dorzolamide with Timolol twice daily. Duration 8 months. Concurrent medication or care: Not applicable
Funding	Other (Supported by a research study grant from Merck Pharmaceuticals, and in part by an unrestricted grant from Research to Prevent Blindness, New York, USA.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DORZOLAMIDE or TIMOLOL versus TIMOLOL MALEATE Protocol outcome 1: Intraocular pressure - Actual outcome: % change in intraocular pressure (right eye) at 8 months; Group 1 (SE): -14.68 (4.6); Group 2 (SE): -1.53 (4.6) Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Matched at baseline for age and gender; Group 1 Number missing: 1, Reason: Discontinued participation after initial baseline visit; Group 2 Number missing: 1, Reason: Discontinued participation after initial baseline visit - Actual outcome: % change in intraocular pressure (left eye) at 8 months; Group 1 (SE): -13.18 (4.92); Group 2 (SE): +1.25 (4.92) Risk of bias: All domain - High, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Matched at baseline for age and gender; Group 1 Number missing: 1, Reason: Discontinued participation after initial baseline visit; Group 2 Number missing: 1, Reason: Discontinued participation after initial baseline visit	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Adverse events of pharmacological treatments; Treatment adherence; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Strahlman 1995[638]	People group: COAG and OHT Setting: multi-centre, 34 sites	Group 1 Dorzolamide 2% 3 per	Mean ± SD baseline IOP mmHg reading at	Group 1: 25.2 ± 4.8 Group 2: 25.9 ± 5.3	Funding: Merck and Co Inc.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Study design: RCT Double masked Evidence level: 1+ Duration of follow-up: 12 months	Inclusion criteria: 21–85 years old Sufficient washout period for current medications Untreated IOP of ≥ 23 mmHg Contact lens wearing discontinued 3 weeks prior to study Exclusion criteria: People whose discontinuation of current treatment would cause glaucomatous damage People with corrected visual acuity of worse than 20/60 History of poor response to ocular hypotensive agents History of allergy to agents in trial Contraindications to beta-blockers Clinically significant dry eye syndrome Previous intraocular surgery Ocular trauma Recent ocular inflammation or infection Herpes simplex keratitis or corneal ulcer within 1 year Photophobia or diplopia Premenopausal, pregnant and nursing women	day Group 2 Timolol 0.5% 2 per day (+ placebo for afternoon dose) Group 3 Betaxolol 0.5% 2 per day (+ placebo for afternoon dose) Examination methods: Within each centre, investigators were instructed to use the same Goldman tonometer for all IOP measurements for a given population. IOP was measured at weeks 2 and 4 and months 2, 3, 6, 9 and 12. IOPs measured at 09.30, 12.30 and 15.30hrs Humphrey 24-2 or Octopus perimetry was used for the visual field testing at screening and months 6 and 12	12.30hrs	Group 3: 26.1 ± 5.7	Manufacturers of dorzolamide and Timolol Limitations: Randomisation method and allocation concealment not reported. Although the study states that it was a double-masked design, it was not clear whether the examiners were masked Some people received additional therapy (Timolol or dorzolamide) if IOP was not lowered effectively on monotherapy. The dropout numbers included all people. Notes: 3:1:1 randomisation People were masked
			Mean ± SD end point IOP reading at 12.30hrs 12 months	Group 1: 20.5 ± 5.0 Group 2: 19.9 ± 4.0 Group 3: 20.9 ± 5.4	
			Mean ± SD reduction in IOP mmHg at 12 months (baseline – end point) reading at 12.30hrs	Group 1: 4.7± 4.1 Group 2: 6.0 ± 4.2 Group 3: 5.2 ± 4.9	
			Number of people reporting local ocular side effects	Group 1: 195 Group 2: 44 Group 3: 47 Includes itching, stinging, vision disturbance, eyelid discomfort, conjunctivitis	
			Number of people reporting bitter taste	Group 1: 85 Group 2: 7 Group 3: 9	
			Number of people with cardiovascular systemic side effects	Group 1: 8 Group 2: 8 Group 3: 9 Includes hypertension, angina, tachycardia	
			Reasons for withdrawals (dropouts)	Group 1: Inadequate IOP control=10 Adverse events=37 Administration=14 Group 2: Inadequate IOP control=1	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Concomitant use of systemic beta-blockers or CAIs which may affect IOP All participants n=523 Age (mean): 64 (range 17-85) M/F: 243/280 Dropouts: 89 Group 1 n=313 Age (mean ± SD): 62.1 ± 11.6 M/F: 136/177 Black/non-black: 4/309 OHT/COAG: 120/220* Dropouts: 61 Group 2 n=103 Age (mean ± SD): 63.8 ± 11.4 M/F: 53/50 Black/non-black: 2/101 OHT/COAG: 44/68* Dropouts: 13 Group 3 n=107 Age (mean ± SD): 60.7 ± 12.0			Adverse events=6 Administration=6 Group 3: Inadequate IOP control=6 Adverse events=3 Administration=6	to treatment assignment.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	M/F: 54/53 Black/non-black: 3/104 OHT/COAG: 33/83* Dropouts: 15 * based on eye rather than people				

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Tomita 2004[657] Study design: RCT Single masked Evidence level: 1+ Duration of follow-up: 3 years	People group: NTG Setting: multi-centre (3 sites) Japan Inclusion criteria: Untreated IOP ≤ 21 mmHg Evidence of optic nerve head change and VF changes Best-corrected visual acuity ≥ 15/20 – no media opacities Refractive errors not exceeding -8 or +6D MD Humphrey not exceeding -12.0dB Discontinuation of previous glaucoma treatments of 4 weeks Exclusion criteria: History of ocular, rhinological, neurologic or systemic disorders accounting for optic	Group 1 Latanoprost 0.005% 1 per day Group 2 Timolol 0.5% 2 per day Examination methods: Average of 2 IOP measurements adopted for baseline IOP. Goldmann tonometry used. Subsequent IOP measurements were taken every month at 09.00 before morning dose. Humphrey perimetry used for visual field defects every 6 months.	Mean ± SD baseline IOP mmHg	Group 1: 15.0 ± 1.6 Group 2: 15.9 ± 2.0	Funding: Not reported but study conducted by the Department of Ophthalmology, University of Tokyo. Gifu University of Medicine and Yamanashi University School of Medicine. Limitations: Open label study Additional outcomes: Notes: No data on adverse events Randomly assigned to
			Mean ± SD end point IOP (3 years) mmHg	Group 1: 12.9 ± 2.2 Group 2: 14.0 ± 2.0	
			Mean ± SD reduction in IOP mmHg at 3 years (baseline – end point)	Group 1: 2.1 ± 2.35** Group 2: 1.9 ± 2.17** p value Not reported not significant at any time point using repeated measure ANOVA	
			% reduction both groups	13-15% p value Not reported not significant at any time point using repeated measure ANOVA or t test	
			Mean ± SD baseline Mean deviation for VF dB	Group 1: -6.0 ± 2.1 Group 2: -5.9 ± 2.3	
			Mean ± SD end point Mean deviation for VF	Group 1: -6.3 ± 3.2 Group 2: -5.6 ± 2.9	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	nerve head damage History of haemodynamic crisis Previous surgery or laser treatment in either eye All participants n=62 Age (mean): Not reported M/F: Dropouts: 15 (24%) Group 1 n=31 Age (mean ± SD): 56 ± 10 M/F: 14/17 Dropouts: 8 Group 2 n=31 Age (mean ± SD): 54.3 ± 8.5 M/F: 15/16 Dropouts: 7	If VF measurement did not meet reliability criteria, it was repeated after 1 month. Abnormal VF at least 3 adjacent test points. Stereoscopic optic disc photographs taken every 6 months and analysed using 3D image analysis programme.	dB (3 years) Estimated rate of change of MD ± SE value per year	 Group 1: -0.34 ± 0.17 Group 2: -0.10 ± 0.18 p value: Not significant	groups using a computer-generated list kept in a sealed envelope. Optic disc stereo photographs were analysed by a masked observer. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426] (bimatoprost)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Tsai, 2005[664]	People group: POAG	Group 1 Brimonidine 0.2% 2 per	Mean ± SD baseline diurnal IOP mmHg	Group 1: 24.2 ± 1.3 Group 2: 23.9 ± 1.1	Funding: Conducted at Chang

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Study design: RCT Evidence level: 1 + Duration of follow-up: 12 months	Setting: single centre, China Inclusion criteria: Diagnosis of bilateral POAG Best-corrected visual acuity of 20/50 or better in each eye Untreated IOP between 22 and 30 mmHg in each eye >35 years old Exclusion criteria: History of previous glaucoma medicine in previous 4 weeks Previous laser or surgical treatments Co-existing retinal disease or non-glaucomatous optic neuropathy Corneal abnormalities Lens opacity worse than NC3/NO3 VF loss > 20dB Diabetes mellitus Pregnancy or childbearing potential Contraindications or hypersensitivity to either of the medicine in trial All participants n=44	day Group 2 Timolol 0.5% Gel (Timoptic) 1 per day at 08.00 Examination methods: IOP measured using Perkins applanation tonometry every 2 months. At 12 months, VF examined using Humphrey perimetry. RNFL thickness measured using scanning laser polarimetry			Gung Memorial Hospital, Taiwan, Republic of China Limitations: Open label and examiners not masked. IOP reduction and visual field progression were not primary outcomes Additional outcomes: RNFL thickness significantly decreased from baseline for Timolol compared to brimonidine
			Mean ± SD end point diurnal IOP (12 months) mmHg	Group 1: 18.6 ± 0.9 Group 2: 18.7 ± 1.1	
			Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 5.6 ± 0.8 Group 2: 5.3 ± 0.5 p value: between group using ANOVA for repeated measures=0.16	
			Number of people with local ocular side effects	Group 1: Not reported Group 2: Not reported	
			Number of people with cardiovascular systemic side effects	Group 1: Not reported Group 2: Not reported	
			Reasons for withdrawals (dropouts)	Group 1: Inadequate IOP control=2 Allergic blepharoconjunctivitis=1 Group 2: Inadequate IOP control=2	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Age (mean): Not reported M/F: Not reported Dropouts: 5 Group 1 n=22 Age (mean): 61.9 ± 8.6 M/F: Not reported Dropouts: 3 Group 2 n=22 Age (mean): 60.0 ± 9.4 M/F: Not reported Dropouts: 2				

Study	Varma 2010[671]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=FC: 278; Latanoprost: 287; Timolol: 289)
Countries and setting	Conducted in Germany and USA; Setting: 38 sites in the USA and 37 sites in Germany
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months

Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women 18 years of age or older with unilateral or bilateral primary open-angle, pigmentary or pseudoexfoliation glaucoma, or with ocular hypertension, were eligible if the pre-study IOP was ≥ 30mmHg without ocular hypotensive medication or ≥ 25mmHg with prior therapy
Exclusion criteria	Not reported
Recruitment or selection of people	Not reported
Age, gender and family origin	Age – Mean (SD): FC: 62.3 (12.8); Latanoprost– 63.2 (12.2); Timolol– 63.8 (11.6). Gender (M:F): Male: FC – 134; Latanoprost – 145; Timolol – 132. Family origin: White: FC – 229, Latanoprost – 242, Timolol – 239; African-American: FC – 38, Latanoprost – 37, Timolol – 35; Other: FC – 11, Latanoprost – 8, Timolol – 15
Indirectness of population	No indirectness
Interventions	(n=278) Intervention 1: Fixed combination solutions - Prostaglandin analogue with beta-blockers. Latanoprost and Timolol once per day. Duration 6 months. Concurrent medication or care: Not applicable (n=287) Intervention 2: Prostaglandin analogues - Latanoprost. Once daily. Duration 6 months. Concurrent medication or care: Not applicable (n=289) Intervention 3: Beta-blockers – Timolol maleate. Twice daily. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Study funded by industry (Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROSTAGLANDIN ANALOGUE WITH BETA-BLOCKERS versus LATANOPROST	

Protocol outcome 1: Intraocular pressure - Actual outcome: Change in diurnal IOP fluctuation from baseline at 26 weeks; Group 1 (SE): -0.68 (0.22); Group 2 (SE): 0.11 (0.22) Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROSTAGLANDIN ANALOGUE WITH BETA-BLOCKERS versus TIMOLOL MALEATE Protocol outcome 1: Intraocular pressure - Actual outcome: Change in diurnal IOP fluctuation from baseline at 26 weeks; Group 1 (SE): -0.68 (0.22); Group 2 (SE): 0.36 (0.22) Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LATANOPROST versus TIMOLOL MALEATE Protocol outcome 1: Intraocular pressure - Actual outcome: Change in diurnal IOP fluctuation from baseline at 26 weeks; Group 1 (SE): 0.11 (0.22); Group 2 (SE): 0.36 (0.22) Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Adverse events of pharmacological treatments; Treatment adherence; Quality of life (validated score)

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Vass 2007[672] Study design: Systematic Review Evidence level: 1++	People group: All people with Ocular Hypertension (POAG people included but all the studies in this category were in OHT people). Inclusion criteria:	Group 1 Beta-blocker Group 2 Placebo or no treatment.	Incidence of visual field defect progression: (OHT people)	Group 1 (beta-blocker): 45/469 (9.6%) Group 2 (placebo/untreated): 64/466 (13.7%) Peto OR: 0.67 (95% CI: 0.45, 1.00); 8 studies Heterogeneity: Chi^2=4.00, df=6 (P=0.68), I^2=0%	Funding: Department of Ophthalmology and Clinical Pharmacology, University of Vienna Limitations: IOP change from baseline not reported as an outcome Quality assessment not reported

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Duration of follow-up: Minimum treatment 12 months (range 12 months to 10 years).	Minimum treatment duration 1 year. People with a mean IOP above 21 mmHg. Exclusion criteria: People with Normal Tension Glaucoma. Trials excluded on methodology if graded inadequate on allocation concealment. All participants n= 4,979 from 26 trials Age (mean): Not reported M/F: Not reported Dropouts: Not reported White: 2,907; African: 562; Hispanic: 59; Asian: 15 Family origin was not reported for 16 of the trails included in the systematic review Sample range: 18-1,636		Sensitivity analysis Dropouts due to medicine-related adverse events: Long-term studies concerning incidence of visual field progression (follow-up of at least 3 years):	Group 1: 18/253 Group 2: 26/246 OR: 0.64 (95% CI: 0.34, 1.19); 4studies Heterogeneity: Chi²=0.17, df=2 (P=0.92), I²=0% Group 1: 17/255 Group 2: 14/248 Peto OR: 1.24 (95% CI: 0.59, 2.58); 4 studies Heterogeneity: Chi²=2.05, df=2 (P=0.36), I²=2.4% Group 1: 44/444 Group 2: 62/438 Peto OR: 0.67 (95% CI: 0.45, 1.01); 6 studies Heterogeneity: Chi²=3.91, df=5 (P=0.56), I²=0%	in detail for each trial Additional outcomes: Interclass comparisons. Sensitivity analysis also conducted to determine the effect of excluding trials falling below a quality threshold with either exclusion of trials scoring C (inadequate) on any aspect of methodological trial quality or exclusion of trials that had assumed that both eyes within an individual were independent (fellow eye used as a control group). Notes: Studies included in Vass 2007 that do not meet guideline inclusion criteria because eyes were randomised Wishart & Batterbury, 1992 and Kass et al., 1989

RCTs included in VASS 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - participants	Age (mean/ range)	Mean Baseline IOP mmHg	% African-Caribbean /% Family History	Quality Check	Notes
Epstein et al., 1989 [US][186]	Timolol 0.5% 2 per day versus no treatment	5 years	Glaucoma Clinical Centre and MSD	OHT	107	60	BB: 24.0 ± 1.3 NT: 23.9 ± 1.6	10/62	Randomisation Method: Not reported Allocation concealment: No Masked outcome assessment: Yes Incomplete outcome data: No Moderate risk of bias	No IOP figures, estimate from graph. Open label No previous treatment. VF defects using Goldmann or Octopus perimeters
Heijl & Bengtsson, 2000 [Sweden][264]	Timolol 0.5% 2 per day versus placebo	10 years	MSD, Järnhardt Foundation and Malmö Hospital	OHT (30% PEX or PG)	90	63	BB: 27.1 ± Not reported NT: 26.2 ± Not reported	Not reported / 38	Randomisation method: Yes Allocation concealment: Yes Masked outcome assessment: Yes Incomplete outcome data: No Low risk of bias	Eyes with previous anti-glaucoma therapy were permitted with a washout of 2 weeks.
Kamal et al., 2003 [UK][310]	Betaxolol 0.5% 2 per day versus placebo	5 years	Guide Dogs for the Blind, Blue Light Fund and Alcon	OHT	356	66 (>35)	BB: 26.3 ± 2.3 NT: 25.6 ± 2.2	Not reported / Not reported	Randomisation method: Yes Allocation concealment: Yes Masked outcome assessment: Yes Incomplete outcome data: No Low risk of bias	No previous treatment. Conversion to glaucoma defined by AGIS criteria
Kitazawa, 1990 [Japan][337]	Timolol 0.5% 2 per day versus	2 years	Not reported	OHT	20	Not reported	Not reported	Not reported / Not reported	Randomisation method: Not reported Allocation concealment: Not reported	No IOP data. Study does not report whether treatment was first option

RCTs included in VASS 2007 that meet guideline inclusion criteria										
STUDY	**Intervention**	**Duration**	**Funding**	**Population Disease severity**	**Size N - participants**	**Age (mean/ range)**	**Mean Baseline IOP mmHg**	**% African-Caribbean /% Family History**	**Quality Check**	**Notes**
	placebo								Masked outcome assessment: Not reported Incomplete outcome data: No High risk of bias	VF defects using Humphrey perimeter
Schulzer et al., 1991 [Canada][596]	Timolol 0.25% - 0.5% 2 per day versus no Treatment	6 years	MSD and Canadian MRC	OHT	137	60 (>45)	BB: 26.3 ± 3.5 NT: 26.1 ± 3.2	Not reported / 31	Randomisation method: Not reported Allocation concealment: Not reported Masked outcome assessment: Yes Incomplete outcome data: No Moderate risk of bias	Open label No previous treatment. VF defects using Goldmann or Octopus perimeters
Schwartz et al., 1995 [US][600]	Timolol 0.5% 2 per day versus placebo	1 to 2 years	MSD	OHT (43% PEX or PG)	37	60	BB: 23.1 ± 2.5 NT: 23.7 ± 3.6	8 / 22	Randomisation method: Yes Allocation concealment: Not reported Masked outcome assessment: Yes Incomplete outcome data: No Low risk of bias	Results by presented by eye No previous treatment. VF defects using Goldmann perimeter

Study details	**Participants**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Vetrugno 2004[674] Study design: RCT Unmasked Evidence level: 1 + Duration of follow-up: 6 months	People group: POAG only Setting: single centre, Italy Inclusion criteria: Diagnosis of POAG Age 40-60 People who do not smoke IOP < 16 mmHg after 12 months pre-treatment with Timolol Refraction ± 3 D ≥ 0.1 in study eye > 10% reduction of pulsatile ocular blood flow pOBF after 12 months pre-treatment with Timolol Systolic brachial pressure 120 – 140 mmHg Diastolic brachial pressure 70-90 mmHg Heart rate 66-80 bpm BMI normal Normal blood haematological test results Exclusion criteria: Cardiovascular abnormalities (atherosclerosis, carotid stenosis) Use of systemic vasoactive therapy (beta-blockers, Ca agonists, nitroglycerin derivatives) Types of glaucoma other than	Group 1 Bimatoprost 0.3 % 1 per day at 21.00 Group 2 Timolol 0.5% 2 per day Examination methods: IOP and pOBF measured at 09.00 each study visit. pOBF measured on a tonograph but IOP measurement methods not reported	Mean ± SD baseline diurnal IOP mmHg	Group 1: 17.00 ± 1.69 Group 2: 16.75 ± 2.38	Funding: Author reported that the study was not funded by the industry. Limitations: The study was actually looking at the effect of bimatoprost on people where their IOP has already been lowered effectively with Timolol. Open label study. Treatments were not masked – may affect reporting of adverse events. Outcome assessment was not masked either but same investigator carried out all the tests. Small study Additional outcomes: pOBF mean ± SD Notes: No serious adverse events were noted in either group but adverse events were not reported for Timolol
			Mean ± SD end point diurnal IOP (6 months) mmHg	Group 1: 13.5 ± 1.31 Group 2: 15.75 ± 1.67	
			Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 3.5 ± 1.84** Group 2: 1.0 ± 2.28** p value compares IOP at end point between groups (not reduction) p using unpaired t test is < 0.01	
			Conjunctival hyperaemia and itching	Group 1: 5 Group 2: 0	
			↑ periorbital pigmentation and eyelash changes	Group 1: 2 Group 2: 0	
			Number of people with cardiovascular systemic side effects	Group 1:=Not reported Group 2:=Not reported	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	POAG All participants n=38 Age (mean ± SD): 51.7 ± 4.8 M/F: 22/16 Family origin: Not reported Dropouts: 0 Group 1 n=19 Age (mean ± SD): 52.1 ± 5.01 M/F: 12/7 Dropouts: 0 Group 2 n=19 Age (mean ± SD): 51.2 ± 4.12 M/F: 10/9 Dropouts: 0				**Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426](bimatoprost) Computer-generated randomisation sequence.

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
Watson 1996[681] Study design: RCT Double	People group: COAG and OHT Setting: Multi-centre – 14 centres, UK Inclusion criteria: Age ≥ 40 years old	Group 1 Latanoprost 0.005% 1 time per day night and placebo	Mean ± SD baseline diurnal IOP mmHg	Group 1: 25.2 ± 3.4 Group 2: 25.4 ± 3.6	Funding: Supported by Pharmacia (now Pfizer), Sweden which manufactures
			Mean ± SD end point diurnal IOP (6 months)	Group 1: 16.7 ± 2.6	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
masked Evidence level: 1+ Duration of follow-up: 6 months	Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. Completion of adequate washout period for sympathomimetics, CAI and miotics. Exclusion criteria: People on topical beta-blockers within 6 months of study Angle closure glaucoma history Ocular trauma Previous filtration or laser surgery for glaucoma within 6 months of study Dry eye syndrome Ocular inflammation or infection within 3 months of the study People who wear contact lenses Those with contraindications for beta-blockers Women of childbearing potential and nursing mothers People who would not benefit from monotherapy All participants n=294 Age (mean): 65 ± 10 M/F: 191/103 Dropouts: 26 (8.8%) Family origin: White: 285; Black: 9	morning for 6 months Group 2 Timolol 0.5% 2 times per day morning and evening for 6 months Examination methods: IOP measured by Goldmann Applanation Tonometry - 3 readings taken at each visit (09.00, 13.00, 17.00hrs) and mean taken for statistical analysis. Blood and urine samples taken at baseline and last visit. Iris photography taken Visual Field analysis	mmHg	Group 2: 17.1 ± 2.6	latanoprost Limitations: It was not clear whether the analysis of IOP was calculated on an ITT basis. Additional outcomes: Detailed analysis of conjunctival hyperaemia Notes: **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[426] (bimatoprost) Computer-generated randomisation sequence. People and examiners were
			Mean ± SD reduction in diurnal IOP mmHg at 6 months (baseline – end point)	Group 1: 8.5 ± 3.68** Group 2: 8.3 ± 3.47** p value Not reported – not significant (using covariate analysis)	
			% reduction in IOP at end point of 6 months	Group 1: 33.7 Group 2: 32.7	
			Number of people with local ocular side effects	Group 1: 215 Group 2: 158 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Number of people with ↑ iris pigmentation	Group 1: 2 Group 2: 0	
			Number of people with cardiovascular systemic side effects	Group 1: 32 Group 2: 28 Includes respiratory infection, bronchitis, arterial hypotension, angina and shortness of breath	
			Reasons for withdrawals (dropouts)	Group 1: Inadequate IOP control=2 Local side effects=2 Breathing problems=1 Bad compliance or lost people=6 Contraindicated prescription=1 Group 2: Breathing or respiratory problems=3	

Study details	Participants	Interventions	Outcome measures	Effect size	Comments
	Group 1 n=149 Age (mean): 64.7 ± 9.5 M/F: 98/51 Dropouts: 12 Family origin: White: 143; Black: 6 OHT only: 80 COAG or COAG and OHT: 69 Group 2 n=145 Age (mean): 65.3 ± 10.5 M/F: 93/52 Dropouts: 14 Family origin: White: 142; Black: 3 OHT only: 68 COAG or COAG and OHT: 77			Arterial hypotension or bradycardia=2 Headaches=2 Local side effects=5 Previous Timolol=1 Self-withdrawal=1	masked to treatment allocation.

Study	Whitson 2013[688]
Study type	RCT (People randomised; Parallel)
Number of studies (number of participants)	1 (n=679)
Countries and setting	Conducted in the USA; Setting: 65 academic and private practice study sites throughout the USA
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months

Method of assessment of guideline condition	Adequate method of assessment or diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18 years of age with a clinical diagnosis of open-angle glaucoma or ocular hypertension in at least 1 eye. Intraocular pressure had to be between 24mmHg and 36mmHg at the 08.00 time point and between 21mmHg and 36mmHg at the 10.00 time point at both eligibility visits. All IOP readings in both eyes at both eligibility visits had to be 36mmHg or less.
Exclusion criteria	People were excluded if they had a history of ocular trauma or intraocular surgery within the past 6 months or ocular infection, inflammation, or laser surgery within the past 3 months. They were also excluded if they had any form of glaucoma other than open-angle glaucoma; chronic, recurrent, or severe inflammatory eye disease; central corneal thickness > 620micrometres in either eye; Shaffer angle grade <2 in either eye; cup or disc ratio >0.80 (horizontal or vertical measurement) in either eye; severe central visual field loss in either eye, defined as sensitivity ≤ 10 decibels in at least 2 of 4 visual field test points closest to the point of fixation; clinically significant or progressive retinal disease; corrected distance visual acuity worse than 0.6 LogMAR; or other ocular pathology that could preclude administration of an alpha-adrenergic agonist or a topical carbonic anhydrase inhibitor. People could also not have a recent history of taking medications prohibited during the study, including high-dose salicylate therapy within 4 weeks of the first eligibility visit and any medications or substances used on a chronic basis that could affect IOP and that had not been on a stable dosing regimen for at least 30 days before the screening visit; current use of any prohibited medications, including monoamine oxidase inhibitors, psychotropic medicine that augment an adrenergic response and any additional ocular hypotensive medications; history of active, severe, unstable, or uncontrolled systemic disease precluding safe administration of a topical alpha-adrenergic agonist or carbonic anhydrase inhibitor; hypersensitivity to alpha-adrenergic agonist medicine, topical or oral carbonic anhydrase inhibitors, sulphonamide derivatives or any component of the study medications; or any condition requiring treatment with glucocorticoids, unless the glucocorticoid could be safely discontinued during the study. Women could not be pregnant, lactating, or of childbearing potential (unless they were abstinent or using a highly effective method of birth control).
Age, gender and family origin	Age – Mean (SD): 64.9 (10.4). Gender (M:F): Not reported. Family origin: White: 529 (77.9%); Black: 130 (19.1%); Asian: 9 (1.3%); Multiracial: 3 (0.4%); Other: 8 (1.2%)
Indirectness of population	No indirectness
Interventions	(n=218) Intervention 1: Fixed combination solutions – Carbonic anhydrase inhibitors with sympathomimetics. Brinzolamide 1% and brimonidine 0.2%. Duration 6 months. Concurrent medication or care: Not applicable

	(n=229) Intervention 2: Carbonic anhydrase inhibitors. Brinzolamide 1%. Duration 6 months. Concurrent medication or care: Not applicable (n=232) Intervention 3: Sympathomimetics - Brimonidine tartrate. Brimonidine 0.2%. Duration 6 months. Concurrent medication or care: Not applicable
Funding	Other (Alcon Research Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS WITH SYMPATHOMIMETICS versus CARBONIC ANHYDRASE INHIBITORS

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 14/218, Group 2: 1/229

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 27
- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 5/218, Group 2: 1/229

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 27

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS WITH SYMPATHOMIMETICS versus BRIMONIDINE TARTRATE

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 14/218, Group 2: 5/232

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 57
- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 5/218, Group 2: 3/232

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 57

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CARBONIC ANHYDRASE INHIBITORS versus BRIMONIDINE TARTRATE

Protocol outcome 1: Adverse events of pharmacological treatments
- Actual outcome: Adverse events: allergic reaction at 6 months; Group 1: 1/229, Group 2: 5/232

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 58; Group 2 Number missing: 57

- Actual outcome: Adverse events: hyperaemia at 6 months; Group 1: 1/229, Group 2: 3/232 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 27; Group 2 Number missing: 57	
Protocol outcomes not reported by the study	Visual field defect; Optic nerve damage; Vision loss; Intraocular pressure; Treatment adherence; Quality of life (validated score)

H.5.2 Laser treatment for COAG

Table 3: Laser treatment for COAG

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rolim & Paranhos, 2007[575] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum treatment 6 months but collected outcomes at 12 and 24	**Patient group:** POAG, primary & secondary pigmentary glaucoma, pseudoexfoliative glaucoma. **Inclusion criteria**: Any age, gender or nationality. RCTs only comparing laser trabeculoplasty with no intervention, with medical treatment, with surgery or comparing different modalities. **Exclusion criteria**: Studies with OHT patients **Primary Outcomes:** Failure to control IOP	**Comparison 2:** Argon laser trabeculoplasty (ALT) v medication in newly diagnosed participants **Studies included**: Gandolfi 2005, Moorfields (Migdal) 1994. **Comparison 3:** ALT v medication in participants already on maximal medical therapy. **Studies included**: Moriarty 1988 and Sherwood 1987. **Comparison 4:** ALT v trabeculectomy **Studies included:** AGIS 2002, Watson 1984 and Moorfields (Migdal) 1994.	**Comparison 2:** ALT v medication in newly diagnosed participants		**Funding:** Not stated. Conducted at the Universidade Federal de São Paulo, Brazil **Limitations:** Excludes OHT patients **Notes:** Literature search date to June 2007. Studies included in Rolim 2007 that are excluded from guideline **Bergea 1992** as both study arms received
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and Gandolfi 2005	***Relative Risk at 0-24 months*** Moorfields 1994 1.36 (95% CI: 0.50, 3.66) ***Relative Risk at 0 – 5 years*** Moorfields 1994 1.83 (95% CI: 0.93, 3.61) ***Relative Risk at 3-4 years*** Gandolfi 2005 1.20 (95% CI: 0.46, 3.15) (data not presented in Rolim)	
			Bronchial reactivity	Gandolfi. At 3 and 4 years there was a tendency for a reduced risk ratio in the ALT group but the figure was not statistically significant.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
months where possible.	Failure to stabilise visual field Failure to stabilise optic neuropathy **Secondary Outcomes:** Necessity of adding or changing therapy or intervention when IOP is uncontrolled Adverse Events (severe/minor) including: IOP spikes, Uveitis, cyclitis, hypoema, PAS formation, corneal oedema, persistent IOP elevation, loss of vision, bronchial spasm Quality of life measures Economic data	**Comparison 6:** Selective laser trabeculoplasty (SLT) v ALT **Studies included:** Damji 2006 Comparisons 2, 3, 4 and 6 are relevant to the clinical question "What is the effectiveness (and comparative effectiveness) of Laser Trabeculoplasty (ALT or SLT) in lowering IOP in patients with suspected or definite COAG (including POAG & NTG) **Intervention Details:** ALT mainly performed with 50 µm spot, 50 – 100 burns, 0.8 to 2.0 Watts.0.1 sec exposure. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in Watson 1984, AGIS, Moorfields (Migdal) 1994 and Damji 2006 ***Performance Bias*** - care providers and recipients could not be masked to intervention in most comparisons so criteria was	**Comparison 3:** ALT + Medication v Medication		additional stepped medications including with timolol and acetazolamide. **Glaucoma Laser Trial (GLT)** because fellow eyes were randomised to ALT or medications
			Failure to Control IOP ≥21mmHg for Sherwood 1987 and ≥ 22mmHg for Moriarty 1988	***Relative Risk at 0-24 months*** Sherwood 1987 1.08 (95% CI: 0.02, 0.31) ***Relative Risk at 0-24 months*** Moriarty 1988 0.41 (95% CI: 0.22, 0.77)	
			Comparison 4: ALT v trabeculectomy		
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and need for second intervention in sequence	***Relative Risk at 0-6 months*** AGIS & Moorfields 3.4 (95% CI: 1.60, 6.18) ***Relative Risk at 0-24 months*** AGIS & Moorfields 2.03 (95% CI: 1.38, 2.98)	
			Optic neuropathy progression	Optic disc was photographed in Moorfields and Watson study but not reported	
			Comparison 6: Selective laser trabeculoplasty (SLT) v ALT		
			Failure to Control IOP	***Relative Risk at 12 months*** Damji 2006 1.27 (95% CI: 0.84, 1.90)	
			Mean ± SD score of flare in anterior chamber	SLT – 1.00 ± 0.6 ALT – 0.8 ± 0.6. Not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		not used ***Detection Bias*** - assessment of outcomes masked for AGIS and Gandolfi 2005 ***Attrition Bias*** – ITT analysis performed for AGIS and Damji 2006 and follow up described. Watson 1984 did not report loss to follow up. Moorfields (Migdal) 1994 was not an ITT analysis.			

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

Table 4:RCTs included in ROLIM 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
AGIS 2002[1] [USA]	TAT v ATT	5 years	National Eye Institute, NIH, USA	Advanced POAG	591 (789)	67 median (35 - 80)	ALT: 24.0 ± 4.7 Trab: 24.6 ± 6.1	56 / 38	Selection: A Detection: D Attrition – FU: A Attrition – ITT: A Low risk of bias	Rolim includes results after 1st intervention in sequence only. Data obtained from study authors. Failure criterion is need for 2nd intervention in sequence
Damji et al., 2006[158] [Canada]	SLT V ALT	12 months	Lumenis (manufacturer of SLT)	COAG Uncontrolled IOP > 16 mmHg on max medication (38% previous ALT)	152 (176)	69.1 ± 10.52	ALT: 23.4 ± 4.2 SLT: 23.8 ± 4.9	NR/ NR	Selection: A Detection: D Attrition – FU: B Attrition – ITT: A Low risk of bias	Patients remained on current medications throughout follow up. Unacceptable IOP criteria ≥ 20 mmHg
Gandolfi et al., 2005[219] [Italy]	ALT V Timolol 0.5% 2/day	4 years	Research, Science & technology University, Rome	POAG with IOP ≥ 22 mmHg	32	44-67	ALT: 24.5 ± 2.0 Meds: 24.4 ± 1.5	NR/ NR	Selection: B Detection: D Attrition – FU:B Attrition – ITT: A Low risk of bias	Looks at respiratory adverse events but reports change in IOP from baseline. Number of patients with unacceptable IOP > 22mmHg excluded from study.
Migdal et al., 1994[449] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 years	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: D Attrition – FU: A Attrition – ITT: B Low risk of bias	Data obtained from study authors Pilocarpine included in medications Unacceptable IOP criteria ≥ 22 mmHg

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Moriarty et al., 1988[466] [Jamaica]	ALT + Medication V Medication	12 months	NR	POAG with IOP ≥22mmHg	30 (48)	62 (27-77)	ALT: 32.3 ± NR Meds: 29.2 ± NR	100/NR	Selection: B Detection: D Attrition – FU: C Attrition – ITT: A High risk of bias	Medication - pilocarpine 4% & oral acetazolamide 250mg; 4 patients also used timolol 0.5% Unacceptable IOP criteria ≥ 22 mmHg
Sherwood et al., 1987[613] [UK]	ALT + Medication V Medication	35 (30-40) months	Locally organised research scheme (GMC)	POAG with IOP >21mmHg	25 (50)	72.54 (50-90)	ALT: 23.8 ± NR Meds: 23.8 ± NR	NR/NR	Selection: A Detection: D Attrition – FU:A Attrition – ITT: A Low risk of bias	Medication - between minimum of 2 and maximum of 4 of the following: timolol, pilocarpine, sympathomimetics and acetazolamide Failure criteria ≥ 21 mmHg
Watson et al., 1984[682] [UK]	ALT v Trab	6 months	2 UK hospitals (Addenbrookes + Sunderland Eye Infirmary)	Severe COAG or evidence of progression not responding to medications	61 (95)	70 (38 – 86)	Site 1 ALT: 25.2 ± 5.5 Trab: 30.4 ± 8.6 Site 2 ALT: 33.7 ± 10.1 Trab: 39.5 ± 10.6	NR/ NR	Selection: A Detection: D Attrition – FU: C Attrition – ITT: C Moderate risk bias	Reports change in IOP from baseline for each treatment by hospital

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

H.5.3 Surgical treatment for COAG

Table 5: Trabeculectomy vs. pharmacological treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Burr et al., 2004[90] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum length of follow-up was 12 months.	**Patient group:** POAG, NTG, pigmentary glaucoma, Pseudo-exfoliative glaucoma. **Inclusion criteria**: Any gender or nationality >18 years only **Possible interventions:** Trabeculectomy ± MMC or 5F Non-penetrating surgery ± MMC or 5F Other surgery including drainage Trans-scleral cytophotocoagulation (TSCPC) **Exclusion criteria:** Studies where medical arm included laser. **Primary Outcomes:** Progressive visual field loss according to criteria described for each trial Quality of Life	**Comparison 2:** Medications v trabeculectomy **Intervention Details:** **Surgery** Trabeculectomy in 3 Studies. Migdal 1994 (Moorfields Trial), Jay 1988 (Glasgow trial), Lichter 2001 (CIGTS trial) **Medications** Migdal 1994 (Moorfields Trial)- miotics, Sympathomimetic or beta-blocker + oral CAI Jay 1988 (Glasgow trial) - miotics, Sympathomimetic or beta-blocker + oral CAI Lichter 2001 (CIGTS trial) – Beta blockers + other not specified. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in	**Comparison 1:** Medications v Scheie's procedure ***(no longer performed)***		**Funding:** Non industry funded (Cochrane Review). **Limitations:** Includes Studies with miotics (pilocarpine). Outcome assessment was not masked Migdal 1994 (Moorfields) and Jay1988 (Glasgow trial) were not ITT analyses as the treatment failures had been excluded. **Notes:** Literature search date to August 2003. An updated search was run in February 2005 but no new studies were found. **Additional Outcomes:**
			Comparison 2: Medications v trabeculectomy		
			Progressive Visual Field Loss (Mean change in visual field score from baseline)	**Jay 1988 (Glasgow trial)** At 4.6 years mean follow-up 27/57 medical patients and 13/50 trab patients had progressed by at least one stage. **Migdal 1994 (Moorfields Trial)** Friedman Visual field analysis 3.92 (95% CI: 2.02 – 5.82) favours Trab. Signif Humphrey automated perimetry (introduced 2yrs after start of study) Medical: 25/40 (63%) progressed Trab:34/48 (71%) progressed OR:0.69 (95% CI: 0.29 – 1.67) No significant difference **Lichter 2001 (CIGTS trial)** VF Score change from baseline – 1yr -0.5 (95% CI: -1.10 – 0.10) VF Score change from baseline – 5yr 0.30 (95% CI: -0.45 – 1.05) No significant difference at 1 or 5yrs ANOVA Mean VF score difference between treatment groups over follow up time -0.36 (95% CI: -0.67 to -0.05)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Secondary Outcomes: Change in IOP Progression of optic disc or nerve fibre damage Reduction of LogMAR score ≥ 0.3 (Snellen visual acuity ≥ 2 lines) Adverse Events (severe/minor) including: mortality, loss of eye due to infection or inflammation, severe irreversible reduction in vision, visually significant cataract, incidence of cataract surgery, need for additional surgery or medication, transient decrease in central vision from complications, systemic side effects (cardiovascular and COPD, CNS defects), local side effects (eye irritation, watering, redness, discomfort) Economic data	Lichter 2001 (CIGTS trial), Jay 1988 (Glasgow trial), Migdal 1994 (Moorfields Trial), ***Performance Bias*** - NR ***Detection Bias*** - Assessment of outcomes was not masked for any of the Studies apart from QoL in CIGTS – telephone administered questionnaire ***Attrition Bias*** Jay 1988 (Glasgow trial): 25/57 in medication group and 30/50 not available for final analysis. IOP analysis not ITT Migdal 1994 (Moorfields Trial): IOP and VF analysis not ITT. Lichter 2001 (CIGTS trial): at 5 years 37/607 lost to follow-up. Analysis was ITT		Adjusting for cataract mean VF: -0.28 (95% CI: -0.59 to 0.03) No significant difference Logistic Regression (adjusting for baseline VR, age, sex, race, diagnosis, diabetes and time in study) Risk of progressive VFL of at least 3 units from baseline between treatment groups: OR= 0.74 (95% CI: 0.54 – 1.01) Adjusted for cataract: OR = 0.75 (95% CI: 0.55 – 1.02) No significant difference	Optic disc change (Jay 1988) Health related quality of life in Lichter 2001 (CIGTS trial) Economic measures in Migdal 1994 (Moorfields Trial) Visual Acuity Loss (All studies) Burr 2004 reported OR for VF progression for CIGTS and also Number of patients with unacceptable IOP for Moorfields but did not did not actual dichotomous outcome figures so they could not be included in the meta-analysis. Jampel et al., 2005[293] paper describes perioperative
			Mean reduction in IOP from baseline mmHg	**Jay 1988 (Glasgow trial) [short term only]** 6.0 (95% CI:2.64 – 9.36) **Migdal 1994 (Moorfields Trial)** **Short term** (51/56 Medical/Surgery) 6.2 (95% CI: 3.92 – 8.48) **Medium term** (50/56 Medical/Surgery) 1.6 (95% CI: -0.69 – 3.89) **Long term** (46/56 Medical/Surgery) 3.4 (95% CI: 1.04 – 5.76) [Both above studies exclude failures from the point of failure]. **Lichter 2001 (CIGTS trial)** At year one (595 pts) 3.6 (95% CI: 2.78 – 4.42) Favours Trab Signif At 5 years (384 pts) 1.9 (95% CI: 0.85 – 2.95)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				Favours Trab. No significant difference.	complications for the CIGTS study and reports number of trabs with no augmentation = 177/465 eyes, Number with 5FU = 266/465 eyes and number with MMC = 22/465 eyes
			Adverse Events	**Mortality** **Jay 1988 (Glasgow trial)** At last follow up (mean 4.6yrs) 12/112 (14%) of recruited pts died. 7in the medical group, 8 in the Trab group and 1 unknown. **Severe irreversible reduction in vision** **Jay 1988 (Glasgow trial)** At one year, 6/46 (13%) eyes in the medical group had lost central fixation and in the following 2 years, a further 2 in the same group. No pts in the Trab group lost central fixation over mean follow up of 33 months. **Visually significant cataract** **Total from all Studies** 57/403 for trabeculectomy 24/416 for medications. RR: 2.45 (95% CI: 1.55 to 3.87)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Table 6: RCTs included in BURR 2004 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Jay & Murray, 1988[296] Glasgow [UK]	Trab v Medical	7yrs max (mean 4.6yrs)	NR	Newly diagnosed POAG 65% moderate 35% severe	107 50 Trab 57 Meds	NR	Meds: 37.8 ± NR Trab: 37.8 ± NR	0/ NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Pilocarpine included in medication* *Treatment failures excluded from analysis*
Lichter et al., 2001[399] CIGTS [USA]	Trab v Medical	Min 5 yrs	Non industry – National Institutes of Health, National Eye Institute grants	91% POAG (mean visual field defects 4.8units on a scale of 0 to 20) C/D range 0.6-0.7 Mild glaucoma	607 300 Trab 307 Meds	57.5 (range 28-75)	Meds: 27 ± NR Trab: 27 ± NR	44 / NR	Selection: A Detection: C Attrition – FU: A Attrition – ITT: A Low risk of bias	*Main medication was beta-blockers*
Migdal et al., 1994[450] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 yrs	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Data obtained from study authors* *Pilocarpine included in medications* *Failure criteria ≥22 mmHg* *Treatment failures excluded from analysis*

Cochrane Quality Assessment Grades: A =Acceptable, B=Unclear, C=inadequate

Evidence Table 1 Trabeculectomy plus pharmacological augmentation vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wilkins et al., 2005[690] Study design: Systematic Review Evidence level: 1++ Duration of follow-up: Minimum follow up 12 months	Patient group: POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc. 3 population sub-groups considered: High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. Primary trabeculectomy Inclusion criteria: RCTs with intraoperative Mitomycin C (MMC) administered at any concentration or dose compared to placebo or control. Primary Outcomes: Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP despite additional	Intervention Details: Surgery was performed with or without Mitomycin C delivered intraoperatively at concentrations of 0.1 – 0.5 mg/ml saline for between 1 and 5 minutes. Quality Assessment: *Selection Bias* – randomisation and allocation concealment was graded as A adequate, B unclear or C inadequate, only studies with A or B were included *Performance Bias* - checking whether recipients or those providing care were masked to treatment allocation. If not then study deemed as high risk of bias.	Failure at 12 months Primary Trabeculectomy (338 patients)	Costa 1996, Martini 1997, Robin 1997, Szymanski 1997 Relative Risk: 0.37 in favour of MMC Signif. (CI 95% 0.26 – 0.51) p value: 0.00004	Funding: MRC and Moorfields Eye Hospital Limitations: Includes trials a proportion of patients with closed-angle glaucoma (CACG). Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc. Notes: Latest literature search to March 2005 Studies included in Wilkins 2005 that are excluded from guideline Andreanos 1997 includes high patients with previous surgery Carlson 1997 includes combination cataract surgery Shin 1995 includes combination cataract surgery Shin 1998 includes high patients with previous surgery and combination cataract surgery Cohen 1996 includes CACG but proportion is not defined
			Mean IOP at 12 months Primary Trabeculectomy	Costa 1996, Martini 1997, Szymanski 1997 Weighted Mean Difference: 5.41 mmHg in favour of MMC Signif. (CI 95% 7.34 – 3.49) p value: <0.00001 Robin 1997 did not report IOP at 12 months	
			Wound leak	Primary Trabeculectomy Szymanski 1997 Odds Ratio: 1.65 in favour of control Not signif. (CI 95% 0.16 – 17.47) p value: 0.7	
			Hypotony	Primary Trabeculectomy Costa 1996, Martini 1997, Szymanski 1997 Odds Ratio: 1.05 in favour of control Not signif. (CI 95% 0.23 – 4.68) p value: 1.0	
			Expulsive Haemorrhage	*No events reported*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	medications) Mean IOP at 12 months Secondary Outcomes: Wound leaks detected by positive Seidel test Hypotony IOP < 5 mmHg Late endophthalmitis infection Expulsive or choroidal haemorrhage Shallow anterior chamber Cataract – reduction in optical clarity Quality of Life assessments and patients perspectives	*Detection Bias* - checking whether assessment of outcomes was masked. If not then study deemed as high risk of bias. *Attrition Bias* – checking whether analysis was done on an ITT basis and if rates of follow up were similar in each group. If not then study deemed as high risk of bias.	Cataract	Primary Trabeculectomy Costa 1996, Martini 1997, Szymanski 1997, Robin 1997 Relative Risk: 1.93 in favour of control Not signif. (CI 95% 0.98 – 3.80) p value: 0.6	Turacli 1996 – includes 17% closed-angle glaucoma patients & 22% secondary glaucomas (congenital, neovascular etc) Wu 1996 – secondary glaucomas (congenital, neovascular etc)
			Shallow Anterior Chamber	Primary Trabeculectomy Costa 1996, Martini 1997 Odds Ratio: 1.14 in favour of control Not signif. (CI 95% 0.42 – 3.07) p value: 0.8	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wormald et al., 2001[694] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum follow up 12 months	**Patient group:** POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc. 3 population sub-groups considered: High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. Primary trabeculectomy **Inclusion criteria**: RCTs with postoperative 5-Fluorouracil (5-FU) administered injections at any concentration or dose compared to placebo or control. **Primary Outcomes:** Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP > 22 mmHg despite additional medications)	**Intervention Details:** Surgery was performed with or without postoperative injections of 5-FU in 0.1 or 0.5 ml saline solution **Quality Assessment:** A quality score was applied to each study Clear description of inclusion/exclusion criteria (YES-1/NO-0) Was study randomised? (YES with description-2/ONLY STATED – 1/NO-0) Was study double blind? (YES with description-2/ONLY STATED – 1/NO-0) Was there a description of withdrawals & dropouts? (YES-1/NO-	Failure at 12 months Primary Trabeculectomy (338 patients)	Goldenfeld 1994, Ophir 1992 Relative Risk: 0.21 in favour of 5-FU Signif. (CI 95% 0.06 – 0.68) p value: 0.009	**Funding:** Moorfields Eye Hospital **Limitations:** Includes trials a proportion of patients with closed-angle glaucoma (CACG). Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc. **Notes:** Latest literature search to January 2008 – no new studies to add Studies included in Wormald 2001 that are excluded from guideline **Gandolfi 1997** includes combination cataract surgery **Loftfield 1991** conference abstract **FFSSG 1996** 32% Secondary angle-closure glaucoma and 33% other types including secondary open-angle, pigmentary glaucoma and
			Mean IOP at 12 months Primary Trabeculectomy	Goldenfeld 1994, Ophir 1992 Weighted Mean Difference: 4.67 mmHg in favour of 5-FU Signif. (CI 95% 2.74 – 6.60) p value: <0.00001	
			Wound leak	Primary Trabeculectomy Goldenfeld 1994, Ophir 1992 Relative Risk: 0.47 in favour of 5-FU Not Signif. (CI 95% 0.04 – 4.91) p value: 0.5	
			Hypotonous maculopathy	Primary Trabeculectomy Goldenfeld 1994, Relative Risk: 2.82 in favour of control Not Signif. (CI 95% 0.12 – 66.62)	
			Endophthalmitis	*No events reported*	
			Cataract	Primary Trabeculectomy Chaudhry 2000 Relative Risk: 6.00 in favour of control Not signif. (CI 95% 0.76 – 47.49)	
			Shallow Anterior Chamber	Inconsistently reported among trials	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Secondary Outcomes: Wound leaks detected by positive Seidel test Hypotony IOP < 5 mmHg Late endophthalmitis infection Expulsive or choroidal haemorrhage Shallow anterior chamber Corneal and conjunctive epithelial erosions	0) Were statistics methods described? (YES-1/NO-0) Allocation concealment was also assessed as A-adequate, B-unclear, C-inadequate			primary angle closure glaucoma (proportions not specified) **O'Grady 1993** includes combination cataract surgery **Ruderman 1987** includes 69% secondary glaucomas (congenital, neovascular etc.) **Wong 1994** includes combination cataract surgery

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egbert et al., 1993[179] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** Mean approx. 9 months	**Patient group:** West African patients with advanced POAG, CACG & traumatic glaucoma **Setting:** single centre - Ghana **Inclusion criteria:** Non-phakic glaucoma **Exclusion criteria:** NR **<u>All patients</u>** **N:** 59 (61 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** NR **<u>Group 1</u>** **N:** 31 **Age (mean ± SD):** 58.9 (range 22-83) **M/F:** 23/8 **Eyes with previous operations**: 4 **Mean IOP:** 33.4 (range 16-76) **Drop outs:** NR	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 50 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Preoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry, gonioscopy and ophthalmoscopy. ***Postoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry Day 1, and over 1st week. Other follow-up visits were irregular.	**Mean IOP at final visit (mean follow-up 9 months)**	**Group 1:** 24.5 (range 4-74) **Group 2:** 17.3 (range 6-35) **p value:** 0.05 (Mann-Whitney U test)	**Funding:** Partially funded by Research to Prevent Blindness - USA **Limitations:** West African population only Includes 4% CACG patients & 4% traumatic glaucoma patients 61 eyes started study but only 55 were included in the analysis. Dropouts per group not reported. Follow up time is limited. Complications such as bleb infections could increase in the 5-FU group with longer follow up. Randomisation method, allocation concealment and masking of outcome assessment were not mentioned. **Additional outcomes:** Visual acuity
			Number of eyes with acceptable IOP (<20 mmHg without medications at 12 months	Group 1: 10/31 Group 2: 17/24 p value: 0.02 signif.	
			Number of eyes with unacceptable IOP >20mmHg at end point (9 mths)	Group 1: 21/31 Group 2: 7/24 p value: NR	
			Number of eyes with unacceptable IOP >15mmHg at end point (9 mths)	Group 1: 26/31 Group 2: 13/24 p value: NR	
			Number of patients on postoperative medications	Group 1: 16 (46%) Group 2: 5 (24%) p value: 0.02 (Chi-squared) signif.	
			Hyphaema	Group 1: 1/31 Group 2: 0/24 p value:	
			Cataract progression	Group 1: 3/31 Group 2: 4/24 p value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 24 **Age (mean ± SD):** 60.6 (range 36-76) **M/F:** 12/12 **Mean IOP:** 29.2 (range 18-46) **Drop outs:** NR		Flat anterior chamber	Group 1: 2/31 Group 2: 2/24 p value:	**Notes:** No postoperative 5FU injections were performed
			Conjunctival wound leak	Group 1: 2/31 Group 2: 4/24 p value: Not signif.	
			Corneal epithelial defects	Group 1: 0/31 Group 2: 0/24 p value:	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Leyland et al., 2001[392] **Study design:** RCT **Evidence level:** 1+ Double blind **Duration of follow-up:** 30	**Patient group:** POAG, chronic closed-angle glaucoma & pseudoexfoliative glaucoma **Setting:** single centre - UK **Inclusion criteria:** POAG, CACG (13%), PXF Established disc cupping and glaucomatous field loss Uncontrolled IOP ≥ 18 years **Exclusion criteria:** Other glaucomas such as congenital, uveitic, traumatic Previous surgery Laser treatment within last 6 months Pregnant women **<u>All patients</u>** **N:** 39 (43 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>**	**Group 1** Trabeculectomy + 0.9% Sodium Chloride for 5 minutes on surgical sponge **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 25 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Postoperative:*** Visual acuity, bleb appearance, IOP, lens clarity and fundus appearance monitored at each visit at 1 day, 1 week, 1, 3, 6, 12 months.	**Mean IOP at 12 months**	**Group 1:** 15.3 ± NR **Group 2:** 14.7 ± NR **p value:** Not signif.	**Funding:** NR **Limitations:** Includes 5/40 (13%) CACG patients Primary outcomes not reported **Additional outcomes:** Bleb analysis **Notes:** 1 postoperative 5FU injections was performed on a patient in group 1 Double blind study with allocation concealment
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	Group 1: NR Group 2: NR p value:	
			Cataract progression (late surgery)	Group 1: 4/17 Group 2: 5/23 p value:	
			Shallow anterior chamber	Group 1: 3/17 Group 2: 7/23 p value: 0.06	
			Conjunctival wound leak	Group 1: 3/17 Group 2: 7/23 p value:	
			Corneal punctate epithelial keratopathy	Group 1: 3/17 Group 2: 5/23 p value:	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 17 **Age (mean ± SD):** 66.7 ± 11.4 **M/F:** 10/7 **Mean IOP:** 28.1 ± 6.8 **Visual Field (Mean Db):** -15.1 ± 10.1 **Drop outs:** 2 **Group 2** **N:** 23 **Age (mean ± SD):** 64.8 ± 12.2 **M/F:** 10/7 **Mean IOP:** 27.7 ± 5.7 **Visual Field (Mean Db):** -14.4 ± 9.1 **Drop outs**: 1				

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
RASHEED, 1999[563] **Study design:** RCT (single blind) **Evidence level:** 1 + **Duration of follow-up:** 18 months	**Patient group:** POAG & CACG **Setting:** single-centre - Egypt **Inclusion criteria:** Bilateral POAG or CACG (16%) uncontrolled on medical therapy **Exclusion criteria:** None detailed **<u>All patients</u>** **N:** 25 (50 eyes) **Age (mean):** 50.3 ± 14.1 **M/F:** 12/13 **Mean IOP:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 25 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.1 ± 3.14 **Pre-op Medications**: 3.7 ± 0.3 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Mitomycin C. 0.3 – 0.4 mg/ml for 4 minutes depending on risk of failure **Examination methods:** Not clearly stated but infer that IOP, changes in optic disc and VF progression measured.	**Mean IOP during last 6 months of study (months 12-18)**	**Group 1:** 16.1 ± 5.1 **Group 2:** 10.2 ± 3.9 **p value:** NR	**Funding:** NR **Limitations:** Includes 4/25 (16%) CACG patients States as single blind though no details given Some discrepancies in the statistical tests Allocation concealment and masking of outcome assessment not reported **Additional outcomes:** Argon laser suture lysis **Group 1:** 21/25 **Group 2:** 13/25 **Notes:** Computerised randomisation Fellow eyes randomised
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	Group 1: 12/25 (48%) Group 2: 21/25 (84%) p value: NR *p = 0.016 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with unacceptable IOP >20mmHg at 12 months	Group 1: 17/25 Group 2: 7/25 p value: NR	
			Hyphaema	Group 1: 2/25 Group 2: 2/25 p value:	
			Cataract progression	Group 1: 1/25 Group 2: 1/25 p value:	
			Wound leak	Group 1: 3/25 Group 2: 10/25 p value: 0.44 (Chi-squared) *p = 0.051 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Bleb scarring	Group 1: 6/25 Group 2: 1/25 p value: 0.04 (Chi-squared)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): see above **M/F:** see above **Mean IOP:** 28.0 ± 3.19 **Pre-op Medications**: 3.7 ± 0.6 **Drop outs**: 0			*p = 0.1 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Table 7: Summary of RCTs included in WORMALD 2001 and WILKINS 2005 that met guideline inclusion criteria

STUDY	Intervention MMC	Duration (months)	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Costa et al., 1996[140] [Brazil]	0.2 mg/ml for 3 minutes v Placebo	18	NR	Medically uncontrolled POAG + *14% CACG*	28 (28)	67.0	MMC: 26.35 ± 6.68 Placebo: 24.92 ± 7.07	32 / NR	Allocation concealment – B unclear	Primary trabeculectomy Randomisation unclear Double masked Failure criteria >15 mmHg without medication
Goldenfeld et al., 1994[238] [Israel]	5 x 1/day 5 mg injections over first 15 postoperative days	20	Partially by Research to Prevent Blindness	Medically uncontrolled POAG or PXF	62 (62)	67.3 range (46 - 84)	5-FU: 25.0 ± 6.22 NT: 27.4 ± 12.05	10 / NR	Quality Score = 4 Allocation concealment – B unclear	Randomisation was adequate but, allocation concealment and masking of outcome assessment were not reported. Failure criteria >21 mmHg with medications
Martini et al., 1997[430] [Italy]	0.1 mg/ml for 3 minutes v NT	12	NR	Medically uncontrolled COAG	48 (60)	65.5	MMC: 28.8 ± 7.4 NT: 28.4 ± 9.2	NR / NR	Allocation concealment – B unclear	Computer randomisation Investigator masked Failure criteria >18 mmHg with or without medication. Some patients had previous laser treatment
Ophir & Ticho 1992[513] [Israel]	5 x 1/day 5 mg injections over first 10 postoperative days	18	NR	Medically uncontrolled POAG + 18% CACG	50 (50)	63.2	5-FU: 25.7 ± 2.1 NT: 25.9 ± 2.4	48 / NR	Quality Score = 1 Allocation concealment – B unclear	Randomisation, allocation concealment and masking of outcome assessment were not reported. Failure criteria >20 mmHg with medications
Robin et al., 1997[574] [USA]	MMC 1 - 0.2 mg/ml for 2 mins MMC 2 - 0.2 mg/ml for 4	12	NR	Medically uncontrolled COAG + *39% CACG*	300 (300)	57	T: 29.1 ± NR MMC 1: 28.1 ± NR MMC 2: 30.6 ± NR MMC 3: 30.9 ± NR	NR / NR	Allocation concealment –A adequate	Double masked study Failure criteria >19 mmHg with or without medication. Some patients had previous laser treatment

	mins MMC 3 – 0.4 mg/ml for 2 mins									
Szymanski et al., 1997[649] [Poland]	0.2 mg/ml or 0.5 mg/ml for 5 min v Placebo	18	NR	Medically uncontrolled POAG	29 (29)	47.8	All: 21.6 ± 4.2	NR / NR	Allocation concealment – B unclear	Randomisation, allocation concealment, masking of outcome assessment not reported. IOP control is not primary outcome Failure criteria >15 mmHg with medication

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Table 8: Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Singh et al., 1997[623] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** mean 10.0±4.41 months (difference between groups p=0.70)	**Patient group:** West African POAG patients **Setting:** Cape Coast Christian Eye Clinic, Ghana **Inclusion criteria:** Diagnosis of POAG based on visual acuity, slit lamp examination, Goldmann applanation tonometry, gonioscopy and post dilation ophthalmoscopy **Exclusion criteria:** NR **<u>All patients</u>** **N:** 81 **Age (mean ± SD):** 53.6 P-value for diff = 0.73 **M/F:** 49/32 P-value for diff = 0.29 **Mean IOP:** 30.1 (17-55) P-value for diff = 0.46 **Drop outs:** 0	**Group 1** Primary trabeculectomy with intraoperative use 0.5mg/ml MMC for 3.5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Group 2** Primary trabeculectomy with intraoperative use 50 mg/ml 5-FU for 5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Examination methods:** 90-diopter lens at the slit lamp examination and applanation tonometry. Indirect ophthalmoscopy was reserved for eyes with unexplained vision loss or shallow anterior chamber. Visits were at 3, 7, and 14	**Mean (range) IOP at follow-up (mmHg) at mean follow-up of 10 months**	**Group 1:** 13.7 (2-30) **Group 2:** 16.3 (4-36) **p value:** 0.05 (Chi-square test)	**Funding:** NR **Limitations:** Patients and medical staff were not kept blind Only partially applicable (West African patients) Only 81 of the 85 patients randomised were followed up for at least 3 months postoperatively. **Notes:** The surgical technique and postoperative care did not vary for individual surgeons based on choice of antimetabolites. Randomisation by coin flipping prior to surgery **Additional outcomes:** 22/44 in the MMC group and 23/37 in the
			IOP success (with or without medications – not explicitly stated) at mean follow-up of 10 months	IOP < 21mmHg Group 1: 41/44 (93.2%) Group 2: 27/37 (73.0%) p value: 0.01 (Chi-square test) IOP < 18mmHg Group 1: 31/44 (70.5%) Group 2: 21/37 (56.8%) p value: 0.21 (Chi-square test) IOP < 15mmHg Group 1: 28/44 (63.6%) Group 2: 19/37 (51.4%) p value: 0.26 (Chi-square test)	
			Number of patients with unacceptable IOP (with or without medications – not explicitly stated) at mean follow-up of 10 months	IOP > 21mmHg Group 1: 3/44 (93.2%) Group 2: 10/37 (73.0%) p value:	
			Proportion of patients taking IOP-lowering	Group 1: 10/44 Group 2: 9/37	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 44 **Age (mean ± SD):** 54.1 **M/F:** 29/15 **Mean IOP:** 30.7 (20-47) **Drop outs:** 0 **Group 2** **N:** 37 **Age (mean ± SD):** 52.7 **M/F:** 20/17 **Mean IOP:** 32.0 (22-45) **Drop outs:** 0	days postoperatively.	medication at final follow-up	p value: 1 (Fisher's exact calculated by NCC-AC)	FU group had preoperative visual acuity of 6/60 or worse in the treated eye. .
			Eyes with no change in postoperative visual acuity	Group 1: 32/44 Group 2: 27/37 p value: 0.96 (Chi-square test)	
			Eyes with more than two-line decrease in visual acuity	Group 1: 6/44 Group 2: 7/37 p value: 0.53 (Chi-square test)	
			Flat anterior chamber	Group 1: 1/44 Group 2: 0/37 p value: 1 (Fisher's exact calculated by NCC-AC)	
			Cataract	Group 1: 3/44 Group 2: 3/37 p value: 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP<6mmHg)	Group 1: 2/44 Group 2: 2/37 p value: 1 (Fisher's exact calculated by NCC-AC)	
			Persistent wound leak	Group 1: 0/44 Group 2: 0/37 p value: NA	
			Endophthalmitis	Group 1: 0/44 Group 2: 0/37 p value: NA	

2009

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil, VA=visual acuity

Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Zadok et al., 1995[711] **Study design:** RCT Investigator who followed up the patients was masked to intervention. **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** Single centre in Israel. **Inclusion criteria:** Adult patients with medically uncontrolled POAG. **Exclusion criteria:** NR **<u>All patients</u>** **N:** 20 (20 eyes) **Age (mean):** NR **M/F:** 11/9 **Mean IOP:** see below. P-value for diff = 0.22. **Drop outs:** 0 **<u>Group 1</u>** **N:** 10 **Age (mean):** 70.8±8.0 **M/F:** 7/3 **Mean IOP:** 24.0±1.9 **Drop outs:** 0	**Group 1** Cairn's filtering procedure in which a surgical sponge soaked in a 0.2mg/ml MMC was placed between the conjunctiva and episclera for five minutes. The tissues were then rinsed with 100ml of balanced salt solution. **Group 2** Cairn's filtering procedure in which 5 mg of 5-FU (0.5ml of a 10 mg/ml solution) were injected subconjunctivally 180 degrees from the filtering site once daily up to seven times during the first week after surgery. **Examination methods:** NR IOP measured at 1week, 2 weeks, 1	**Mean post-operative IOP (mmHg)**	***6 months:*** **Group 1:** 11.1 ± 4.8 **Group 2:** 14.1 ± 4.9 **p value:** 0.1 (Student's t test) ***12 months:*** **Group 1:** 11.6 ± 4.2 **Group 2:** 14.3 ± 3.7 **p value:** 0.1 (Student's t test)	**Funding:** NR **Limitations:** Randomisation method not clear Surgeon and patients unblinded Examination methods NR Small sample size Inclusion/exclusion criteria for patients enrolment NR **Additional outcomes:** Visual acuity at 12 months was stable within 1 line of baseline in all eyes in both groups. Mean change in IOP rate at 12 months was 53.4% ± 20.3% with MMC and 43.4% ± 21.3% with 5-FU
			Mean change in IOP from baseline at postoperative measurement	*6 months:* Group 1: 12.9 ± NR Group 2: 11.6 ± NR p value: NR *12 months:* Group 1: 12.4 ± NR Group 2: 11.4 ± NR p value: NR	
			Number of patients with acceptable IOP (<20 mmHg without medications) at 12 months	Group 1: 8/10 Group 2: 7/10 p value: 1 (Fisher's exact calculated by NCC-AC)	
			Number of patients with unacceptable IOP > 20 mmHg at 12 months	Group 1: 2/10 Group 2: 3/10	
			Corneal epithelial defect	Group 1: 0/10 Group 2: 3/10	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 10 **Age (mean):** 66.6±7.6 **M/F:** 4/6 **Mean IOP:** 25.7±3.8 **Drop outs:** 0	month, 2 months, 6 months and 12 months.		p value: 0.2 (Fisher's exact calculated by NCC-AC)	**Notes:**
			Wound leakage	Group 1: 2/10 Group 2: 2/10 p value: 0.6 (Fisher's exact calculated by NCC-AC)	
			Shallow anterior chamber	Group 1: 1/10 Group 2: 1/10 p value: 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP between 4 and 6 mmHg)	Group 1: 0/10 Group 2: 1/10 p value: 1 (Fisher's exact calculated by NCC-AC)	

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, Sig=<0.05, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil

Table 9: Viscocanalostomy vs. deep sclerectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[181] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** POAG + Pigmentary glaucoma (PG) + Pseudoexfoliation glaucoma (PXF) Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** Previous intraocular surgery <21 years **<u>All patients</u>** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG**: 20 **PG**: 3 **PXF**: 7 **White**: 30 **<u>Group 1</u>**	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not used	**Mean IOP ± SD at 6 months** Mean change in IOP from baseline at 6 months	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test Group 1: 16.0 ± 11.23* Group 2: 11.91 ± 9.19* Group 3: 10.08 ± 3.92* p value: NR	**Funding:** NR (requested info from author but no response) **Limitations:** Randomisation method was not clear Allocation concealment was not reported Masking of outcome assessment was not reported No adverse events reported IOP control is not the primary outcome **Additional outcomes:** Visual acuity Induced astigmatism **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **<u>Group 2</u>** **N:** 10 **Age (mean):** 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **<u>Group 3</u>** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1				Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Table 10: Non-penetrating surgery vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Carassa et al., 2003[103] **Study design:** RCT Single-blind Surgeon was masked to treatment allocation **Evidence level:** 1+ **Duration of follow-up:** 24 months	**Patient group:** COAG (POAG + Pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Italy **Inclusion criteria:** POAG or PXF Uncontrolled IOP > 21 mmHg on maximal medical therapy or IOP ≤ 21 mmHg with intolerance to current medications or poor compliance ≥ 45 years **Exclusion criteria:** Other ocular disease including congenital glaucoma or angle closure glaucoma Previous ocular surgery Abnormality preventing reliable tonometry **<u>All patients</u>** **N:** 50 (50 eyes) **Age (mean):** NR **M/F:** 20/30 **Mean IOP:** NR **Drop outs:** 1	**Group 1** Trabeculectomy + 5FU ** **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** Baseline IOP measured using slit lamp mounted applanation tonometer. Postoperative visits at 1 day, 1 week, 1, 2, 3 months and every months thereafter	**Mean IOP ± SD at 6 months**	**Group 1:** 12.76 ± 2.44 **Group 2:** 16.46 ± 4.96 **p value:**	**Funding:** Self-funded (confirmed by author) **Limitations:** Randomisation method was not reported Masking of outcome assessment was not reported Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** Ocular discomfort score at 12 months Reduction in visual acuity at end point **Notes:** **9 eyes received postoperative 5-FU injections and 2 eyes received argon laser suture lysis but these were allowed in treatment protocol and not considered as a
			Mean IOP ± SD reduction at 6 months	Group 1: 10.12 ± 6.32* Group 2: 8.29 ± 4.81*	
			Mean IOP ± SD at 12 months	Group 1: 13.04 ± 3.08 (n=25) Group 2: 16.38 ± 5.05 (n=24) p value: 0.01 (unpaired t-test) signif. *p = 0.0074 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD reduction at 12 months	Group 1: 9.84 ± 6.24* Group 2: 8.37 ± 4.82*	
			Mean IOP ± SD at 24 months	Group 1: 14.04 ± 4.64 (n=25) Group 2: 16.29 ± 5.10 (n=24) p value: 0.11 (unpaired t-test) *p = 0.12 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 24 months	Group 1: 8.76 ± NR Group 2: 8.46 ± NR p value: NR	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at	Group 1: 80% (n=20) (22/25) Group 2: 76% (n=19) (19/25) p value: 0.6 (log rank test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 25 eyes **Age (mean ± SD):** 68 ± 10.5 **M/F:** 10/15 **Mean ± SD IOP:** 22.88 ± 7.18 **Visual acuity**: 0.42 ± 0.3 **White:** 25 **Preoperative medications**: 3.06 (range 2-5) **POAG**: 22 **PXF**: 3 **Drop outs:** 0 **Group 2** **N:** 25 eyes **Age (mean ± SD):** 67.4 ± 15.8 **M/F:** 10/15 **Mean ± SD IOP:** 24.75 ± 6.73 **Visual acuity**: 0.56 ± 0.34 **White:** 25 **Preoperative medications**: 3.12 (range 2-5) **POAG**: 24 **PXF**: 1 **Drop outs:** 1 eye converted to trab but considered as withdrawal		12 months		treatment failure For group 2, any further intervention was considered a failure. * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Kaplan-Meier cumulative % Failure to control IOP without medications at 12 months	Group 1: 3/25 Group 2: 6/25	
			Kaplan-Meier cumulative % probability of IOP success (<16 mmHg without medications) at 24 months	Group 1: 72% (n=18) Group 2: 56% (n=14) p value: 0.17 (log rank test)	
			Number of eyes requiring re-operation (treatment failure)**	Group 1: 0/25 Group 2: 4/25 p value: NR *p = 0.12 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes requiring additional medications (treatment failure)**	Group 1: 5/25 Group 2: 2/25 p value: NR *p = 0.42 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema (1-2 mm)	Group 1: 1/25 (4%) Group 2: 3/24 (12.5%)	
			Hypotony	Group 1: 5/25 (20%) Group 2: 0/24 (0%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Choroidals	Group 1: 1/25 (4%) Group 2: 0/25 (0%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chiselita, 2001[128] **Study design:** RCT Single Blind **Evidence level:** 1+ **Duration of follow-up:** 18 months	Patient group: POAG Setting: single centre - Romania Inclusion criteria: Symmetrical POAG with uncontrolled IOP on maximal medical therapy Both eyes > 23 mmHg on at least 2 medications > 40 years old Exclusion criteria: Asymmetrical POAG Secondary OAG Angle-closure glaucoma Previous eye surgery Previous argon laser treatment within 30 days <u>All patients</u> N: 17 (34 eyes) Age (mean): 60.17 ± 7.3 M/F: 9/8 Mean IOP: NR Drop outs: 0	Group 1 Trabeculectomy (Cairns) Group 2 Non-penetrating Deep Sclerectomy Examination methods: *Preoperative:* Visual acuity, biomicroscopy, gonioscopy, Goldmann applanation tonometry, Humphrey VF analysis, fundus examination, C/D ratio *Postoperative:* Included visual acuity, Humphrey VF analysis, C/D ratio repeated every 3 months. Diurnal IOP curves measured at 1, 2, 3, 6, 12, 18 months. All measurements performed by same physician masked to allocation	Mean IOP ± SD at 18 months	Group 1: 17.27 ± 1.2 (n=17) Group 2: 20.90 ± 4.0 (n=17) p value: <0.0015 ANCOVA	Funding: NR Limitations: Randomisation method unclear Allocation concealment not reported Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve Additional outcomes: Kaplan-Meier cumulative probability for achieving postoperative IOP >30% less than preoperative IOP Notes: No antimetabolite use or postoperative goniopuncture. Fellow eyes randomised
			Mean IOP ± SD at 6 months	Group 1: 16.41 ± 1.8 Group 2: 19.17 ± 3.6	
			Mean change in IOP from baseline at 6 months	Group 1: 10.88 ± 1.96* Group 2: 8.53 ± 2.40*	
			Mean IOP ± SD at 12 months	Group 1: 16.78 ± 1.6 Group 2: 20.35 ± 4.5	
			Mean change in IOP from baseline at 12 months	Group 1: 10.51 ± 2.56* Group 2: 7.35 ± 3.35*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 12 months	Group 1: 92.59% (16/17) Group 2: 44.57% (8/17) p value: 0.00034 (Cox's F Test) signif.	
			Kaplan-Meier cumulative % probability number of eyes with unacceptable IOP without medications at 12 months	Group 1: 1/17 Group 2: 9/17 p value:	
			Number requiring	Group 1: 6/17	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 N: 17 Age (mean): see above M/F: see above Mean IOP: 27.29 ± 2.08 Visual Acuity: 0.47 ± 0.26 C/D Ratio: 0.75 ± 0.11 Drop outs: 0 Group 2 N: 17 Age (mean): see above M/F: see above Mean IOP: 27.70 ± 2.22 Visual Acuity: 0.48 ± 0.23 C/D Ratio: 0.75 ± 0.12 Drop outs: 0		postoperative medications	Group 2: 9/17 p value: Not signif.	* As standard deviations for the change in IOP from baseline were not reported, they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook.
			Hyphaema	Group 1: 7/17 Group 2: 0/17 p value: 0.003 (Chi-squared)	
			Inflammation	Group 1: 2/17 Group 2: 0/17 p value: not signif. (Chi-squared)	
			Cataract	Group 1: 4/17 Group 2: 0/17 p value: 0.0279 (Chi-squared)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cillino et al., 2005[133] & Cillino et al., 2008[132] **Study design:** RCT Single Blind **Evidence level:** 1+ Single blind **Duration of follow-up:** 12 months	**Patient group:** POAG and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Italy **Inclusion criteria:** IOP > 21 mmHg on maximal medications Visual field deterioration **Exclusion criteria:** Cataract Other ocular diseases Previous eye surgery **<u>All patients</u>** **N:** 40 (40 eyes) **Age (mean):** NR **M/F:** 20/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>** **N:** 21 **Age (mean):** 68.9 ± 6.4	**Group 1** Punch Trabeculectomy (Crozafon-De Laage) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Group 2** Non-penetrating Deep Sclerectomy (DS) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Examination methods:** ***Preoperative:*** Goldmann applanation tonometry, Humphrey VF analysis, slit lamp examination ***Postoperative:*** IOP measured at each visit at 1 day, 1, 2, 3 weeks, 1, 3, 6, 9 & 12 months. Investigators were blinded	**Mean IOP ± SD at 6 months**	**Group 1:** 13.8 ± 4.0 **Group 2:** 14.4 ± 2.6 **p value:** 0.78 ANOVA	**Funding:** NR **Limitations:** Allocation concealment not reported **Additional outcomes:** **Notes:** Author confirms use of computer to generate randomisation sequence NdYAG: goniopuncture was performed in 4/19 eyes in the DS group * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from
		Mean change in IOP from baseline at 6 months	Group 1: 14.2 ± 5.29* Group 2: 15.2 ± 4.39*	
		Mean IOP ± SD at 12 months	Group 1: 16.1 ± 3.8 (n=21) Group 2: 14.5 ± 4.0 (n=19) p value: 0.53 ANOVA	
		Mean change in IOP from baseline at 12 months	Group 1: 11.9 ± 6.94* Group 2: 15.1 ± 4.14* p value: NR	
		Mean IOP ± SD at 24 months**	Group 1: 16.9 ± 2.4 Group 2: 16.8 ± 3.4 p value: 0.99 ANOVA	
		Mean IOP ± SD at 48 months**	Group 1: 17.8 ± 3.6 Group 2: 17.6 ± 3.4 p value: 0.97 ANOVA	
		Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	Group 1: 15/21 (71%) Group 2: 15/19 (79%) p value: 0.72 (Fishers exact test)	
		Number of eyes with acceptable IOP (<17	Group 1: 13/21 (62%) Group 2: 12/19 (63%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 10/11 **Mean IOP:** 28.0 ± 6.0 **POAG:** 15 **PXF:** 6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** 71.9 ± 7.1 **M/F:** 10/9 **Mean IOP:** 29.6 ± 5.8 **POAG:** 12 **PXF:** 7 **Drop outs:** 3		mmHg without medications at 12 months	p value: 0.81 (Fishers exact test)	baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook. **A paper with longer term data was published by the same author in 2008[132]. The outcome data have been reported in this evidence table but they do not affect the main outcome data reported at 12 months.
			Failure to control IOP without medications at 12 months	Group 1: 6/21 Group 2: 3/19	
			Hypotony (<5 mmHg for > 2 weeks)	Group 1: 8/21 Group 2: 0/19 p value: 0.003 (Fishers exact test) signif	
			Hyphaema	Group 1: 9/21 Group 2: 4/19 p value: 0.26 (Fishers exact test)	
			Inflammation	Group 1: 4/21 Group 2: 1/19 p value: 0.49(Fishers exact test)	
			Flat anterior chamber	Group 1: 2/21 Group 2: 0/19 p value: 0.046 (Fishers exact test)	
			Shallow anterior chamber	Group 1: 7/21 Group 2: 1/19 p value: 0.046 (Fishers exact test)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[181] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** POAG + Pigmentary glaucoma (PG) + Pseudoexfoliative glaucoma (PXF) Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** Previous intraocular surgery <21 years **<u>All patients</u>** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG**: 20 **PG**: 3 **PXF**: 7 **White**: 30 **<u>Group 1</u>**	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not	**Mean IOP ± SD at 6 months**	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test	
			Mean change in IOP from baseline at 6 months	Group 1: 16.0 ± 11.23* Group 2: 11.91 ± 9.19* Group 3: 10.08 ± 3.92* p value: NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **Group 2** **N:** 10 **Age (mean):** 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **Group 3** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1	used			

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
El Sayyad et al., 2000[185] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single centre – Saudi Arabia **Inclusion criteria:** Symmetrical POAG with uncontrolled IOP > 21 mmHg on maximal medical therapy > 35 years old **Exclusion criteria:** Previous eye surgery Patients with significant posterior segment eye disorders **<u>All patients</u>** **N:** 39 (78 eyes) **Age (mean):** 53.4 ± 9.6 **M/F:** 24/15 **Mean IOP:** NR **Drop outs:** 0 (patients failing sclerectomy procedure were replaced) **<u>Group 1</u>**	**Group 1** Trabeculectomy **Group 2** Non-penetrating Deep Sclerectomy **Examination methods:** ***Preoperative:*** Visual Acuity, applanation tonometry, slit lamp examination & ophthalmoscopy ***Postoperative:*** Details of examinations not reported but measurements taken at 1 day, 1 week, 1 month then at 3, 6, 9 and 12 months	**Mean IOP ± SD at 6 months**	**Group 1:** 13.7 ± 5.4 (n=39) **Group 2:** 14.9 ± 4.3 (n=39) **p value:** 0.28 (unpaired t test)	**Funding:** NR **Limitations:** Randomisation method was not clear Allocation concealment was not reported Masking of outcome assessment was not reported **Additional outcomes:** Postoperative glaucoma meds at 12 months **Group 1:** 0.27 ± 0.5 **Group 2:** 0.30 S 0.4 Visual Acuity (Snellen lines) at 12 months No significant difference **Notes:** Fellow eyes randomised
			Mean change in IOP from baseline at 6 months	Group 1: 14.5 ± 5.1 Group 2: 13.2 ± 4.2 p value: 0.16 (unpaired t test)	
			Mean IOP ± SD at 12 months	Group 1: 14.1 ± 4.6 (n=39) Group 2: 15.6 ± 4.2 (n=39) p value: 0.13 (unpaired t test)	
			Mean change in IOP from baseline at 12 months	Group 1: 14.1 ± 6.4 Group 2: 12.3 ± 4.2 p value: 0.15 (unpaired t test)	
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	Group 1: 33/39 (85%) Group 2: 31/39 (79%) p value: 0.55 (Chi squared)	
			Failure to control IOP <21 mmHg without medications	Group 1: 6/39 Group 2: 8/39	
			Hyphaema	Group 1: 3/39 Group 2: 1/39 p value: 0.6 (Chi-squared)	
			Hypotony	Group 1: 1/39 Group 2: 0/39 p value: 0.9 (Chi-squared)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 39 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.2 ± 4.7 **Pre-op glaucoma meds:** 2.6 ± 0.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 39 **Age (mean):** see above **M/F:** see above **Mean IOP:** 27.9 ± 5.9 **Pre-op glaucoma meds:** 2.4 ± 0.7 **Drop outs:** 0		Intensive Uveitis	Group 1: 2/39 Group 2: 0/39 p value: 0.47 (Chi-squared)	Goniopuncture with Nd:YAG laser was performed in 4/39 eyes in NPDS group and Argon laser suture lysis was performed in 17/39 eyes in trabeculectomy group. 5-FU was used postoperatively 17/39 eyes of the NPDS group and 15/39 in the trabeculectomy group
			Cataract	Group 1: 1/39 Group 2: 0/39 p value: 0.9 (Chi-squared)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jonescu-Cuypers et al., 2001[305] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG (all white patients) **Setting:** single centre - Germany **Inclusion criteria:** Uncontrolled high tension glaucoma on maximal medications IOP > 30 mmHg with or without medication Glaucomatous damage defined by VF loss or progressive cupping **Exclusion criteria:** Those with previous ocular surgery Legally blind fellow eye Corneal abnormalities preventing applanation tonometry **<u>All patients</u>** **N:** 20 patients (20 eyes) **Age (mean):** 62.5 ± 13.1 **M/F:** 11/9 **Mean IOP:** 29.65 ± 6.45 **Drop outs:** 0 **All white patients** **<u>Group 1</u>**	**Group 1** Trabeculectomy (Cairns modification) **Group 2** Viscocanalostomy (Stegmann)** **Examination methods:** ***Preoperative*** IOP measurement, visual acuity, gonioscopy, slit lamp biomicroscopy, indirect ophthalmoscopy of the retina, biomorphometry of papilla by laser scanning, VF testing with Humphrey and ultrasonography for scleral thickness. ***Postoperative*** IOP measurement, biomorphometry of papilla by laser scanning, VF testing with Humphrey. Examinations monthly for 6-8 months after surgery	**Mean postoperative IOP ± SD - Follow-up time not specified**	**Group 1:** 15.6 ± 3.17 (n=10) **Group 2:** 18.3 ± 5.03 (n=10) **p value:** NR *p = 0.17 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=10 in both groups)*	**Funding:** NR (emailed author) **Limitations:** Randomisation method not clear Outcome assessment was not masked **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to
			Mean change in IOP from baseline mean follow up of 6 months (range 6-8 months)	Group 1: 12.5 ± 5.06* Group 2: 12.29 ± 4.97* p value:	
			Number of eyes with acceptable IOP (<20 mmHg without medications or need for re-operation) at follow up of 6 months (range 6-8 months)	Group 1: 5/10 (50%) Group 2: 0/10 (0%) p value: NR *p = 0.03 2-sided Fishers exact test calculated by NCC-AC as ITT (n=10 in both groups)*	
			Failure to control IOP without medications or a need for further surgery at follow up of 6 months (range 6-8 months)	Group 1: 5/10 (50%) Group 2: 10/10 (100%)	
			Bleeding into conjunctiva	Group 1: 0/10 Group 2: 1/10 p value: NR	
			Leaking Bleb	Group 1: 1/10 Group 2: 0/10	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 28.1 ± 5.84 **C/D ratio**: 0.67 ± 0.26 **Drop outs:** 0 **Group 2** **N:** 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 31.2 ± 6.96 **C/D ratio**: 0.85 ± 0.13 **Drop outs:**	**2/10 in the viscocanalostomy group had trabeculectomies with mitomycin C and 1/10 in same group had a sclerectomy due to IOP spikes		p value: NR	deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kobayashi et al., 2003[340] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single setting - Japan **Inclusion criteria:** IOP ≥ 22mmHg on maximal medical therapy **Exclusion criteria:** Angle-closure, post-traumatic, uveitic, neovascular or dysgenetic glaucoma Patients needing combined cataract procedures **<u>All patients</u>** **N:** 25 (50 eyes) **Age (mean):** 62..5 ± 7.4 **M/F:** 11/14 **Mean IOP:** NR **Drop outs:** 0/25 **<u>Group 1</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 24.8 ± 2.6	**Group 1** Trabeculectomy (Cairns) with 0.04% MMC sponges after dissection Laser suture lysis was performed if bleb was flat or target IOP not reached **Group 2** Viscocanalostomy (Stegmann) Goniopuncture with Nd:YAG laser performed after if target pressure not reached **Examination methods:** ***Baseline examinations:*** Humphrey VF test, gonioscopy, scanning laser tomography. IOP measured at 3 visits in 2 week period prior to study and 3 measurements averaged. ***Postoperative***	Mean IOP ± SD at 6 months	Group 1: 11.8 ± 4.6 (n=25) Group 2: 16.9 ± 2.8(n=25) p value: <0.0001 student t-test	**Funding:** Self-funded. **Limitations:** Allocation concealment was not reported Masking of outcome assessment was not reported **Additional outcomes:** VF change as Mean Deviation at 12 months **Group 1**: -0.30 ± 0.85 **Group 2**: -0.21 ± 0.28 Change in visual acuity at 12 months **Notes:** Eyes randomised. Patient received viscocanalostomy in 1 eye and trabeculectomy in the fellow eye. "nd procedure was performed 1-2 weeks after the first.
			Mean change in IOP from baseline at 6 months	Group 1: 13.0 ± 5.4 Group 2: 8.1 ± 3.5 p value: <0.0001 student t-test signif. *p = 0.0005 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 12 months	Group 1: 12.6 ± 4.3 (n=25) Group 2: 17.1 ± 1.5 (n=25) p value: <0.0001 student t-test	
			Mean change in IOP from baseline at 12 months	Group 1: 12.3 ± 5.2 Group 2: 7.8 ± 3.1 p value: <0.0001 student t-test signif. *p = 0.0006 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with acceptable IOP (<20 mmHg & change in IOP or >30% without medications) at 12 months	Group 1: 22/25 (88%) Group 2: 15/25 (60%) p value: 0.024 (Chi-squared) *p = 0.051 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			IOP < 16 mmHg without medication at 12 months	Group 1: 20/25 (80%) Group 2: 10/25 (40%) p value: 0.0039 (Chi-squared) *p = 0.009 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in*	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	VF Mean Deviation: -12.81 ± 5.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 25.0 ± 2.2 **VF Mean Deviation**: -13.72 ± 4.97 **Drop outs:** 0	***examinations:*** Patients reviewed at 1, 3 days, 1, 2 weeks and 1, 2, 3, 4, 5, 6, 9, 12 months after surgery. 3 IOP measurements taken in each eye and mean used. Optic nerve was examined with Goldmann lens and tomography performed at 1 year interval. V F measured at 6 months and 12 months.		*both groups)*	14/25 (56%) viscocanalostomy eyes received goniopuncture with Nd:YAG laser post-surgery.
			Failure to control IOP without medications or a need for further surgery at 12 months	Group 1: 3/25 Group 2: 10/25	
			Complete failure defined by need for further surgery or loss of Visual Function	Group 1: 0/25 Group 2: 1/25 p value: Not signif.	
			Hypotony	Group 1: 5/25 (20%) Group 2: 0/25 p value: 0.0184 (Chi-squared).	
			Hyphaema	Group 1: 4/25 (16%) Group 2: 0/25 p value: 0.0371	
			Failed Bleb	Group 1: 2/25 (8%) Group 2: NR p value: NR	
			Bleb Formation	Group 1: NR Group 2: 5/25 p value: NR	
			Cataract formation	Group 1: 2/25 Group 2: 0/25 p value: Not signif.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Luke et al., 2002[413] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, pseudoexfoliative glaucoma (PXF) & pigmentary glaucoma (PG) **Setting:** single centre - Germany **Inclusion criteria** Uncontrolled IOP on maximal medications >21 years old **Exclusion criteria:** Previous ocular surgery **<u>All patients</u>** **N:** 60 (60 eyes) **Age (mean):** 61.4 ± 17.6 **M/F:** 57/31 **Mean IOP:** 27.1 ± 7.1 **Drop outs:** 0 **POAG:** 33 **PXF:** 20 **PG:** 7 **<u>Group 1</u>** **N:** 30 **Age (mean):** NR	**Group 1** Trabeculectomy (Cairns) **Group 2** Viscocanalostomy **Examination methods:** ***Preoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry ***Postoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry performed daily for 1 week, then at 1, 6, 12 months Laser suture lysis was performed on 11/30 eyes in trabeculectomy group	**Mean IOP ± SD at 6 months**	**Group 1:** 15.5 ± 3.0 **Group 2:** 16.0 ± 4.1 **p value:** 0.15 student t-test	**Funding:** Not reported **Limitations:** Randomisation method is unclear Allocation concealment was not reported Masking of outcome assessment was not reported Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in
			Mean change in IOP from baseline at 6 months	Group 1: 16.78 ± 6.45* Group 2: 11.2 ± 4.98* p value: NR	
			Mean IOP ± SD at 12 months	Group 1: 15.0 ± 3.5 Group 2: 17.1 ± 5.4 p value: 0.15 student t-test	
			Mean change in IOP from baseline at 12 months	Group 1: 11.9 ± 6.41* Group 2: 10.1 ± 3.87* p value: NR	
			Kaplan-Meier cumulative % probability of IOP success (<22 mmHg without medications) at 12 months	Group 1: 56.7% (n=30) (17/30) Group 2: 30% (n=30) (9/30) p value: 0.041 (log rank test) signif.	
			Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or a need for further surgery at 12 months	Group 1: 13/30 Group 2: 21/30	
			Hyphaema	Group 1: 8/30 (26.7%) Group 2: 3/30 (10%) p value: 0.095 (Chi-squared)	
			Hypotony (<6 mmHg)	Group 1: 11/30 (36.7%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: NR **Mean IOP:** 26.9 ± 7.4 **Drop outs:** 0 **Number of Medications:** 2.5 ± 1.1 **<u>Group 2</u>** **N:** 30 **Age (mean):** NR **M/F:** NR **Mean IOP:** 27.2 ± 6.9 **Drop outs:** 0 **Number of Medications:** 2.9 ± 0.9	if IOP was uncontrolled		Group 2: 6/30 (20%) p value: 0.152 (Chi-squared)	the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Cataract Progression	Group 1: 2/30 (6.7%) Group 2: 0/30 p value: 0.15 (Chi-squared)	
			Bleb formation	Group 1: 30/30 Group 2: 17/30 p value: <0.001 (Chi-squared)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yalvac et al., 2004[700] **Study design:** RCT **Evidence level:**	Patient group: POAG Setting: single centre - Turkey Inclusion criteria: Uncontrolled POAG on maximal medical therapy Exclusion criteria:	Group 1 Trabeculectomy (Cairns) Group 2 Viscocanalostomy (similar to Stegmann) Examination methods:	Mean IOP ± SD at 6 months	Group 1: 16.0 ± 5.3 (n=25) Group 2: 18.1 ± 5.2 (n=25) p value: 0.206 (unpaired t-test) *p = 0.16 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	**Funding:** NR (requested info from author but no response) **Limitations:** Randomisation method was not clear
			Mean change in IOP from baseline at 6	Group 1: 24.1 ± 7.84* (n=25) Group 2: 15.7 ± 5.73* (n=25)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
1+ **Duration of follow-up:** 36 months (mean follow up 18 months range 6-38)	Congenital glaucoma, angle closure glaucoma, neovascular glaucoma, traumatic glaucoma & uveitic glaucoma Previous ocular surgery <u>All patients</u> N: 50 (50 eyes) Age (mean): NR M/F: 36/14 Mean IOP: NR Drop outs: 0 <u>Group 1</u> N: 25 eyes Age (mean ± SD): 66.8 ± 10.2 M/F: 19/6 Mean ± SD IOP: 37.7 ± 9.0 Preoperative medications:: 3 (range 2-4) Drop outs: 0 <u>Group 2</u> N: 25 eyes Age (mean ± SD): 63.6 ± 12.6 M/F: 17/8 Mean ± SD IOP: 36.0 ± 8.0	*Preoperative:* IOP measurement by applanation tonometry, visual acuity, gonioscopy, slit lamp biomicroscopy, indirect ophthalmoscopy of the optic nerve, VF examination using Humphrey 24-2. *Postoperative:* IOP measurement by Goldmann applanation tonometry, visual acuity, gonioscopy, slit lamp biomicroscopy, fundoscopy Patients were examined at 1 day, 1 week, 1, 3 & 6 months, 1, 2 & 3 years. No antimetabolites were used	months		Allocation concealment not reported Masking of outcome assessment was not reported Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Notes:** * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar
			Mean IOP ± SD at 12 months	Group 1: 16.3 ± 3.9 (n=25) Group 2: 20.3 ± 5.6 (n=25) p value: 0.027 (unpaired t-test) signif. *p = 0.005 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 12 months	Group 1: 24.1 ± 7.82* (n=25) Group 2: 15.7 ± 5.71* (n=25)	
			Mean IOP ± SD at 24 months	Group 1: 18.6 ± 4.3 (n=25) Group 2: 21.6 ± 10.8 (n=25) p value: 0.43 (unpaired t-test) *p = 0.21 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 36 months	Group 1: 16.0 ± 7.1 (n=25) Group 2: 17.8 ± 4.6 (n=25) p value: 0.69 (unpaired t-test) *p = 0.29 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 6 months	Group 1: 17/25 66.2% Group 2: 13/25 52.9% p value: 0.311 (log rank test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Preoperative medications: 3.1 (range 2-4) Drop outs: 0		Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or need for further surgery at 6 months	Group 1: 8/25 Group 2: 12/25	enough to viscocanalostomy to produce an equivalent effect size. **Additional outcomes:** Visual acuity change
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 3 years	Group 1: 14/25 55.1% Group 2: 9/25 35.3% p value: 0.228 (log rank test)	
			Number of eyes requiring additional medications postoperatively	Group 1: 10/25 (40%) Group 2: 13/25 (52%) *p = 0.40 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Transient early Hypotony IOP < 5 mmHg	Group 1: 7/25 (28%) Group 2: 1/25 (4%) p value: 0.002 (Chi-squared) signif. *p = 0.049 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema	Group 1: 2/25 (8%) Group 2: 1/25 (4%)	
			Bleb encapsulation	Group 1: 3/25 (12%) Group 2: 1/25 (4%)	
			Cataract	Group 1: 7/25 (28%) Group 2: 2/25 (8%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				p value: 0.002 (Chi-squared) signif. *p = 0.14 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yarangumeli et al., 2005[705] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, chronic angle closure glaucoma (CACG) and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Turkey **Inclusion criteria:** Uncontrolled high tension glaucoma on maximal medications **Exclusion criteria:** High risk patients requiring antimetabolites such as those with previous ocular surgery Secondary or developmental glaucoma < 40 years old History of ocular inflammation or trauma **<u>All patients</u>** **N:** 22 (44 eyes) **Age (mean):** 64.3 ± 10.5 **M/F:** 12/10 **Mean IOP:** NR **Drop outs:** 0 **POAG:** 7	**Group 1** Trabeculectomy (Cairns/Watson modification) **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** IOP measured by Goldmann tonometry by same observer. Preoperatively and at 1, 2, 4 and 12 weeks postoperatively then every 3 months for 1st year and 6 month intervals thereafter. No antimetabolites in either group	**Mean IOP ± SD at 6 months**	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	**Funding:** Self-funded (confirmed by author) **Limitations:** **4/22 patients had CACG but these were excluded from the Number of patients with unacceptable IOP results Outcome assessment was not masked **Additional outcomes:** Diffuse elevated blebs Thin walled, multi-cystic blebs Low-lying, localised blebs **Notes:** One eye randomised using coin tossing to first treatment group. Less than 2 months later fellow eye received remaining procedure. Eye to be randomised to 1st treatment was the one with most severe glaucoma, otherwise coin
			Mean change in IOP from baseline at 6 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 9.89* **p value:**	
			Mean IOP ± SD at 12 months	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	
			Mean change in IOP from baseline at 12 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 10.41* **p value:**	
			Number of eyes with acceptable IOP (<18 mmHg without medications) at 12 months	**Group 1:** 14/22 (64%) **Group 2:** 13/22 (59%) **p value:** 0.75 (Chi-squared)	
			Number of eyes with unacceptable IOP without medications at 12 months	**Group 1:** 7/18** **Group 2:** 8/18**	
			Hyphaema	**Group 1:** 1/22 **Group 2:** 1/22 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	PXF: 11 **CACG**: 4 **<u>Group 1</u>** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 39.3 ± 11.9 **Drop outs:** 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 38.6 ± 12.5 **Drop outs:** 0		**Persistent hypotony**	**Group 1:** 2/22 **Group 2:** 1/22 **p value:** NR	used to select eye. * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[185] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Cataract progression	**Group 1:** 7/22 **Group 2:** 2/22 **p value:** NR	

Abbreviations: **NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.**

Table 11: Non-penetrating surgery plus augmentation vs. non-penetrating surgery

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Neudorfer et al., 2004[490] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** At least 24 months. Clinical visits that extended longer than 27 months were considered as 2 year postoperative follow ups.	**Patient group:** POAG **Setting:** single centre - Israel **Inclusion criteria:** Open angle glaucoma patients: IOP ≥ 22 mmHg with maximal medications Glaucomatous disc cupping Visual field defect Open angles on gonioscopy **Exclusion criteria:** Secondary glaucoma, neovascular or juvenile glaucomas iridocorneal endothelial syndrome uveitis **<u>All patients</u>** **N:** 26 (26 eyes) **Age (mean ± SD):** NR **M/F:** 13/13 **Mean IOP:** **Drop outs:** 0	**Group 1** Deep Sclerectomy with collagen implant only **Group 2** Deep Sclerectomy with collagen implant + MMC 0.3mg/ml for 3 minutes **Examination methods:** IOP. Best corrected visual acuity for distance based on the results of retinoscopy and manifest refraction.	**Mean preoperative IOP**	**Group 1:** 26.5 ± 2.5 **Group 2:** 31.5 ± 5.7 **p value: significant**	**Funding:** NR **Limitations:** Mean preoperative IOP significantly higher in the MMC group than in control despite randomisation. Patients receiving MMC had been taking significantly greater mean number of medications preoperatively. Study was underpowered to detect a difference between the groups Randomisation method, allocation concealment and masking of outcome assessment were not reported **Additional outcomes:** **Visual acuity**
			Mean IOP at 12 months	Group 1: 17.2 ± 3.9 Group 2: 15.6 ± 3.5 p value: significant baseline-12 months for each group not between groups	
			IOP % difference from baseline to 12 months	Group 1: 34.8 ± 15.3 Group 2: 47.8 ±18.1 p value: not significant between groups	
			Mean IOP at 24 months	Group 1: 17.8 ± 2.8 Group 2: 15.8 ± 5.6 p value: significant baseline-24 months for each group not between groups	
			IOP % difference from baseline to 24 months	Group 1: 32.1 ± 12.2 Group 2: 48.1 ± 17.2 p value: p = 0.01 significant	
			IOP success <21 mmHg without medications	Group 1: 5/13 Group 2: 4/13 p value: not significant	
			Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 12 months	Group 1: 2/13 Group 2: 0/13	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 13 **Age (mean ± SD):** 65.8 ± 6.8 **M/F:** 5/8 **Mean IOP:** 26.5 ± 2.5 **Drop outs:** 0 **Group 2** **N:** 13 **Age (mean ± SD):** 68.1 ± 8 **M/F:** 8/5 **Mean IOP:** 31.5 ± 5.7 **Drop outs:** 0		Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 24 months	Group 1: 1/13 Group 2: 1/13	**deterioration (>2 lines on the Snellen chart)** Group 1: 0/13 Group 2: 0/13 **Visual acuity deterioration (1 line on the Snellen chart due to cataract formation)** Group 1: 1/13 Group 2: 2/13 **Notes:**
			Mean number of medications at baseline	Group 1: 2.9 ± 0.6 Group 2: 3.7 ± 0.6 p value: $p < 0.05$ significant	
			Mean number of medications at 12 months	Group 1: 1.3 ± 1.2 Group 2: 1.8 ± 1.5 p value: significant baseline-12 months for each group not between groups	
			Mean number of medications at 24 months	Group 1: 1.8 ± 0.9 Group 2: 2.0 ± 1.5 p value: significant baseline- 24 months for each group not between groups	
			Complications at 24 months	Postoperative Hyphaema Group 1: 1/13 Group 2: 2/13 Filtering blebs Group 1: 2/13 Group 2: 3/13 Neither bleb leak nor hypotony were present in any of the patient groups.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc.

H.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

H.6 Complementary and alternative interventions

None.

H.7 Organisation of care

H.7.1 Service models for case finding, referral filtering and diagnosis

No relevant clinical studies were identified.

H.7.2 Skills required by healthcare professionals

Table 12: Service Provision

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Azuara-Blanco et al., 2007[40] **Study design:** Prospective observational Observer masked	**Patient group:** 671 referrals from community optometrists in Grampian, Scotland. **Inclusion criteria:** >18 years **<u>All patients</u>** **N:** 100 (165 randomised, 65 chose not to participate)	**Group 1:** 3 community optometrists (CO) that had received in-house training by a consultant ophthalmologist and glaucoma specialist as part of glaucoma optometric service. Training included practical sessions, glaucoma clinics, teaching on diagnostic interventions **Group 2:**	**Inter-observer** (consultant-optometrist) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.39 - 0.67) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	**Funding:** Scottish Executive Health Department **Limitations:** The method of weighting of the kappa statistic was not clearly defined and the
			Inter-observer (junior doctor–consultant) agreement for *all management decisions* (1-5)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.45 (0.31 - 0.59) (moderate) 95% CI calculated by NCC-AC using SE 0.07 from study	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
	Age (mean): 67 **M/F:** 52/48 **Mean IOP (mmHg**): 26 **Family history**: 24 **Black**: 1 **Glaucoma diagnosis (management decisions **) by consultant** Normal & discharged: **35** Suspect or OHT requiring review: **32** Suspect or OHT requiring treatment: **8** Glaucoma: **23** Glaucoma requiring urgent treatment: **2**	Junior (trainee) ophthalmologist **Group 3:** Consultant ophthalmologist **Examination methods:** Each CO examined all 671 referrals for: Visual acuity (Snellen chart) VF (threshold strategy 24-2 SITA) Corneal thickness (ultrasound pachymetry) Slit lamp biomicroscopy to assess anterior segment and optic disc Goldmann tonometry Gonioscopy Refraction Risk factors The junior doctor and consultant ophthalmologist examined the 100 patients randomised into the study in the hospital outpatient department with same tests except for IOP measurements	Inter-observer (junior doctor–optometrist) agreement for *all management decisions* (1-5)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.45 (0.31 - 0.59) (moderate) 95% CI calculated by NCC-AC using SE 0.07 from study	kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977) **Additional Outcomes:** **Notes:** The community optometrists were masked to randomised patient selection. Participants were required not to disclose details of previous consultations.
			Inter-observer (consultant-optometrist) agreement for *diagnosis* of glaucoma (4-5 v 1-3)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.70 (0.54 - 0.87) (substantial) 95% CI calculated by NCC-AC using SE 0.083 from study	
			Inter-observer (junior doctor–consultant) agreement for *diagnosis* of glaucoma (4-5 v 1-3)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.54 (0.35 - 0.73) (moderate) 95% CI calculated by NCC-AC using SE 0.098 from study	
			Inter-observer (junior doctor–optometrist) agreement for *diagnosis* of glaucoma (4-5 v 1-3)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.22 (0.02 - 0.42) (fair) 95% CI calculated by NCC-AC using SE 0.101 from study	
			Inter-observer (consultant-optometrist) agreement for *treatment required* (3-5 v 1-2)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.72 (0.57 - 0.86) (substantial) 95% CI calculated by NCC-AC using SE 0.076 from study	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
			Inter-observer (junior doctor–consultant) agreement for *treatment required* (3-5 v 1-2)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.55 (0.37 - 0.73) (moderate) 95% CI calculated by NCC-AC using SE 0.09 from study	
			Inter-observer (junior doctor–optometrist) agreement for *treatment required* (3-5 v 1-2)** weighted kappa statistic κ_w	Mean (95%CI) κ_w = 0.62 (0.45 - 0.79) (substantial) 95% CI calculated by NCC-AC using SE 0.088 from study	
			Diagnosis of glaucoma (with reference standard defined by consultant)	Group 1 Sensitivity: 0.76 (95% CI: 0.57-0.89) Specificity: 0.93 (95% CI: 0.85-0.97) Group 2 Sensitivity: 0.66 (95% CI: 0.48-0.81) Specificity: 0.89 (95% CI: 0.80-0.95)	
			Treatment of glaucoma (with reference standard defined by consultant)	Group 1 Sensitivity: 0.73 (95% CI: 0.57-0.85) Specificity: 0.96 (95% CI: 0.88-0.99) Group 2 Sensitivity: 0.64 (95% CI: 0.47-0.78) Specificity: 0.90 (95% CI: 0.80-	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
				0.95)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Banes et al., 2000[50] **Study design:** Prospective observational Observer masked	**Patient group:** patients from general glaucoma clinic. Moorfields Eye Hospital Some patients had other ocular pathologies. Most patients had a diagnosis of POAG and were on medical treatment **Inclusion criteria:** NR **<u>All patients</u>** **N:** 54 **Age (mean):** NR **M/F:** NR No demographic data was reported	**Group 1:** 1 senior optometrist **Group 2:** 1 general ophthalmologist (research fellow) **Examination methods:** Visual fields were carried out by a technician before assessment. Both optometrist and research fellow carried out the following: Clinical history of medication including adverse events Slit lamp biomicroscopy to assess anterior segment and optic disc VCD Drawing of disc Haemorrhages Disc size VF (24-2) plots were considered Stable Progressive Non-glaucoma Unreliable Goldmann tonometry Gonioscopy	Inter-observer agreement for visual field assessment (right eyes) kappa statistic κ* (% agreement)	= 0.81 (very good) (92%) (3 eyes had missing data and 4 eyes were disagreed upon)	**Funding:** NR **Limitations:** No confidence intervals for kappa The kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977) **Additional Outcomes:** **Notes:** * kappa was calculated excluding missing values Patients were randomly distributed to optometrist and research fellow by clerk but the optometrist did
			Inter-observer agreement for visual field assessment (left eyes) kappa statistic κ* (% agreement)	= 0.80 (good) (91%)	
			Inter-observer agreement for management recommendations (right eyes) kappa statistic κ* (% agreement)	= 1.00 (very good) (100%) (Group 2 had not recorded data for 3 eyes)	
			Inter-observer agreement for management recommendations (left eyes) kappa statistic κ* (% agreement)	= 0.93 (very good) (98%) (6 eyes had missing data and 1 eye was disagreed upon)	
			Inter-observer agreement for follow up recommendations kappa statistic κ* (% agreement)	= 0.97 (very good) (98%) (5 eyes had missing data and 1 eye was disagreed upon)	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		Management of patient according to clinical state was assessed Continue with treatment Change treatment Stop treatment Consider surgery Length of time to next appointment < 2 months 3 months 6 months 1 year Discharge			not see any postoperative or complicated cases. The research fellow was masked to the observations of the optometrist

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Banes et al., 2006[49] **Study design:** Prospective + Retrospective observational study	**Patient group:** 350 patients attending glaucoma outpatient services at Moorfields, UK **Inclusion criteria:** Diagnosis of glaucoma (POAG, CACG, secondary and NTG) or OHT **Exclusion criteria:** New and postoperative patients **<u>All patients</u>** **N:** 350 **Age (median):** NR **M/F:** NR Dropouts: 1 (one hospital record could not be retrieved) No demographic data was reported	**Group 1** 4 certified optometrists with a College of Optometry diploma in glaucoma in hospital setting with patient assessment and management experienced gained from 3 – 10 years of 1-2 half day sessions/week. Training consisted of patient assessments in supportive environment with access to an ophthalmologist. **Group 2** 3 medical clinicians (associate specialists) working part-time in glaucoma clinics for ≥ 10 years **Group 3** 2 consultant ophthalmologists **retrospectively** reviewed the patient records and clinical decisions and made independent management decisions **Examination methods:** Optic disc assessment for glaucomatous damage or normal disc was performed independently of the main study using 134 stereo	**Detection of glaucomatous disc** using 134 stereo pairs (with glaucomatous damage defined checking against previously published data)	**Group 1** Sensitivity: range 77.8% - 88.2% Specificity: range 76.0% - 79.0% **Group 2** Sensitivity: range 64.7% - 74.2% Specificity: range 82.3% - 93.0%	**Funding:** NR **Limitations:** Mean kappa statistic not reported with confidence intervals **Additional outcomes:** **Notes:** Patients allocated by clinic clerk on a sequential basis to specialist ophthalmologist or optometrist (50 patients each) ***Weighted kappa statistic κ_w** Weights assigned for time to next clinical appointment: 1.0 = agreement; 0.75 = 1 step away disagreement; 0.5 =
			Inter-observer agreement for visual field status (kappa statistic & % agreement)	Group 3 (Consultant 1) v Group 1 κ = 0.33 fair (55%) Group 3 (Consultant 2) v Group 1 κ = 0.27 fair (54%) Mean κ = 0.30 fair Group 3 (Consultant 1) v Group 2 κ = 0.22 fair (44%) Group 3 (Consultant 2) v Group 2 κ = 0.21 fair (43%) Mean κ = 0.22 fair	
			Inter-observer agreement for clinical management 1 (kappa statistic & % agreement)	Consultant 1 v Group 1 (certified optometrists) κ = 0.67 good (79%) N=199 (3% missing data) Consultant 1 v Group 2 (general ophthalmologists) κ = 0.52 moderate (71%) N=150 (5.3% missing data)	
			% agreement for clinical management 2	Consider cataract surgery: Group 3 (Consultant 1) v Group 1 94% Group 3 (Consultant 1) v Group 2 91%	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		pairs of disc photographs. Results were compared to previously published data. All patients had a visual field test performed by a technician before clinical assessment. The optometrists and medical clinicians then performed a structured clinical assessment on each of their 50 patients then used the clinical data to make management decisions on 5 aspects of patient care: Visual field status (stable, progression, unreliable, non-glaucoma, other) Clinical management 1 (no treatment, continue, start/increase treatment, reduce) Clinical management 2 (consider glaucoma surgery, consider cataract surgery, change treatment due to intolerance, reinforce compliance, discuss with consultant) Planned tests (disc photographs, HRT, VF, IOP phasing Time to next appointment in		Consider glaucoma surgery: Group 3 (Consultant 1) v Group 1 95% Group 3 (Consultant 1) v Group 2 99% Reinforce Compliance: Group 3 (Consultant 1) v Group 1 97% Group 3 (Consultant 1) v Group 2 99% Discuss with consultant: Group 3 (Consultant 1) v Group 1 72% Group 3 (Consultant 1) v Group 2 81%	2 steps away disagreement ; 0.25 = 3 steps away disagreement, 0 = 4 steps away disagreement and disagreement for discharge and missing data Kappa value agreement 0.00 to 0.2 = poor 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very good
			% agreement for planning of tests	Visual Field: Group 3 v Group 1 mean 62% (C1 & C2) Group 3 v Group 2 mean 54% (C1 & C2) Imaging: Group 3 v Group 1 mean 73% (C1 & C2) Group 3 v Group 2 mean 61% (C1 & C2) Phasing: Group 3 v Group 1 mean 98% (C1 & C2) Group 3 v Group 2 mean 100% (C1 & C2) Disc Photo: Group 3 v Group 1 mean 91% (C1 & C2) Group 3 v Group 2 mean 100% (C1 & C2)	
			Next clinic appointment weighted kappa statistic κ_w * and % agreement	Group 3 (Consultant 1) v Group 1 (certified optometrist) κ_w = 0.35 fair (79%) Group 3 (Consultant 1) v Group 2 (general ophthalmologist) κ_w = 0.29 fair (73%)	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		months (1-2, 3, 6 9 12, discharge)			

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2000[257] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereo photographs retrospectively selected from of glaucomatous and non-glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereo photographs <u>**All patients**</u> **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): **Definitely non-glaucomatous ≤10)**: 11 **Definitely glaucomatous ≥90)**: 15 **Suspicious (11-89)**: 22	**Group 1** 3 optometrists with 4 years accredited training ≥ 4 years post registration experience. None had specialist shared care expertise **Group 2** 2 general ophthalmologists. One SPR and one associate specialist in medical ophthalmology. Neither had sub-speciality training although the associate specialist had responsibility for reporting on fundus/disc photographs **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box Each observer	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** Range from 0.23 (fair) to 0.64 (substantial)	Mean κ_w = **0.46 (moderate)**	Funding: College of optometrists Limitations: No confidence intervals available for Mean weighted kappa statistic or SD No patient demographics Notes: Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph *Weighted kappa statistic κ_w Weights assigned to each observation for VCD were equal to 1 minus (difference between estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc. until 1.0 difference
			Inter-observer (ophthal-optom) agreement in estimating VCD **1 x standard deviation of difference scores**	Mean SD = 0.19 (range 0.13 – 0.22) (4/6 mean differences were significantly different p<0.01)	
			Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio **weighted kappa statistic κ_w ***	Mean κ_w = NR Range from 0.29 (fair) to 0.65 (substantial)	
			Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio **1 x standard deviation of difference scores**	Mean SD = NR (range 0.09 – 0.15) (3/6 mean differences were significantly different p<0.01)	
			Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent **(kappa statistic -**	Mean κ = **0.77 (substantial)** Range from 0.61 (substantial) to 0.91 (almost perfect)	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
	Patient demographics were not reported	Estimated vertical cup disc ratio (VCD) Grading of narrowest rim width estimate Haemorrhage present or absent Also graded using simple ranking/ordinal scales Focal pallor of neuroretinal rim Extent of peri-papillary atrophy Steepness of cup-edge Cribriform sign as present or absent	**unweighted)**	% agreement ranges from 90-98%)	= 0. Smaller disagreements were weighted more heavily Kappa value agreement (Landis and Koch 1977) -1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect
			Inter-observer (ophthal-optom) agreement on neuroretinal rim pallor **weighted kappa statistic κ_w ***	Mean κ_w = **0.23 (fair)**	
			Inter-observer (ophthal-optom) agreement on peri-papillary atrophy **weighted kappa statistic κ_w ***	Mean κ_w = **0.45 (moderate)**	
			Inter-observer (ophthal-optom) agreement on steepness of cup edge **weighted kappa statistic κ_w ***	Mean κ_w = **0.50 (moderate)**	
			Inter-observer (ophthal-optom) agreement on cribriform sign **weighted kappa statistic κ_w ***	Mean κ_w = **0.48 (moderate)**	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2001[256] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereo photographs retrospectively selected from of glaucomatous and non-glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereo photographs **<u>All patients</u>** **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): **Definitely non-glaucomatous ≤10)**: 11	**Group 1** 6 optometrists with 4 years accredited training. 2 had 1 year of post-registration experience, 2 had 4 years of post-registration experience and 2 had ≥ 10 years of post-registration experience. None had been involved in shared care schemes or had specialist training. All employed full or part-time in primary care optic role. **Group 2** 6 general ophthalmologists: 2 SPR and 2 SHOs and 2 consultants with subspecialty expertise in glaucoma. **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** Inter-observer (ophthal-optom) agreement in estimating VCD 1 x standard deviation of difference scores Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio weighted kappa statistic κ_w * Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio 1 x standard deviation of difference scores	Mean (95%CI) κ_w = **0.36** (0.31 - 0.41) **(fair)** Range for κ_w from 0.06 (slight) to 0.63 (substantial) Mean (95%CI) SD = 0.18 (0.17 - 0.20) Range 0.10 – 0.28 (25/36 mean differences were significantly different p<0.01 or <0.001 or <0.0001) Mean (95%CI) κ_w = 0.35 (0.29 - 0.41) (fair) Range for κ_w from -0.01 (poor) to 0.77 (substantial) Mean (95%CI) SD = 0.11 (0.11 - 0.12) Range 0.08 – 0.15 (23/36 mean differences were significantly different p<0.01 or <0.001 or <0.0001)	**Funding:** NR **Limitations:** No patient demographics **Notes:** Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph ***Weighted kappa statistic** Weights assigned to each observation for VCD were equal to 1 minus (difference between

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
	Definitely glaucomatous ≥90): 15 **Suspicious (11-89)**: 22 Patient demographics were not reported	Each observer Estimated vertical cup disc ratio (VCD) uncorrected for disc size Grading of narrowest rim width estimate Haemorrhage present or absent The features were discussed between each observer and the researcher prior to grading. All 12 observers had opportunity to read instructions for grading criteria	Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent (unweighted kappa statistic)	Mean (95%CI) κ = 0.42 (0.37 – 0.47) (moderate) Range 0.12 (slight) to 0.72 (substantial)	estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc. until 1.0 difference = 0. Smaller disagreements were weighted more heavily Kappa value agreement (Landis and Koch 1977) -1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spry, 1999[628] & Gray, 2000[242] [Bristol Shared Care Glaucoma Study] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** 2 years Computer generated random numbers and allocation concealment	**Patient group:** glaucoma patients and glaucoma suspects attending glaucoma clinic **Setting:** Bristol Eye Hospital, UK **Inclusion criteria:** 50 years Glaucoma suspects Stable (no change in visual field (VF) over last year) glaucoma Primary open angle glaucoma Pigment dispersion glaucoma Pseudoexfoliative glaucoma Informed consent Ability to cooperate with examination Snellen visual acuity (VA) ≥ 6/18 in both eyes **Exclusion criteria:** <50 years Unstable glaucoma Normal tension glaucoma Secondary glaucoma Narrow angle glaucoma Other coexisting ocular	**Group 1** Routine follow up** in Hospital Eye Service (HES) comprising by a general ophthalmologist: VF analysis with Henson CFS2000/CFA3000 Single IOP measurement using Goldmann Applanation Tonometry (GAT) Vertical cup-disc ratio (VCD) using direct ophthalmoscopy or indirect binocular ophthalmoscopy **Group 2** Structured 6 monthly follow-up at specially trained (instruction through lectures and demonstrations from study researchers) Community Optometrist (CO) comprising: VF analysis using Henson CFA 3000 132 point threshold related	**Mean number of points missed on visual field testing ± SD** ***Better Eye***	**Group 1:** 7.9 ± 12.0 **Group 2:** 6.8 ± 10.8 **Difference between means:** 0.07 (95% CI: -1.86, 2.04) **p value:** 0.94 **(ANCOVA)*** **not signif.**	**Funding:** MRC, International Glaucoma Association, R&D Directorate NHS Executive South and West and Avon Health Authority **Limitations:** **Notes:** ***ANCOVA**: analysis of covariance was performed for each outcome variable comparing the 2 follow up groups ***adjusting for baseline measurements***. Control was also considered for age, sex, time from recruitment to follow up, treatment at baseline, treatment at any time (any/none) and diagnosis (glaucoma suspect/established POAG)
			Mean number of points missed on visual field testing ± SD *Worse Eye*	Group 1: 20.2 ± 21.6 Group 2: 18.3 ± 19.9 Difference between means: 0.04 (95% CI: -3.49, 3.40) p value: 0.98 (ANCOVA)* not signif.	
			Mean IOP (mmHg) ± SD *Better Eye*	Group 1: 19.3 ± 5.1 Group 2: 19.3 ± 4.7 Difference between means: 0.26 ± (95% CI: -1.21, 0.68) p value: 0.59 (ANCOVA)* not signif.	
			Mean IOP (mmHg) ± SD *Worse Eye*	Group 1: 19.1 ± 5.5 Group 2: 19.0 ± 5.3 Difference between means: 0.53 ± (95% CI: -1.58, 0.51) p value: 0.32 (ANCOVA)* not signif.	
			Cup disc ratio ± SD *Better Eye*	Group 1: 0.72 ± 0.12 Group 2: 0.72 ± 0.13 Difference between means: 0.00 (95% CI: -0.02, 0.03) p value: 0.70 (ANCOVA)* not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pathology Extensive field loss (>66/12 missed points on Henson 132 point threshold related suprathreshold examination Best corrected VA in either eye worse than 6/18 **<u>All patients</u>** **N:** 403 **<u>Group 1 (HES)</u>** **N:** 200 **Age (mean ± SD):** 69.4 ± 8.8 **M/F:** 115/85 **Mean glaucoma suspects** **Male**: 48 **Female**: 30 **Family history**: 35 **Previous cataract extraction**: 14 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.18 **Drop outs:** 38 (died = 7, moved = 2, general health = 6, lost to follow up = 23) **<u>Group 2 (CO)</u>** **N:** 203 **Age (mean ± SD):** 68.0 ± 8.3	suprathreshold examination Repeat VF examination on 50% patients Single IOP measurement using GAT VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil) **Examination methods:** A research clinic reference standard (RCRS) examination was performed on each patient at baseline pre-randomisation and 2 year follow up comprising: VF analysis using Henson CFA 3000 132 point threshold related suprathreshold examination Repeat VF examination Triple IOP measurement using GAT VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil)	Cup disc ratio ± SD *Worse Eye*	Group 1: 0.74 ± 0.13 Group 2: 0.74 ± 0.14 Difference between means: 0.00 (95% CI: -0.03, 0.03) p value: 0.70 (ANCOVA)* not signif.	**$Adjusted Intraclass Correlation Coefficient (ICC)**: The ICC is an equivalent to a quadratic weighted kappa statistic as a chance corrected measure of agreement which corrects for systematic bias, weighting discrepancies according to square of the differences between the paired measurements. **ICC = <0.2** "slight agreement"; **ICC = 0.21-0.40** "fair agreement"; **ICC = 0.41-0.60** "moderate agreement; **ICC = 0.61-0.80** "substantial agreement; **ICC = ≥ 0.80** "almost perfect agreement. **For HES group mean
			VCD (inter centre agreement) *Right Eye*	Mean Difference: -0.05 (95% CI: -0.03, -0.07) $Adjusted ICC: 0.50 (moderate agreement) N=360	
			VCD (inter centre agreement) *Left Eye*	Mean Difference: 0.05 (95% CI: 0.03, 0.07) $Adjusted ICC: 0.54 (moderate) N=358	
			IOP mmHg (inter centre agreement) *Right Eye*	Mean Difference: 0.4 (95% CI: -0.05, 0.85) $Adjusted ICC: 0.45 (moderate) N=388	
			IOP mmHg (inter centre agreement) *Left Eye*	Mean Difference: 0.6 (95% CI: 0.13, 1.07) $Adjusted ICC: 0.40 (fair) N=388	
			VF points missed (inter centre agreement) *Right Eye*	Mean Difference: 1.1 (95% CI: -0.38, 2.58) $Adjusted ICC: 0.55 (moderate) N=287	
			VF points missed (inter centre agreement)	Mean Difference: 0.7 (95% CI: -0.80, 2.20) $Adjusted ICC: 0.61 (substantial) N=287	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: 103/100 **Mean glaucoma suspects** **Male**: 51 **Female**: 44 **Family history**: 48 **Previous cataract extraction**: 8 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.17 **Drop outs:** 19 (died = 5, moved = 4, general health = 3, other = 7)	Stereo photographic analysis of VCD by observer 1 Stereo photographic analysis of VCD by observer 2	*Left Eye*		time to first follow up 10.7 ± 5.4 months (range 3 – 24 months) Median number of visits within 2 year period was 2.8 (range 0-8) **Additional outcomes:** RCRS v HES (all outcomes and RCRS v CO (all outcomes

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Theodossiades & Murdoch, 2001[654] **Study design:** Prospective observational	**Patient group:** Volunteers from Moorfields Eye Hospital glaucoma clinics, UK **Inclusion criteria:** Wide range of normal and glaucomatous disc features **<u>All patients</u>** **N:** 50 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by consultant**): **No glaucoma**: 27 **Early glaucoma**: 4 **Moderate glaucoma**: 5 **Advanced glaucoma**: 14 Patient demographics were not reported	**Group 1** 8 community optometrists based in high street optometric practices. 6 also worked part-time in the hospital eye service but not for glaucoma. Optometrists received 2 hours of lectures on assessment of optic nerve head **Group 2** Consultant ophthalmologist with specialist interest in glaucoma **Examination methods:** Both undilated eyes of each patient were first examined by the consultant ophthalmologist using slit lamp biomicroscopy and one eye selected for examination by optometrist. Optometrists assessed one undilated eye through a direct ophthalmoscope of each patient for the following parameters: Vertical disc diameter	**Inter-observer agreement in Vertical disc diameter** weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.34** (0.26 - 0.42) **(fair)**	**Funding:** International Glaucoma Association **Limitations:** No patient demographics Weighting method for VCD and vertical disc diameter was not reported Observer masking was not reported Patients were not recruited in a randomised or consecutive fashion. **Notes:** Kappa value agreement based on (Landis and Koch 1977) 0.00 to 0.2 = poor
			Inter-observer agreement in VCD weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.84** (0.81 - 0.87) **(very good)**	
			Inter-observer agreement in Neuroretinal configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.58 - 0.76) **(good)**	
			Inter-observer agreement in Cup shape kappa statistic κ_w	Mean (95%CI) κ_w = **0.66** (0.58 - 0.74) **(good)**	
			Inter-observer agreement in Neuroretinal rim colour kappa statistic κ_w	Mean (95%CI) κ_w = **0.32** (0.25 - 0.38) **(fair)**	
			Inter-observer agreement in Vessel configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.40 - 0.65) **(moderate)**	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		Vertical cup disc ratio (VCD) Neuroretinal configuration Cup shape Neuroretinal rim colour Vessel configuration Haemorrhage Extent of peri-papillary atrophy Health status of optic nerve head These were then used to give a final opinion on presence or absence of glaucomatous damage	**Inter-observer agreement in Haemorrhage** kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.45 - 0.89) **(good)**	0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very good
			Inter-observer agreement in Peri-papillary atrophy kappa statistic κ_w	Mean (95%CI) κ_w = **0.22** (0.14 - 0.29) **(fair)**	
			Inter-observer agreement in Health status of optic nerve head kappa statistic κ_w	Mean (95%CI) κ_w = **0.62** (0.53 - 0.70) **(good)**	
			Health status of optic nerve head (reference standard defined consultant)	Sensitivity: **0.90** (95% CI: 0.86 - 0.94) Specificity: **0.73** (95% CI: 0.66 - 0.80)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc.**

H.8 Provision of information for patients

None.

H.9 Prognostic risk tools

H.9.1 Increased risk of conversion to COAG

H.9.2 Increased risk of COAG progression

Appendix I: Health economic evidence tables

I.1 Prognostic risk tools

I.1.1 Increased risk of conversion to COAG

No relevant economic evaluations were identified.

I.1.2 Increased risk of COAG progression

No relevant economic evaluations were identified.

I.2 Tests used in case finding, diagnosis and reassessment

I.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

No relevant economic evaluations were identified.

I.2.2 Accuracy of IOP tests

No relevant economic evaluations were identified.

I.2.3 Central corneal thickness measurement evidence

None.

2009

I.2.4 Visual field evidence

None.

I.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

No relevant economic evaluations were identified.

I.3 Reassessment intervals

I.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

Study	[Burr 2012[91]]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcomes: QALYs) **Study design:** Discrete event simulation **Approach to analysis:** Simulating 10,000 individuals through the discrete event simulation which compared strategies covering: risk stratification, surveillance and treatment pathways of OHT, conversion to OAG, treatment pathways of OAG, and progression through OAG severity stages to visual impairment. Five different surveillance strategies were compared and mean costs and QALYs were calculated for each	**Population:** 10,000 individuals simulated through the model for each strategy. Every individual that enters the model has confirmed OHT based on an IOP>21mmHg and no ocular comorbidity. **Baseline characteristics of the simulated population[(a)]:** Initial age: 58.1 Male: 100% IOP: 24.19mmHg CCT: 574.7µm PSD: 1.71 dB VCD ratio: 0.37 **Intervention 1[(b)]:** Treat all **Intervention 2[(b)]:** SOH (hospital)	**Total costs (mean per patient):** Intervention 1: £3,393 Intervention 2: £3,956 Intervention 3: £4,696 Intervention 4: £5,087 Intervention 5: £6,862 Incremental (2−1): £562 Incremental (3−2): £740 Incremental (4−3): £391 Incremental (5−4): £1,776 (95% CI: NR; p=NR) **Currency & cost year:** 2009/10 UK pounds **Cost components incorporated:** Costs of monitoring visits (IOP only visits and full assessment visits in	**QALYs (mean per patient):** Intervention 1: 9.7866 Intervention 2: 9.7932 Intervention 3: 9.7920 Intervention 4: 9.7923 Intervention 5: 9.7931 Incremental (2−1): 0.0066 Incremental (3−2): 0.0012 fewer Incremental (4−3): 0.0003 Incremental (5−4): 0.0008	**ICER (Intervention 2 versus Intervention 1):** £85,312 per QALY gained (pa) **ICER (Intervention 3 versus Intervention 2):** Dominated **ICER (Intervention 4 versus Intervention 2):** Dominated **ICER (Intervention 5 versus Intervention 2):** Dominated **ICER (Intervention 5 versus Intervention 4)[(c)]:** £2,220,000 per QALY gained (pa) **Analysis of uncertainty:** Deterministic sensitivity analysis was conducted varying: • the 5-year risk of conversion from 6%-50% • the unit price of PGA • the unit price of monitoring visits Scenario analysis was also conducted. A groups of variables were identified that

strategy. **Perspective:** UK NHS **Time horizon**: 20 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 3[(b)]:** SOH (primary care) **Intervention 4[(b)]:** NICE guidelines (conservative) **Intervention 5[(b)]:** NICE guidelines (intensive)	secondary care setting and primary/community setting), costs of medication and costs of surgery.		would unequivocally favour 'SOH hospital' which were adherence to treatment, higher precision of IOP measurement with GAT (lower precision in community) and lower accuracy for testing of OAG progression in the community. Threshold analysis was performed on adherence to treatment. Cost-effectiveness results were sensitive to variations in the rate of adherence. Increasing adherence rate for the monitoring pathways reduces the ICER for intervention 2 vs. intervention 1. At 95% adherence the ICER is reduced to £934,736.84 per QALY. Varying the unit cost of the monitoring visit from £51 to £68 changes the incremental cost of intervention 2 vs. intervention 1 from £1,694 to £1,702.

Data sources

Health outcomes: Patient characteristics (age, IOP, CCT, VCD ratio, measure of visual field loss, PSD) were drawn from the Rotterdam dataset. Mortality was taken from UK interim life tables (2007-9) males. The risk of conversion to OAG for the SOH pathways was developed using the risk-predicting algorithm based on the pooled OHTS-EGS model which provides an estimate of the 5-year risk of developing OAG. This was extrapolated for subsequent 5-year periods (beyond 5 years) using the same risk prediction tool but entering the level for each of the individuals characteristics at the start of that 5-year period. Baseline risk of progression into moderate and severe OAG and visual impairment were obtained from a systematic review conducted by Burr et al. Progression of treated individuals was delayed (compared to the baseline risk) depending on treatment efficacy and adherence to treatment. Data on IOP were based on the Rotterdam and Moorfields data sets. The error term of a regression model (presented in the same HTA report) was used to estimate the uncertainty surrounding the measurement of IOP by ophthalmologists in secondary care. It was assumed that ophthalmologists in secondary care can detect conversion to OAG with a sensitivity and specificity equal to 1. Data on ability of a non-ophthalmologist to detect conversion to OAG (for the SOH primary strategy) was taken from Azuara-Blanco (2007). The percentage reduction in IOP from treatment was taken from data reported in the NICE guidance (CG85). Data on adherence to treatment was based on expert opinion. Proportion of people that convert to OAG and have surgery was taken from Burr et al. (2009). Treatment were assumed to work solely by reducing IOP, and if they reduced it by more than 15% then IOP was considered on target. Treatment effect for those who had converted to COAG came from Maier 2005. Adherence of 75% was assumed for those under surveillance and 50% for the treat all community pathway where their IOP would be measured yearly by an optometrist. **Quality-of-life weights:** EQ-5D data obtained from 255 OAG individuals from Aberdeen and Leeds as well as members of the International Glaucoma Association (moderate = 0.7471, severe = 0.7133, visually impaired = 0.535). Mild OGA was assumed to be the same utility as OHT (0.8015). **Cost sources:** Unit costs for an ophthalmology service outpatient visit from the Scottish National Statistics Information Services Division to cost a visit to measure IOP only (£90). This cost was doubled for the cost of a full assessment in secondary care (£180). For

the SOH primary strategy, the cost of a non-ophthalmologist assessment in a primary care / community setting was assumed to be that of an NHS sight test fee (£20.70) and half the fee for IOP only assessment (£10.35). Medication costs were taken from the BNF assuming one bottle (of non-proprietary timolol) per month. For PGA, the unit costs of Xalatan and Xalacom were selected to calculate the annual cost of PGA and combination therapy. The cost of surgery was obtained from NHS reference costs (2008-9).

Comments

Source of funding: NIHR **Limitations:** The interventions are broad spanning over risk stratification, monitoring and treatment decisions. For different intervention strategies, a number of things are simultaneously different making it difficult to attribute differences in costs and QALYs to particular elements of the interventions. The comparison of the two different NICE guideline strategies are the only interventions that are relevant to this review question as the only thing that differs from the conservative and the intensive interventions are the monitoring intervals. This is why the ICER comparing the intensive strategy to the conservative strategy has been presented. The NICE guideline strategies assume that people are continuously monitored in ongoing loops. This is a misinterpretation of how the NICE guideline CG85 would be followed by clinicians in practice. They do not accurately reflect usual care as in reality, a number of people would be discharged from the services (for example if their IOP was significantly lower at a future appointment and they were no longer considered to be at risk). The model does not have a restriction on the number of times a person can return for an IOP check at 2 to 4 months after a new treatment is begun. This could have led to an overestimation of the number of IOP visits in the model and an underestimation of the cost effectiveness of the strategies. In reality, clinicians would usually find the adequate drop combination to control IOP. The 'treat all' strategy does not take into account the costs that would be required to train community optometrists to be able to judge whether they believe someone is at a high risk of conversion to COAG. Due to the complexity of the DES model, PSA was not explored and therefore joint parameter uncertainty and its effect on results was not fully explored. The model took a 20 year time horizon was not adequate to capture the number of people that would progress to severe visual impairment. The model did not include the costs of adverse effects of treatment for example respiratory adverse effects from Beta-Blocker medication. **Other:** As the interventions include differences in risk stratification, surveillance and treatment decisions, most of the interventions do not fit the protocol for this review.

Overall applicability: Partially applicable [(d)] **Overall quality** Potentially serious limitations [(e)]

Abbreviations: CCA: cost-consequence analysis; CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; OAG: open-angle glaucoma

(a) The characteristics for each individual were drawn from probability distributions for the characteristics obtained from sources.

(b) See Table 13 *for details of risk stratification rules, surveillance and treatment criteria for each pathway*

(c) The NICE conservative and NICE intensive strategies were the only comparison considered relevant for this review which is why the ICER for intervention 5 vs. 4 has been presented.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Table 13: Additional information on strategies in Burr 2012

	Treat all pathway (Intervention 1)	The SOH pathways (community/hospital) (Intervention 2 and 3)	The NICE pathways (intensive and conservative) (Intervention 4 and 5)

	Treat all pathway (Intervention 1)	The SOH pathways (community/hospital) (Intervention 2 and 3)	The NICE pathways (intensive and conservative) (Intervention 4 and 5)
Risk	All individuals with IOP > 21 mmHg judged to be at high risk of conversion to OAG. No further risk stratification considered.	Used the best available risk prediction tool (see Chapter 4 of HTA report) to inform the choice of initial treatment of individuals. Information on age, VCD ratio, IOP, CCT and a measure of visual field loss (PSD) combined using an algorithm based on the pooled OHTS-EGPS model to calculate the 5-year risk of conversion to OAG. The 5-year risk of developing OAG was grouped into three categories: low (< 6%), intermediate (6–13%) and high (> 13%).	The criteria used to categorise individuals with OHT as low, medium or high risk of conversion to OAG are not explicitly stated. Guidelines provide clear criteria to inform surveillance and treatment decisions, with decisions on surveillance and treatment made on CCT and level of IOP together with age.
Surveillance	No active monitoring: individuals are advised (and assumed) to attend a community optometrist annually for measurement of IOP.	All those starting treatment with a PGA, and those changing to a new medical treatment, have two consecutive (same visit) IOP measurements within 2 months of starting or changing a treatment. Individuals are monitored every 2 years in either a secondary or primary care setting for the 'SOH hospital' and 'SOH primary care' pathways respectively. For the 'SOH primary care' pathway individuals would only be referred to secondary care if IOP was 'off target' or conversion to OAG being detected.	For those with untreated OHT, a full assessment is recommended every 6 or 24 months depending on risk (See CG85). For treated OHT, IOP measurement 2 months after initiating treatment is recommended. Full assessments are every 4, 6 or 12 months depending on risk (see CG85). For the intensive pathway people are monitored at the earliest time within the recommended ranges in the NICE guideline (CG8) and for the conservative pathway people are monitored at the latest time within the recommended ranges of CG85.
Treatment decisions	All individuals with IOP > 21 mmHg are treated with PGAs. If IOP off target (< 15% reduction) from baseline (model entry) then individuals are referred to an ophthalmologist in a secondary-care setting.	Individuals with low risk (5-year risk of conversion < 6%) are not treated. Individuals with intermediate or high risk (5-year risk of conversion ≥ 6%) are treated with a PGA. If IOP off target the sequence of treatments is as outlined in "The sequence of treatment" in the HTA report.	Details of the criteria under which treatment is initiated are provided are in Table 35 of the HTA report. (Also see treatment recommendations in CG85). Medical treatment is stopped when individuals reach 60, 65 or 80 years of age if they are taking BBs, PGAs or combination therapy, respectively. The decision to stop treatment taken only if IOP remains on target and progression to OAG has not occurred. Finally, the decision about what initial treatment to be given is based upon the

	Treat all pathway (Intervention 1)	The SOH pathways (community/hospital) (Intervention 2 and 3)	The NICE pathways (intensive and conservative) (Intervention 4 and 5)
			age and measures of CCT and IOP as defined in Table 35 of the HTA report (also see treatment recommendations in CG85.
Care following conversion to OAG	All surveillance and care once an individual has converted to OAG provided by an ophthalmologist in a secondary-care setting.	All surveillance and care once an individual has converted to OAG provided by an ophthalmologist in a secondary care setting	All surveillance and care once an individual has converted to OAG provided by an ophthalmologist in a secondary care setting.

I.3.2 Optimum intervals for chronic open-angle glaucoma

Study	**Crabb 2012[145]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA outcome: QALYs) **Study design:** Markov model **Approach to analysis:** Figures were developed for a hypothetical cohort of 10,000 people. Markov model of glaucoma health states including: mild, moderate, severe, visually impaired and death, comparing the cost-effectiveness of people newly diagnosed with glaucoma receiving six VF tests in the first two years of clinical management following diagnosis (proposed practice)	**Population:** 10,000 people newly diagnosed with glaucoma. **Cohort settings:** Start age: 50 (28.15%) or 70 (71.85%) Male: 52.9% Proportion in initial health states: if 50 years old; 65% = mild, 21.4% = moderate, 10% = severe, 3.7% = visually impaired. If 70 years old; 66.2% = mild, 20.9% = moderate, 9.3% = severe, 3.7% = visually impaired. **Intervention 1:** Annual VF tests after diagnosis of glaucoma **Intervention 2:**	**Total costs of full simulation (mean per patient):** Intervention 1: £7,765 Intervention 2: £8,059 Incremental (2−1): £294 (95% CI: NR; p=NR) **Currency & cost year:** 2011 UK pounds **Cost components incorporated:** Monitoring costs, treatment costs and implementation costs.	**QALYs of full simulation (mean per patient):** Intervention 1: 6.41 Intervention 2: 6.43 Incremental (2−1): 0.1 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1) (deterministic):** £21,679 per QALY gained (pa) 95% CI: Probability Intervention 2 cost-effective (£20K/30K threshold): 28.35%/57.33% **Analysis of uncertainty:** PSA undertaken with 10,000 simulations. Deterministic sensitivity analyses were also undertaken. DSA identified that the ICERs were most sensitive to uncertainty surrounding the parameters utilised for utility health states. Uncertainty associated with the costs of the different treatment lines was also found to impact on the deviation of the ICER.

compared to annual VF tests (current practice). **Perspective:** UK NHS **Time horizon**: 25 years **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	Six VF tests in the first two years after diagnosis of glaucoma			

Data sources

Health outcomes: A retrospective data analysis was used to identify baseline parameters for the model, as the main driver of the model is that more frequent VF testing will result in earlier detection of progression. To estimate how much earlier this would occur with the proposed practice strategy, the distribution of the rate of progression in a large cohort of UK patient records (archived from Moorfields Eye Hospital in London, Cheltenham General Hospital, Gloucestershire Eye Unit and Calderdale Royal Hospital in West Yorkshire and Queen Alexandra Hospital in Portsmouth) was investigated. This involved the analysis of around 6000 patients. Virtual series of VF tests were then generated to explore different follow-up schemes for newly diagnosed glaucoma patients, comparing annual VF testing with three tests per year in the first two years (details of the statistical model were presented in Chapter 4 of the Crabb et al. (2007) report). This found that in the proposed practice fast progressors would be identified by the fourth year of monitoring, medium progressors by the fifth year, and stable progressors by the twelfth year. In terms of treatment pathways; The effects of treatment on transition were based on a proportional relationship between IOP reduction and the rate of MD progression (a 1mmHg reduction in IOP translates to a 0.1dB/year improvement in MD rate). Three lines of treatment were included in the model, and the type of treatment depends on your progression risk (high or low), age and existing VF damage. Once someone has received a specified number of tests (and depending of patient's underlying risk of progression), a period defined as 'perfect information' starts where the patient's rate of progression is measured with sufficient accuracy to inform and adjust treatment allocation. The health states in the model were defined according to the Bascom Palmer glaucoma staging system of mild. Moderate, severe, and visually impaired. Patients are allocated to one of these health states based on baseline disease severity. Transition probabilities were defined as a function of patient's rate of progression and their initial level of damage following methodology suggested by Hernandez et al. (2008) and Briggs et al. (2006). Progression rate: if 50 years old; 49.2% are stable, 36.4% are slow, 12.2% are medium and 2.3% are fast progressors. If 70 years old; 33.8% are stable, 41% are slow, 21% are medium, and 4.2% are fast progressors.

Quality-of-life weights: Utility weights were derived from Burr et al. (2007) **Cost sources:** Extra VF tests assumed to be performed by technicians and costs of monitoring sourced from *National Schedule of Reference Costs (20010-11* (£56.54 per additional test*)),* treatment costs sourced from Traverso et al. (2005). Implementation costs micro costed; a yearly new incidence of glaucoma population of 10,000 was assumed meaning current practice would require 20,000 tests to be performed and the proposed practice would require 60,000 tests therefore an extra 40,000 tests would be required. A 5 day week was assumed with two people tested per hour per HFA machine, each machine able to perform 4160 VF tests per year therefore 10 machines and 10 technicians would be required to cover the extra tests required. An annual wage of £25,000 was assumed for technician and a £25,000 price per HTA therefore the cost of implementing the infrastructure required to cover the increased number of VF tests was estimated to be £410,000. This was added as a fixed cost within the model for proposed practice.

Comments

Source of funding: The Health Services and Delivery Research (HS&DR) programme, part of the National Institute for Health Research (NIHR) **Limitations:** The estimation of how much earlier progression would be detected from the proposed practice strategy is based on computer simulated retrospective data; not on RCT

data which is why the statistical model conducted to estimate the clinical effectiveness data used in the model was not included in the clinical review of this question. In reality, a number of things, other than just VF test results, are likely to be factored into a consultant's decision on how quickly to escalate a person's treatment plan, how quickly they believe the person is progressing and how frequently they will measure VF, for example the amount of damage identified at diagnosis, the perceived risk of the patient, the experience of the consultant. This might have led to inaccuracies in the estimates of how quickly improved information on progression is obtained. In the model, current practice is assumed to be annual VF tests, whereas in realty many high risk people would have more frequent tests performed, especially if progression was detected. This underestimation of the amount of tests performed in current practice could be biasing the results in favour of the proposed practice strategy. To cover the extra capacity required to carry out the additional tests, a fixed cost covering the cost of the equipment and staff required to perform the tests was added to the proposed practice strategy. These reflect the costs to the individual provider for carrying out the additional tests; however, the micro costing does not include costs such as the administrative costs associated with booking additional appointments. The cost to the NHS would be the amount the provider is reimbursed for an outpatient visit to the ophthalmology department. This may have resulted in the cost of the proposed strategy being underestimated. Sensitivity analysis on this cost reported that increasing the fixed cost to £820,000 resulted in an ICER of £24,706, which is significantly above a willingness to pay of £20,000 per QALY gained. **Other:** The model analysed the full simulation of all 10,000 people in the model and analysed the following cohort subgroups separately: males with starting age 50 (M50), females with starting age 50 (F50), males with starting age 70 (M70), females with starting age 70 (F70). Only the full simulation results have been extracted in this evidence table. Proposed practice was found to be the least cost effective for the M70 cohort and the most cost effective for the F50 cohort. The results of the ICER seem very sensitive to the outputs. The ICER calculated form the incremental numbers they report in the paper (£294/0.1 = £29,400) is much higher than the ICER reported in the paper. This is likely to be down to the outputs being rounded; however, such a large difference weakens the confidence in more frequent VF testing likely to be cost effective.

Overall applicability: Directly applicable[(a)] **Overall quality: Potentially serious limitations**[(b)]

Abbreviations: % CI: 95% confidence interval; CUA: cost-utility analysis; DSA: deterministic sensitivity analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; MD: mean defect; NR: not reported; PSA: probabilistic sensitivity analysis; QALYs: quality-adjusted life years; VF: visual fields

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

I.4 Overview of Treatment

2009

None.

I.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

I.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

None.

I.5.2 Laser treatment for COAG

None.

I.5.3 Surgical treatment for COAG

None.

I.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

I.6 Complementary and alternative interventions

None.

I.7 Organisation of care

I.7.1 Service models for case finding, referral filtering and diagnosis

Study	Azuara-Blanco 2016[39]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Deterministic decision analytic Markov model **Approach to analysis:** Markov model of glaucoma diagnosis and progression comparing four initial triage	**Population:** People referred from community optometrists or general practitioners to hospital eye services with any possible glaucoma-related findings. **Cohort settings:** Start age: 40 Male: 100% (Assumed to have an eye test approx. once every 3 years.)	**Total costs (mean per person):** Intervention 1: £2,791 Intervention 2: £2,917 Intervention 3: £2,952 Intervention 4: £2,961 Intervention 5:	**QALYs (mean per person):** Intervention 1: 19.7701 Intervention 2: 19.7746 Intervention 3: 19.7771 Intervention 4: 19.7771 Intervention 5: 19.778	**ICER (Intervention 2 versus Intervention 1):** Extendedly dominated **ICER (Intervention 3 versus Intervention 1):** £22,904 per QALY **ICER (Intervention 4 versus Intervention 3):** Dominated **ICER (Intervention 5 versus Intervention 3):** £156,985 per QALY gained **Compared to current practice:**

strategies in hospital eye care services (HES) glaucoma clinics. The study compared triaging using different imaging technologies (as part of the triage) to current practice where no initial triaging takes place. Twelve health states including normal, treated and untreated health states for: at risk of glaucoma, mild, moderate, severe glaucoma, sight impaired and a death state. Yearly cycles. The sensitivity and specificity of each triage strategy determined the probability that diagnosis was correct and, depending on this, the health state that people would move to (treated or untreated) and the associated progression of any underlying glaucoma. **Perspective:** UK NHS **Time horizon or Follow-up** 50 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Intervention 1:** GDx test by a technician; IOP and VA by a nurse. If all 3 tests are negative, discharge the person. If any of GDx or IOP or VA tests are positive, refer the person on to diagnosis stage (clinician examination) **Intervention 2:** OCT test by a technician; IOP and VA by a nurse. If all 3 tests are negative, discharge the person. If any of the OCT, IOP or VA tests are positive, refer the person to the diagnosis stage (clinician examination) **Intervention 3:** HRT-MRA test by a technician; IOP and VA by a nurse. If all 3 tests are negative, discharge the person. If any of the HRT-MRA, IOP or VA tests are positive, refer the person to the diagnosis stage (clinician examination) **Intervention 4:** HRT-GPS test by a technician; IOP and VA by a nurse. If all 3 tests are negative, discharge the person. If any of the HRT-GPS, IOP or VA tests are positive, refer the person to the diagnosis stage (clinician examination) **Intervention 5:**	£3,084 Incremental (2-1): £126 Incremental (3-2): £35 Incremental (4-3): £9 Incremental (5-4): £123 (95% CI: NR; p=NR) **Currency & cost year:** 2012 UK pounds **Cost components incorporated:** Diagnostic imaging, staff time, treatment, equipment, and capital costs.	Incremental (2-1): 0.0045 Incremental (3-2): 0.0025 Incremental (4-3): 0 Incremental (5-4): 0.0009 fewer (95% CI: NR; p=NR)	The most cost effective is intervention 3. Although 3 is not cost effective compared to 1, it is cost effective compared to 5. If both are compared to current practice, which is the most expensive alternative, then both 1 and 3 would save costs at the expense of QALYs, but 3 would save much more per QALY lost (1 versus 5=£37,088 saved per QALY lost, and 3 versus 5=£156,985 save per QALY lost). As HRT equipment has been discontinued the committee felt the comparison of intervention 2(using an OCT test within the hospital triage) versus 5 would also be informative. Intervention 2 would save £52,187 per QALY lost compared to current practice (no triage). **Analysis of uncertainty:** Several deterministic sensitivity analyses (SA) were explored. The SAs varied: the annual probability of discharged people having a sight test; the cost of triage tests; the start age of the cohort; the performance of the diagnosing clinician; the diagnostic performance of imaging technologies; the prevalence of glaucoma in the referred population; and utility weights for those 'at risk of glaucoma'. The possibility of a hypothetical pathway, in which people diagnosed as 'at risk of glaucoma' were discharged from the service, was explored to investigate the impact in terms of costs and QALYs. The incremental cost effectiveness of the triage strategies compared with current practice is very sensitive to the costs included in the model especially the cost of the triage station. Current practice becomes cost-effective when the total cost

	Current practice. No initial Triage takes place and everyone is referred directly to the diagnosis stage (clinical examination)			of a triage test increases to £30 and above. Current practice dominates all strategies under the plausible assumption that an NHS provider of care would charge, for the triage station, an NHS reference cost tariff corresponding to an outpatient appointment. Current practice becomes dominant when the cost of an outpatient appointment increases to £61 and above. A key assumption used in the model was that clinicians are 100% accurate in their diagnostic ability. Relaxing this assumption increased further the ICER (favouring triage strategies).

Data sources

Health outcomes: Sensitivity and specificity of strategies and prevalence of 'at risk of glaucoma' data from GATE study (the same HTA). Progression to mild glaucoma from 'at risk of glaucoma' sourced from expert opinion from clinical experts on the research team. Rates of progression to moderate, severe and sight-impaired sourced from literature (Burr et al. 2014). Mortality from interim life tables. Epidemiology data sourced from literature (Burr et al. 2007). **Quality-of-life weights:** EQ-5D UK tariff. Utility weights sourced from literature (Burr et al. 2012) apart from the utility of being in the normal state, which was assumed at 1. **Cost sources:** Treatment costs taken from literature (Burr et al. 2007) of which their costs were based on costs reported in Traverso et al. The treatment costs were inflated to current health price levels. Costs of the diagnosis pathway triage strategies were micro costed and then checked with the steering committee. Time taken to carry out tests and bands of the staff carrying out the tests were assumed (for example, imaging tests would be performed by a band 3 technician ad would take 15 minutes). Unit costs of staff time were calculated from NHS *Agenda for Change* and inflated to current health price levels. People diagnosed with a positive composite test result were referred for a first consultant-led ophthalmology appointment; the cost of this appointment was based on the NHS reference cost (HRG WF01B). Capital costs sourced from specific commercial providers. The initial outlay costs were annuitised over the useful, working lifespan of the piece of equipment (assumed to be 10 years for all equipment) and an annual discount factor of 3.5% was applied to account for the opportunity cost of the investment over time. The equivalent annual cost of each piece of equipment was divided by its estimated maximum number of uses per annum based on 253 working days per year, each taking 15-minute slots over a 7.5-hour working day. This assumption was based on information provided by Moorfields Eye Hospital NHS Foundation Trust (personal communication). The authors were unable to obtain data on capital cost of the GDx diagnostic technology, so it was assumed to be the same as the HRT-III machine.

Comments

Source of funding: National Institute for Health Research (NIHR) **Limitations:** Due to a lack of data on the accuracy of the tests in a triage setting, the parameter estimates were based on the GATE study alone and not from a meta-analysis of multiple studies. The base-case model assumes that the clinician would make a perfect diagnosis and therefore the model structure does not include all possible health states that might be relevant after diagnosis such as a misdiagnosis of those at risk of glaucoma as having glaucoma (initiate unnecessary treatment), or fail to diagnose some glaucoma cases (not initiate treatment). Relaxing this assumption was explored in a sensitivity analysis, the results of which further decreased the cost effectiveness of current practice. The model was not built probabilistically; therefore, the

probability that the interventions are cost effective at different thresholds (20k/30k) could not be estimated. **Other:** Current practice is the most effective strategy but also the most costly with an ICER of £156,985. It can be interpreted that moving from current practice to the HRT-MRA Triaging strategy would produce savings of £156,985 per QALY lost (as HRT-MRA Triaging strategy is less effective than current practice).

Overall applicability:[(a)] Directly applicable **Overall quality**[(b)] Potentially serious limitations

95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: EuroQol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GDx: a tool that uses laser to determine the thickness of the nerve fibre layer; HRT-MRA: Heidelberg Retina Tomograph-Moorfields regression analysis ICER: incremental cost-effectiveness ratio; IOP: Intraocular pressure; NR: not reported; OCT: Optical coherence tomography; QALYs: quality-adjusted life years; VA: visual acuity

(a) Directly applicable, Partially applicable, Not applicable

(b) Minor limitations, Potentially serious limitations, Very serious limitations

Study	**Parkins 2011[531]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: proportion of people not referred to hospital eye services after scheme compared to 100% of people suspected of having COAG related condition referred after initial case-finding appointment in the community) **Study design:** Prospective cohort study with comparative costs **Approach to analysis:** Over 12 months, all referrals in the area were analysed. Total costs of 2 different referral filtering schemes to commissioners were then estimated (a	**Population:** All suspected glaucoma or Ocular Hypertension (OHT) referrals from optometrists relating to people registered with Bexley GPs during the period from April 2007 to March 2008. **Participant characteristics:** N=427 Mean age=NR Male=NR **Intervention 1:** Regular hospital eye service pathway. Everyone suspected of having a COAG related condition is referred directly to HES. No referral filtering in place. **Intervention 2:**	**Total costs (mean per participant)*:** Intervention 1: £132.67 Intervention 2: £50.88 Intervention 3: £127.98 Incremental (2−1): saves £81.79 Incremental (3-1): saves £4.69 (95% CI: NR; p=NR) **Currency & cost year:** 2007/8 UK pounds[(b)] **Cost components incorporated:** For regular HES pathway: first appointment costs, costs of monitoring participants, prior to	**Proportion of people referred to HES after scheme:** Intervention 1: 100% Intervention 2: 24% Intervention 3: 59% (95% CI: NR; p=NR) Incremental (2−1): 86% fewer Incremental (3-1): 41% fewer (95% CI: NR; p=NR) **Of those referred to HES, the proportion still under the care of HES at the end of follow-up period:** Intervention 2: 40%	Both schemes reduce costs compared to having no scheme in place. If it is assumed that the people not referred after the scheme (that would otherwise have been referred) are all false positives then the schemes dominate no scheme as they cost less and do not increase the risks to patients. Unfortunately the study was not able to assess the accuracy of the decisions taken regarding people who were not referred. **Analysis of uncertainty:** None

repeat measures scheme and an enhanced case-finding scheme). The cost of each scheme was compared to a hypothetical scenario of a regular hospital eye service (HES) pathway (intervention 1) where there was no referral filtering; everyone referred straight to HES from initial case-finding appointment. **Perspective:** UK NHS **Follow-up**: 12 months **Discounting:** Costs: NA; Outcomes: NA	Enhanced glaucoma repeat measurement (EGRM) (IOP is tested using air puff, if positive then give Goldmann applanation tonometry). This is all carried out in the same clinic and clinics are reimbursed for the repeat tests. **Intervention 3:** Refinement by the community team after clinical assessment (RCAS). People who are initially suspected of having a COAG related condition are sent to a group of Care Trust funded optometrists with additional training in glaucoma who then carried out a full assessment in community practice prior to any secondary referral.	discharge. For EGRM: refresher training for optometrists, total refinement fees paid, onward referrals, cost of monitoring participants prior to discharge. For RCAS: Training, administrative triage costs, direct referrals to HES, total refinement fees paid, referrals by RCAS, cost of monitoring participants prior to discharge.	Intervention 3: 50%	

Data sources

Health outcomes: Analysis of the participant level data on referrals of people in schemes. **Quality-of-life weights:** NA. **Cost sources:** Fees that applied for optometrists participating in the schemes were used to estimate costs of services provided by schemes. **Payment by Results**: Ophthalmology tariffs 2007/8 used for costs of first and follow-up appointments at the HES. Authors assumed an average of 2.10 visits (1.10 follow-ups) prior to discharge (for participants discharged from HES). Administrative costs for the patient management centre (PMC) team in the RCAS scheme were adjusted to reflect the proportion PMC resource expended on assessing glaucoma related referrals and the cost of organising the resulting primary care booking services.

Comments

Source of funding: NR. **Limitations:** A limitation of the study is that it was not able to assess the accuracy of the decision taken regarding people who were not referred. From a service perspective, reducing the number of referrals to HES is optimal, as it frees up capacity; however, we cannot determine how this would affect clinical outcomes for participants. If referral filtering through either type of scheme were to increase the number of false negatives and therefore miss people who required treatment, those who were missed could end up costing the NHS more money long term, as they would progress to glaucoma faster than if such people were initially picked up. If the rates of false negatives through the schemes are high (we cannot know), it would not be guaranteed that a FN diagnosis would be corrected at the next appointment. However, in areas that do not have any referral filtering in place, around 40% of people are discharged from HES at their first appointment (committee estimate), therefore although we cannot know for certain, it is highly likely that most of the people not referred through the schemes would have been false positives. Another reason one can assume the schemes would not increase the number of false negatives is that more tests are done on people in the schemes

therefore the decisions are likely to be more accurate. Also the tests in the schemes are likely to be better and more accurate than the tests done without schemes (e.g. without scheme referral can be made on IOP>21mmHg on one air puff test whereas in repeat measures scheme all people must have GAT prior to referral). Another limitation is that the study compared the costs of people referred through the scheme to a hypothetical scenario where all people are referred to HES. It does not account for the rate of correct referrals. Small limitation of the study is that tariffs were used to estimate cost of appointments to HES whereas it would be more accurate to use NHS reference costs. **Other:** * As the type of community optometric clinics that signed up to the two different schemes could have systematically differed, the populations referred through the different schemes could also be systematically different. This means the costs of the two schemes cannot be compared to each other; they can only both be compared to the hypothetical scenarios of no scheme being in place. Without taking into account the lifetime health outcomes for participants or modelling average lifetime costs and QALYs produced by the different schemes as well as current practice (referring all to HES), The cost effectiveness of the referral schemes cannot be determined. The schemes might shift costs by reducing short-term costs of referring and monitoring fewer people in HES to increasing long-term costs of more people requiring treatment later.

Overall applicability:[(a)] Directly applicable **Overall quality**[(b)] Potentially serious limitations

Abbreviations: CCA: cost-consequence analysis; COAG: chronic open-angle glaucoma; EGRM: Enhanced glaucoma repeat measurement; HES: hospital eye services; IOP: intraocular pressure; RCAS: Refinement by the community team after clinical assessment

(a) Directly applicable, Partially applicable, Not applicable

(b) Minor limitations, Potentially serious limitations, Very serious limitations

Study	**Peeters 2008** [534]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA (health outcome: proportion of patients becoming blind, years of blindness) **Study design:** Decision analytic Markov model **Approach to analysis:** Three case-finding strategies are analysed and compared. The simulated cohort consists of all initial patients of at least 40 years old visiting an ophthalmic practice. All	**Population:** All initial patients of at least 40 years old, visiting an ophthalmic practice. **Cohort settings:** Start age: 40 years Male: NR **Intervention 1:** tonometry is not performed on anyone **Intervention 2:** tonometry is routinely performed to	**Total costs (mean per patient):** Intervention 1: £156 Intervention 2: £183 Intervention 3: £204 Incremental (2−1): £27 Incremental (3-2) £21 (95% CI: NR; p=NR) **Currency & cost year:** 2001 Dutch Euros (presented here as 2001 UK pounds[(a)]) **Cost components**	**Proportion of patients not becoming blind:** Intervention 1: 0.984 Intervention 2: 0.986 Intervention 3: 0.993 Incremental (2−1): 0.002 Incremental (3−2): 0.007 (95% CI: NR; p=NR) **Years of blindness:** Intervention 1: 0.062 Intervention 2: 0.053	**Extra cost to prevent one person becoming blind:** **(Intervention 2 vs. Intervention 1):** £13,500 **(Intervention 3 vs. Intervention 2):** £3,000 **Extra cost per year of vision saved:** **(Intervention 2 vs. Intervention 1):** £3,000 **(Intervention 3 vs. Intervention 2):**

patients undergo ophthalmoscopy, but tonometry is routinely performed to: (1) no one, (2) high-risk patients only, or (3) all initial patients. The population characteristics are based on data of 1000 initial patients. **Perspective:** The Netherlands societal perspective **Time horizon/Follow-up** 20 years **Discounting:** Costs: 4%; Outcomes: 4%	high-risk patients only **Intervention 3:** tonometry is routinely performed to all initial patient	**incorporated:** Direct costs of diagnosis and treatment which are either once only costs or state dependent costs. The once only costs include: costs of the diagnostic process, and costs for laser treatment and surgery. The state dependent costs include: The costs of outpatient visits and medication. The costs of diagnosis apply to all patients and the costs of treatment apply to diagnosed patients only.	Intervention 3: 0.021 Incremental (2−1): 0.009 fewer Incremental (3−2): 0.032 fewer (95% CI: NR; p=NR)	£656.25 **Analysis of uncertainty:** One-way sensitivity analysis using lower and upper bounds (for which ranges were presented in the paper) of all parameters was performed. Alteration of glaucoma incidence among undiscovered OH patients had the largest impact on results. Incremental cost per year of vision saved for tonometry all strategy (intervention 3) is £3,229 when glaucoma incidence among discharged OH patients is at its lowest. Alteration of blindness incidence among untreated glaucoma patients gives incremental costs per year of vision saved £2,697 when it is lowest, and £857 when it is highest. A two-way sensitivity analysis, which uses the lower values of both above-mentioned parameters, gives the incremental costs £8,471 per year of vision saved.

Data sources

Health outcomes: The population characteristics are based on data gathered from the charts of 1000 initial patients visiting an ophthalmic practice. Patients consecutively visiting a general ophthalmic practice in Maastricht (Medisch Centrum Maastricht AnnadalFMCMA), starting from January 1999. All other health outcomes (transition probabilities) sourced from literature including: diagnostic accuracy of tests, OH development in discharged 'normals', POAG development in discharged OH and in treated OH, proportions of POAG patients who will receive laser or surgery and the success of both, probability of switching therapy and blindness development. Number patients with regular eye visits due to other conditions sourced from hospital data. **Quality-of-life weights:** NA **Cost sources:** The (direct) costs of diagnosis and treatment represent those for the Netherlands. The unit prices related to the outpatient visits, laser trabeculoplasty and surgery are as determined at the University Hospital Maastricht which was performed according to a micro costing method. The prices of medical drugs represent the prices in the Netherlands. The prices of monotherapy and combination therapy are based on the average use of the individual drugs in the Netherlands, combining up to three drugs in combination therapy. The frequency of healthcare use was modelled in accordance with specialist opinion and recommendations of the American Academy of Ophthalmology. The costs due to blindness in connection with the usage of disability facilities in the Netherlands could not be retrieved.

Comments

Source of funding: Dutch Health Care Insurance Council, Diemen, The Netherlands. **Limitations:** The study was assessed as partially applicable as it was conducted in

the Netherlands and therefore the costs and treatment pathways would be likely to differ compared to the UK. Population data comes from people visiting a practice in 1999 so might not reflect a present UK population visiting UK practices. As health outcomes are not expressed in terms of QALYs, the cost effectiveness of the interventions cannot be determined by a NICE willingness to pay threshold as there is not a willingness to pay to prevent one person becoming blind or year of blindness avoided. **Other:** Values reflect IOP measurement by the Goldmann applanation tonometer to diagnose patients with IOP>21mm Hg. Per strategy the proportions of the correct diagnoses have been calculated, using the following assumption: In case of a positive outcome of at least one of the performed tests a patient undergoes further examinations and will be correctly diagnosed within the first 6 months. Values for perimetry were not required for the calculations, even if perimetry contributes to the achievement of a correct diagnosis. Perimetry is performed in case of positive results of testing with ophthalmoscopy and/or tonometry.

Overall applicability: Partially applicable(b) **Overall quality: Potentially serious limitations**(c)

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; NR: not reported
(a) Converted using 2001 purchasing power parities[515]
(b) Directly applicable, Partially applicable, Not applicable
(c) Minor limitations, Potentially serious limitations, Very serious limitations

I.7.2 Skills required by healthcare professionals

None.

I.8 Provision of information for patients

None.

2009

Appendix J: GRADE tables

J.1 Prognostic risk tools

J.1.1 Increased risk of chronic open-angle glaucoma

None.

J.1.2 Increased risk of vision loss

None.

J.2 Tests used in case finding, diagnosis and reassessment

J.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

None.

J.2.2 Accuracy of IOP tests

None.

J.2.3 Central corneal thickness measurement evidence

None.

2009

J.2.4 Visual field evidence

None.

J.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

None.

J.3 Reassessment intervals

J.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

None.

J.3.2 Optimum intervals for chronic open-angle glaucoma

None.

J.4 Overview of Treatment

None.

2009

J.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

J.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

Table 11: Clinical evidence profile: Preservative versus preservative-free solutions

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preservative versus preservative-free solutions	Control	Relative (95% CI)	Absolute		

Glaucomatous visual field loss (critical outcome)– no data reported Normal visual field to visual field defect (critical outcome) – no data reported Progression of glaucomatous visual field defect (critical outcome)– no data reported Vision loss (critical outcome)– no data reported Health-related quality of life (critical outcome) – no data reported												
Change in IOP from baseline (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	20	-	MD 0.4 higher (0.63 lower to 1.43 higher)	⊕⊕OO LOW	IMPORTANT
Major adverse events (no definition – follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/20 (0%)	See comment	-	⊕⊕OO LOW	CRITICAL
								0%		-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence profile: Prostaglandin analogues versus placebo

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Prostaglandin analogues versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Number of participants reaching deterioration endpoint at 24 months (follow-up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	35/231 (15.2%)	59/230 (25.7%)	RR 0.59 (0.41 to 0.86)	105 fewer per 1,000 (from 36 fewer to 151 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: myocardial infarction (follow-up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/231 (0.43%)	2/230 (0.87%)	RR 0.5 (0.05 to 5.45)	4 fewer per 1,000 (from 8 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Change in IOP from baseline (follow-up 24 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	231	230	-	MD 2.7 higher (2.06 to 3.34 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Time to confirmed visual field deterioration (follow-up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	-	Not estimable	-	⊕⊕⊕⊕ HIGH	CRITICAL
Final IOP (follow-up 6 months)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	42	34	-	MD 2.00 lower (3.11 to 0.89 lower)	⊕OOO VERY LOW	IMPORTANT
Adverse events: Allergic reaction (follow-up 6 months)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/47 (4.3%)	12/34 (35.3%)	RR 5.73 (0.34 to 96.66)	1,000 more per 1,000 (from 233 fewer to 1,000 more)	⊕OOO VERY LOW	CRITICAL
Glaucomatous visual field loss (critical outcome) – no data reported Vision loss (critical outcome) – no data reported Health-related quality of life (critical outcome)– no data reported												

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 14: Clinical evidence profile: Beta-blockers versus no treatment

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Beta-blocker**	**No treatment**	**Relative (95% CI)**	**Absolute**		
Visual field progression (follow-up 2-6 years)												
6	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/373 (9.9%)	87/370 (23.5%)	RR 0.77 (0.52 to 1.14)	54 fewer per 1,000 (from 113 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL

Mean change in IOP from baseline (follow-up 2-6 years)											
4	randomised trials	serious[1]	very serious[3]	no serious indirectness	no imprecision	none	319	318	-	MD 2.88 lower (4.14 to 1.61 lower)	⊕OOO VERY LOW	IMPORTANT
Number of participants with an IOP >30mmHg (follow-up 2-10 years)											
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/348 (1.7%)	11/342 (3.2%)	RR 0.56 (0.22 to 1.46)	14 fewer per 1,000 (from 25 fewer to 15 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events: Respiratory (follow-up 5 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/53 (1.9%)	0/54 (0%)	Peto Odds ratio 7.53 (0.15 to 379.54)	-	⊕OOO VERY LOW	CRITICAL
Adverse events: Cardiovascular (follow-up 5 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/53 (7.5%)	0/54 (0%)	Peto Odds ratio 7.99 (1.09 to 58.33)	-	⊕⊕OO LOW	CRITICAL
Glaucomatous visual field loss (critical outcome) – no data reported												
Normal visual field to visual field defect (critical outcome)– no data reported												
Vision loss (critical outcome)– no data reported												
Health-related quality of life (critical outcome)– no data reported												

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
3 Heterogeneity, I^2=75%

Table 15: Clinical evidence profile: Carbonic anhydrase inhibitors versus no treatment

Quality assessment							Number of participants		Effect		Quality	Importance
Number of	Design	Risk of	Inconsistency	Indirectness	Imprecision	Other	Carbonic	No	Relative	Absolute		

studies		bias				considerations	anhydrase inhibitors	treatment	(95% CI)			
Conversion to COAG (follow-up 5 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	46/536 (8.6%)	60/541 (11.1%)	RR 0.77 (0.54 to 1.11)	26 fewer per 1,000 (from 51 fewer to 12 more)	⊕⊕⊕O MODERATE	CRITICAL
Visual field progression (follow-up 5 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	26/536 (4.9%)	38/541 (7%)	RR 0.69 (0.43 to 1.12)	22 fewer per 1,000 (from 40 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of participants with an IOP >35mmHg (follow-up 5 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/536 (0.19%)	12/541 (2.2%)	RR 0.08 (0.01 to 0.64)	20 fewer per 1,000 (from 8 fewer to 22 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

Glaucomatous visual field loss (critical outcome) – no data reported

Normal visual field to visual field defect (critical outcome)– no data reported

Vision loss (critical outcome)– no data reported

Health-related quality of life (critical outcome) – no data reported

Adverse events (critical outcome)- no data reported

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 13: Clinical evidence profile: Fixed combination versus separate combination

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed combination	Separate combination	Relative (95% CI)	Absolute		
Change in IOP from baseline (follow-up 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[1]	none	201	199	-	MD 0.3 lower (0.86 lower to 0.26 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
IOP reduction of ≥ 30% from baseline (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	none	117/201 (58.2%)	133/199 (66.8%)	RR 0.87 (0.75 to 1.01)	87 fewer per 1,000 (from 167 fewer to 7 more)	⊕⊕⊕O MODERATE	IMPORTANT
IOP reduction of ≥ 35% from baseline (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	73/201 (36.3%)	85/199 (42.7%)	RR 0.85 (0.67 to 1.08)	64 fewer per 1,000 (from 141 fewer to 34 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (follow-up 6 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	16/242 (6.6%)	10/239 (4.2%)	RR 1.58 (0.73 to 3.41)	24 more per 1,000 (from 11 fewer to 101 more)	⊕⊕OO LOW	CRITICAL
Mean IOP of ≤ 18mmHg at 6 months (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	138/201 (68.7%)	135/199 (67.8%)	RR 1.01 (0.89 to 1.16)	7 more per 1,000 (from 75 fewer to 109 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Cumulative % of days that participants were adherent with dosing (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41	40	-	MD 17 higher (5.02 to 28.98 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Glaucomatous visual field loss (critical outcome)– no data reported

Normal visual field to visual field defect (critical outcome)– no data reported

Progression of glaucomatous visual field defect (critical outcome)– no data reported

Vision loss (critical outcome)– no data reported

Health-related quality of life (critical outcomes) – no data reported

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 14: Clinical evidence profile: Beta-blocker dosage (0.25% Timolol versus 0.5% Timolol)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Timolol 0.5%	Timolol 0.25%	Relative (95% CI)	Absolute		
Mean change in IOP from baseline - (right and left eye – follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	15	-	MD 1.62 lower (2.95 to 0.29 lower)	⊕⊕OO LOW	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported												
Normal visual field to visual field defect (critical outcome)– no data reported												
Progression of glaucomatous visual field defect (critical outcome) – no data reported												
Vision loss (critical outcome) – no data reported												
Health-related quality of life (critical outcome) – no data reported												
Adverse events (critical outcome)– no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence profile: Prostaglandins versus beta-blockers

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prostaglandins	Beta-blockers	Relative (95% CI)	Absolute		
Change in diurnal IOP fluctuation (follow-up 26 weeks)												
	randomised trials	Very serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	287	289		MD 0.25 lower (0.86 lower to 0.36 higher)	⊕OOO VERY LOW	IMPORTANT

Change in IOP from baseline (follow-up 6 to 36 months)												
12	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	1342	1333	-	MD 1.32 lower (1.79 to 0.84 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Number of participants with acceptable IOP (follow-up 6 to 12 months)												
7	randomised trials	no serious risk of bias	very serious[5]	no serious indirectness	serious[2]	none	546/971 (56.2%)	376/953 (39.5%)	RR 1.54 (1.21 to 1.96)	213 more per 1,000 (from 83 more to 379 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events: Respiratory (follow-up 6 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/330 (7.6%)	24/233 (10.3%)	RR 0.59 (0.35 to 1)	42 fewer per 1,000 (from 67 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Cardiovascular (follow-up 6 to 12 months)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	99/997 (9.9%)	90/713 (12.6%)	RR 0.87 (0.67 to 1.13)	16 fewer per 1,000 (from 42 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Allergic reaction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/149 (0%)	2/145 (1.4%)	RR 0.19 (0.01 to 4.02)	11 fewer per 1,000 (from 14 fewer to 42 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Hyperaemia (follow-up 6 to 12 months)												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	543/1645 (33%)	97/1119 (8.7%)	RR 3.56 (2.92 to 4.33)	222 more per 1,000 (from 166 more to 289 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Glaucomatous visual field loss (critical outcome) – no data reported

Normal visual field to visual field defect (critical outcome) – no data reported

Progression of glaucomatous visual field defect (critical outcome)– no data reported

Vision loss (critical outcome)– no data reported

Health-related quality of life (critical outcome)– no data reported

[1] Heterogeneity, I^2=55%
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] The majority of the evidence had indirect outcomes
[5] Heterogeneity, I^2=85%

Table 16: Clinical evidence profile: Prostaglandin versus sympathomimetic

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prostaglandins	Sympathomimetics	Relative (95% CI)	Absolute		
Change in IOP from baseline (follow-up 6 to 12 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	337	343	-	MD 2.02 lower (2.72 to 1.69 lower)	⊕⊕OO LOW	IMPORTANT
Adverse events: Allergic reaction (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/187 (0%)	16/188 (8.5%)	RR 0.14 (0.05 to 0.36)	73 fewer per 1,000 (from 54 fewer to 81 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: Hyperaemia (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/187 (5.9%)	11/188 (5.9%)	RR 1.01 (0.45 to 2.26)	1 more per 1,000 (from 32 fewer to 74 more)	⊕OOO VERY LOW	CRITICAL

Glaucomatous visual field loss (critical outcome)– no data reported

Normal visual field to visual field defect (critical outcome) – no data reported

Progression of glaucomatous visual field defect (critical outcome) – no data reported

Vision loss (critical outcome) – no data reported

Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: Carbonic anhydrase inhibitor versus sympathomimetic

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbonic anhydrase inhibitors	Sympathomimetics	Relative (95% CI)	Absolute		
Adverse events: Allergic reaction (follow-up 6 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/420 (0.24%)	7/407 (1.7%)	RR 0.22 (0.05 to 0.87)	13 fewer per 1,000 (from 2 fewer to 16 fewer)	⊕OOO VERY LOW	CRITICAL
Treatment discontinuation due to adverse events (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/191 (0.52%)	13/175 (7.4%)	RR 0.07 (0.01 to 0.53)	69 fewer per 1,000 (from 35 fewer to 74 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
% change in IOP from baseline (09.00 – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	145	-	MD 2.00 lower (4.84 lower to 0.84 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
% change in IOP from baseline (11.00 – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	145	-	MD 2.1 higher (0.44 lower to 4.64 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
% change in IOP from baseline (16.00 – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	178	144	-	MD 2.2 lower (5.23 lower to 0.83 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Glaucomatous visual field loss (critical outcome) – no data reported
Normal visual field to visual field defect (critical outcome) – no data reported
Progression of glaucomatous visual field defect (critical outcome) – no data reported
Vision loss (critical outcome) – no data reported
Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence profile: Carbonic anhydrase inhibitor versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbonic anhydrase inhibitors	Beta-blockers	Relative (95% CI)	Absolute		
Adverse events: Hyperaemia - Brinzolamide (2 and 3 times per day – follow-up 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/303 (3.9%)	0/150 (0%)	Peto Odds ratio 4.58 (1.21 to 17.33)	-	⊕⊕OO LOW	CRITICAL
Change in IOP from baseline (%– follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	57	83	-	MD 2.74 higher (1.49 lower to 6.97 higher)	⊕OOO VERY LOW	IMPORTANT
Change in IOP from baseline (mmHg – follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	103	313	-	MD 1.3 higher (0.37 to 2.23 higher)	⊕OOO VERY LOW	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported												

Normal visual field to visual field defect (critical outcome) – no data reported
Progression of glaucomatous visual field defect (critical outcome) – no data reported
Vision loss (critical outcome) – no data reported
Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 19: Clinical evidence profile: Sympathomimetic versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sympathomimetics	Beta-blockers	Relative (95% CI)	Absolute		
Visual field progression (follow-up 12 months)												
3	randomised trials	serious[1]	very serious[3]	no serious indirectness	very serious[2]	none	31/456 (6.8%)	60/373 (16.1%)	RR 0.52 (0.18 to 1.50)	77 fewer per 1,000 (from 132 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Change in IOP from baseline - Trough effect (before morning medication – follow-up 12 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	466	371	-	MD 2.27 higher (1.8 to 2.74 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Change in IOP from baseline - Peak effect (2 hours after morning medication – follow-up 12 months)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	None	466	371	-	MD 0.27 lower (0.98 lower to 0.45 higher)	⊕⊕OO LOW	IMPORTANT
Change in IOP from baseline - Mean diurnal IOP (follow-up 12 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	121	101	-	MD 0.24 lower (0.58 lower to	⊕⊕OO LOW	IMPORTANT

										0.09 higher)		
Adverse events: Allergic reaction - Number of participants with allergic reaction												
1	randomised trials	serious[1]	serious[5]	no serious indirectness	veryserious[2]	none	172/603 (28.5%)	47/614 (7.7%)	RR 8.15 (0.68 to 98.32)	547 more per 1,000 (from 24 fewer to 1000 more)-	⊕OOO VERY LOW	CRITICAL
Treatment discontinuation due to allergic reaction												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/292 (14.7%)	0/191 (0%)	Peto Odds ratio 6.12 (3.23 to 11.61)	-	⊕⊕⊕O MODERATE	CRITICAL
Treatment discontinuation prior to 1 year (follow-up 48 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/99 (36.4%)	8/79 (10.1%)	RR 3.59 (1.77 to 7.28)	262 more per 1,000 (from 78 more to 636 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Treatment discontinuation > 1 year (follow-up 48 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	18/99 (18.2%)	15/79 (19%)	RR 0.96 (0.52 to 1.78)	8 fewer per 1,000 (from 91 fewer to 148 more)	⊕⊕OO LOW	IMPORTANT

Glaucomatous visual field loss (critical outcome) – no data reported

Normal visual field to visual field defect (critical outcome) – no data reported

Vision loss (critical outcome) – no data reported

Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

[3] Heterogeneity, I^2=83%

[4] Heterogeneity, I^2=55%

[5] Heterogeneity, I^2=71%

Table 20: Clinical evidence profile: Fixed combination prostaglandin analogue and beta-blocker versus prostaglandin analogue

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed combination	Single medications	Relative (95% CI)	Absolute		
Change in diurnal IOP fluctuation (follow-up 26 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	278	287		MD 0.79 lower (1.4 lower to 0.18 lower)	⊕OOO VERY LOW	IMPORTANT
Change in IOP from baseline (follow-up 6 months)												
2	randomised trials	very serious[1]	very serious[2]	no serious indirectness	no serious imprecision	none	278	287	-	MD 0.34 lower (1.81 lower to 1.13 higher)	⊕OOO VERY LOW	IMPORTANT
Number of participants with an acceptable IOP (<18mmHg – follow-up 6 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	93/278 (33.5%)	90/287 (31.4%)	RR 1.07 (0.84 to 1.36)	22 more per 1,000 (from 50 fewer to 113 more)	⊕⊕OO LOW	IMPORTANT
Adverse events: Respiratory - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/140 (2.1%)	6/147 (4.1%)	RR 0.53 (0.13 to 2.06)	19 fewer per 1,000 (from 36 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: Cardiovascular - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/140 (3.6%)	1/147 (0.68%)	RR 5.25 (0.62 to 44.38)	29 more per 1,000 (from 3 fewer to 295 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: Hyperaemia - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/140 (2.9%)	2/147 (1.4%)	RR 2.1 (0.39 to 11.28)	15 more per 1,000 (from 8 fewer to 140	⊕OOO VERY	CRITICAL

										more)	LOW	
Glaucomatous visual field loss (critical outcome) – no data reported Normal visual field to visual field defect (critical outcome) – no data reported Progression of glaucomatous visual field defect (critical outcome) – no data reported Vision loss (critical outcome) – no data reported Health-related quality of life (critical outcome) – no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Heterogeneity, I^2=84%[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of evidence had indirect outcomes

Table 21: Fixed combination prostaglandin analogue and beta-blocker versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fixed combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
Change in diurnal IOP fluctuation (follow-up 26 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	278	289		MD 1.04 lower (1.65 lower to 0.43 LOWER)	⊕OOO VERY LOW	IMPORTANT
Change in IOP from baseline - (follow-up 6 months)												
2	randomised trials	very serious[1]	very serious[2]	no serious indirectness	serious[3]	none	278	289	-	MD 1.75 lower (4.00 lower to 0.51 higher)	⊕OOO VERY LOW	IMPORTANT
Number of participants with an acceptable IOP - (<18mmHg – follow-up 6 months)												
2	randomised trials	serious[1]	very erious[5]	no serious indirectness	serious[3]	none	93/278 (33.5%)	48/289 (16.6%)	RR 2.27 (0.99 to 5.23)	211 more per 1,000 (from 2 fewer to 703 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: Respiratory - (follow-up 6 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/140 (2.1%)	7/149 (4.7%)	RR 0.46 (0.12 to 1.73)	25 fewer per 1,000 (from 41 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: Cardiovascular - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/140 (3.6%)	2/149 (1.3%)	RR 2.66 (0.52 to 13.49)	22 more per 1,000 (from 6 fewer to 168 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: Hyperaemia - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/140 (2.9%)	1/149 (0.67%)	RR 4.26 (0.48 to 37.63)	22 more per 1,000 (from 3 fewer to 246 more)	⊕OOO VERY LOW	CRITICAL

Glaucomatous visual field loss (critical outcome) – no data reported

Normal visual field to visual field defect (critical outcome) – no data reported

Progression of glaucomatous visual field defect (critical outcome)– no data reported

Vision loss (critical outcome) – no data reported

Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Heterogeneity, I^2=93%
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[4] The majority of evidence had indirect outcomes
[5] Heterogeneity, I^2=82%

Table 22: Fixed combination carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fixed combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
Change in IOP from baseline - (follow-up 6 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	35	-	MD 0.3 lower (1.32 lower to 0.72 higher)	⊕⊕OO LOW	IMPORTANT
Adverse events: Respiratory - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	0/35 (0%)	Peto odds ratio 3.48 (0.15 to 82.48)	-	⊕OOO VERY LOW	CRITICAL
Adverse events: Hyperaemia - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/30 (13.3%)	18/35 (51.4%)	RR 0.26 (0.1 to 0.68)	381 fewer per 1,000 (from 165 fewer to 463 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Glaucomatous visual field loss (critical outcome) – no data reported Normal visual field to visual field defect (critical outcome) – no data reported Progression of glaucomatous visual field defect (critical outcome) – no data reported Vision loss (critical outcome) – no data reported Health-related quality of life (critical outcome) – no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 23: Fixed combination sympathomimetic and beta-blocker versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fixed combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
Number of participants with an acceptable IOP - (<17.5mmHg – follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	202/385 (52.5%)	127/392 (32.4%)	RR 1.62 (1.36 to 1.92)	201 more per 1,000 (from 117 more to 298 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Adverse events: Allergic reaction - (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/385 (26%)	47/392 (12%)	RR 2.17 (1.58 to 2.97)	140 more per 1,000 (from 70 more to 236 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Glaucomatous visual field loss (critical outcome) – no data reported												
Normal visual field to visual field defect (critical outcome) – no data reported												
Progression of glaucomatous visual field defect (critical outcome) – no data reported												
Vision loss (critical outcome) – no data reported												
Health-related quality of life (critical outcome) – no data reported												

Table 24: Fixed combination carbonic anhydrase inhibitor and beta-blocker versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Fixed combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
% change in IOP from baseline - (right and left eye – follow-up 8 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	11	11	-	MD 13.75 lower (23.06 to 4.43 lower)	⊕⊕OO LOW	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported												
Normal visual field to visual field defect (critical outcome) – no data reported												
Progression of glaucomatous visual field defect (critical outcome) – no data reported												
Vision loss (critical outcome) – no data reported												
Health-related quality of life (critical outcome) – no data reported												
Adverse events (critical outcome) – no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Fixed combination carbonic anhydrase inhibitors and sympathomimetics versus sympathomimetics

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed combination	Single medications	Relative (95% CI)	Absolute		
Adverse events: Allergic reaction - (follow-up 6 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/411 (4.1%)	7/407 (1.7%)	RR 2.49 (1.05 to 5.9)	26 more per 1,000 (from 1 more to 84 more)	⊕OOO VERY LOW	CRITICAL
% change in IOP from baseline - (11am – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	160	145	-	MD 5 lower (7.62 to 2.38 lower)	⊕⊕⊕O MODERATE	IMPORTANT
% change in IOP from baseline - (4pm – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	160	145	-	MD 5.2 lower (8.28 to 2.12 lower)	⊕⊕⊕O MODERATE	IMPORTANT
% change in IOP from baseline - (9am – follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	160	145	-	MD 4.1 lower (6.92 to 1.28 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Treatment discontinuation due to adverse events - (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/193 (10.4%)	13/175 (7.4%)	RR 1.39 (0.72 to 2.72)	29 more per 1,000 (from 21 fewer to 128 more)	⊕⊕OO LOW	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported Normal visual field to visual field defect (critical outcome) – no data reported												

Progression of glaucomatous visual field defect (critical outcome) – no data reported

Vision loss (critical outcome)– no data reported
Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 26: Fixed combination carbonic anhydrase inhibitors and sympathomimetics versus carbonic anhydrase inhibitors

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed combination	Single medications	Relative (95% CI)	Absolute		
% change in IOP from baseline (11am – follow up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	160	178	-	MD 7.1 lower (9.71 to 4.49 lower)	⊕⊕⊕O MODERATE	IMPORTANT
% change in IOP from baseline (4pm – follow up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	160	178	-	MD 3 lower (5.92 to 0.08 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
% change in IOP from baseline (9am – follow up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	160	178	-	MD 2.1 lower (4.78 to 0.58 lower)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse events: Allergic reaction – (follow-up 6 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	17/411 (4.1%)	1/420 (0.24%)	RR 12.06 (2.3 to 63.29)	26 more per 1,000 (from 3 more to 148 more)	⊕⊕OO LOW	CRITICAL

Treatment discontinuation due to adverse events - (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/193 (10.4%)	1/191 (0.52%)	RR 19.79 (2.68 to 146.01)	98 more per 1,000 (from 9 more to 759 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported												
Normal visual field to visual field defect (critical outcome) – no data reported												
Progression of glaucomatous visual field defect (critical outcome)– no data reported												
Vision loss (critical outcome)– no data reported												
Health-related quality of life (critical outcome) – no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 27: Separate combination prostaglandin analogue and beta-blocker versus prostaglandin

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Separate combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
Change in IOP from baseline - (follow-up 6 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79	81	-	MD 0.66 lower (1.44 lower to 0.13 higher)	⊕⊕OO LOW	IMPORTANT
Number of participants with an acceptable IOP - (<18mmHg – follow-up 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	veryserious[2]	none	30/45 (66.7%)	32/46 (69.6%)	RR 0.96 (0.72 to 1.27)	28 fewer per 1,000 (from 195 fewer to 188 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events: Respiratory - (follow-up 6 months)												
1	randomised	very	no serious	no serious	very serious[2]	none	1/49	0/50	Peto Odds	-	⊕OOO	CRITICAL

	trials	serious[1]	inconsistency	indirectness			(2%)	(0%)	7.54 (0.15 to 380.14)		VERY LOW	
Adverse events: Hyperaemia - (follow-up 6 months)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/79 (34.2%)	18/81 (22.2%)	RR 1.54 (0.98 to 2.44)	120 more per 1,000 (from 4 fewer to 320 more)	⊕OOO VERY LOW	CRITICAL
Glaucomatous visual field loss (critical outcome) – no data reported Normal visual field to visual field defect (critical outcome) – no data reported Progression of glaucomatous visual field defect (critical outcome)– no data reported Vision loss (critical outcome)– no data reported Health-related quality of life (critical outcome) – no data reported												

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Separate combination carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Separate combination**	**Single medications**	**Relative (95% CI)**	**Absolute**		
Change in IOP from baseline - (follow-up 6 months)												
2	randomised trials	very serious[1]	very serious[3]	no serious indirectness	serious[2]	none	90	91	-	MD 0.41 higher (1.06 lower to 1.88 higher)	⊕OOO VERY LOW	IMPORTANT
Number of participants with an acceptable IOP - (<21mmHg – follow-up 24 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/30 (56.7%)	37/45 (82.2%)	RR 0.69 (0.49 to 0.97)	255 fewer per 1,000 (from 25 fewer to 419 fewer)	⊕OOO VERY LOW	IMPORTANT
Glaucomatous visual field loss (critical outcome) – no data reported												

Normal visual field to visual field defect (critical outcome)– no data reported

Progression of glaucomatous visual field defect (critical outcome)– no data reported

Vision loss (critical outcome) – no data reported

Health-related quality of life (critical outcome) – no data reported

Adverse events (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Heterogeneity, I^2=76%

Table 29: Separate combination prostaglandin analogue and beta-blocker versus beta-blocker

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GI combination	Single medications	Relative (95% CI)	Absolute		
Number of participants with an acceptable IOP - (<17mmHg – follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/114 (48.2%)	11/112 (9.8%)	RR 4.91 (2.72 to 8.88)	384 more per 1,000 (from 169 more to 774 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events: Hyperaemia - (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	52/145 (35.9%)	13/145 (9%)	RR 4 (2.28 to 7.02)	269 more per 1,000 (from 115 more to 540 more)	⊕⊕⊕O MODERATE	CRITICAL

Glaucomatous visual field loss (critical outcome) – no data reported

Normal visual field to visual field defect (critical outcome)– no data reported

Progression of glaucomatous visual field defect (critical outcome) – no data reported

Vision loss (critical outcome) – no data reported

Health-related quality of life (critical outcome) – no data reported

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

J.5.2 Laser treatment for COAG

None.

J.5.3 Surgical treatment for COAG

None.

J.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

J.6 Complementary and alternative interventions

2009

J.7 Organisation of care

J.7.1 Service models for case finding, referral filtering and diagnosis

J.7.2 Skills required by healthcare professionals

2009

J.8 Provision of information for patients

Appendix K: Forest plots and coupled sensitivity and specificity plots

K.1 Prognostic risk tools

K.1.1 Increased risk of conversion to COAG

Figure 10: Sensitivity and specificity of GPS for predicting conversion to glaucoma

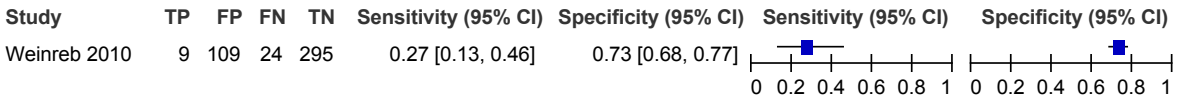
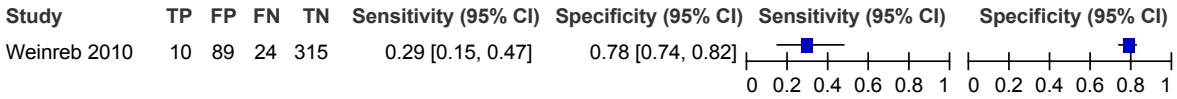
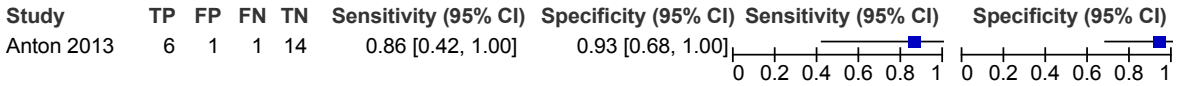


Figure 11: Sensitivity and specificity of GPS for predicting conversion to glaucoma



K.1.2 Increased risk of COAG progression

Figure 12: Sensitivity and specificity of GPA I for predicting progression of glaucoma



K.2 Tests used in case finding, diagnosis and reassessment

K.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

K.2.1.1 OCT

Figure 13: ≥2 quadrants of the angle closed

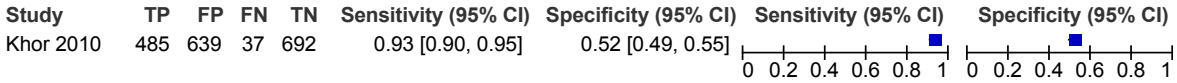


Figure 14: **AOD500, temporal**

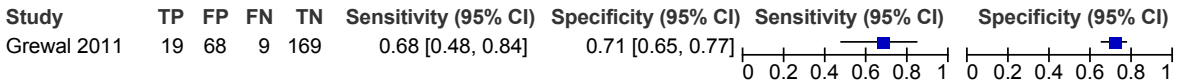


Figure 15: **AOD500, nasal**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	22	68	6	169	0.79 [0.59, 0.92]	0.71 [0.65, 0.77]

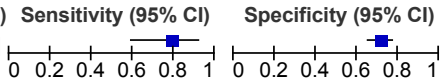


Figure 16: **ACA**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dabasia 2015	37	5	5	31	0.88 [0.74, 0.96]	0.86 [0.71, 0.95]

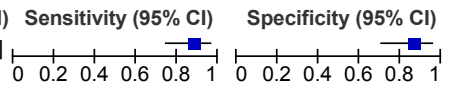


Figure 17: **ACD**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dabasia 2015	30	6	12	30	0.71 [0.55, 0.84]	0.83 [0.67, 0.94]

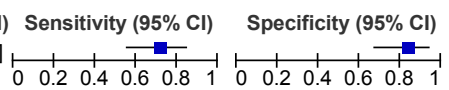


Figure 18: **TISA500, temporal**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	20	45	8	192	0.71 [0.51, 0.87]	0.81 [0.75, 0.86]
Narayanaswamy 2010	278	470	37	680	0.88 [0.84, 0.92]	0.59 [0.56, 0.62]

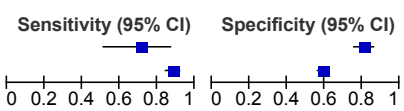
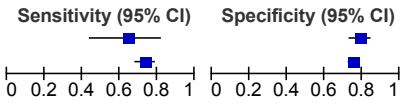


Figure 19: **TISA500, nasal**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	18	50	10	186	0.64 [0.44, 0.81]	0.79 [0.73, 0.84]
Narayanaswamy 2010	231	285	84	865	0.73 [0.68, 0.78]	0.75 [0.73, 0.78]



K.2.1.2 Scheimpflug

Figure 20: **ACD**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	25	65	3	172	0.89 [0.72, 0.98]	0.73 [0.66, 0.78]

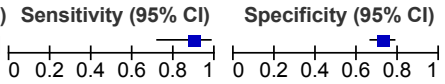
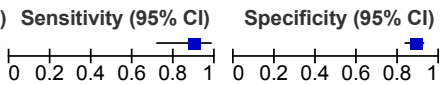


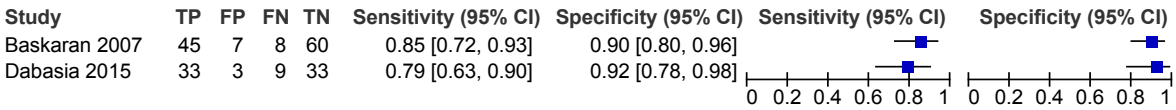
Figure 21: **ACV**

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Grewal 2011	25	28	3	209	0.89 [0.72, 0.98]	0.88 [0.83, 0.92]



K.2.1.3 The van Herick test

Figure 22: **Peripheral ACD < 25% corneal thickness**



K.2.2 Accuracy of IOP tests

K.2.2.1 Coupled sensitivity and specificity forest plots

Figure 23: Sensitivity and specificity of Pulsair non-contact tonometry for detection of IOP ≥21mmHg

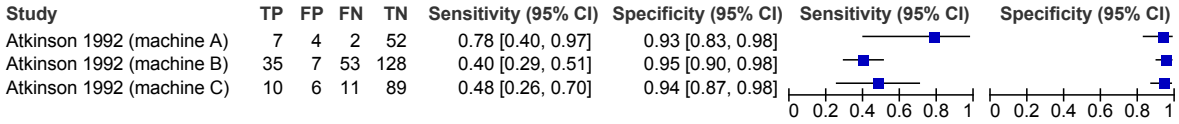


Figure 24: Sensitivity and specificity of Reichert Tono-Pen AVIA for detection of IOP ≥21mmHg

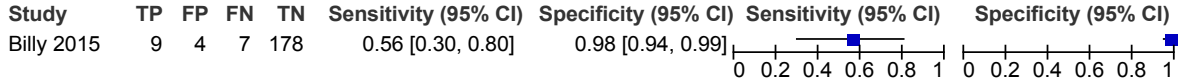
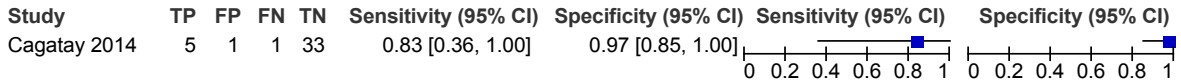
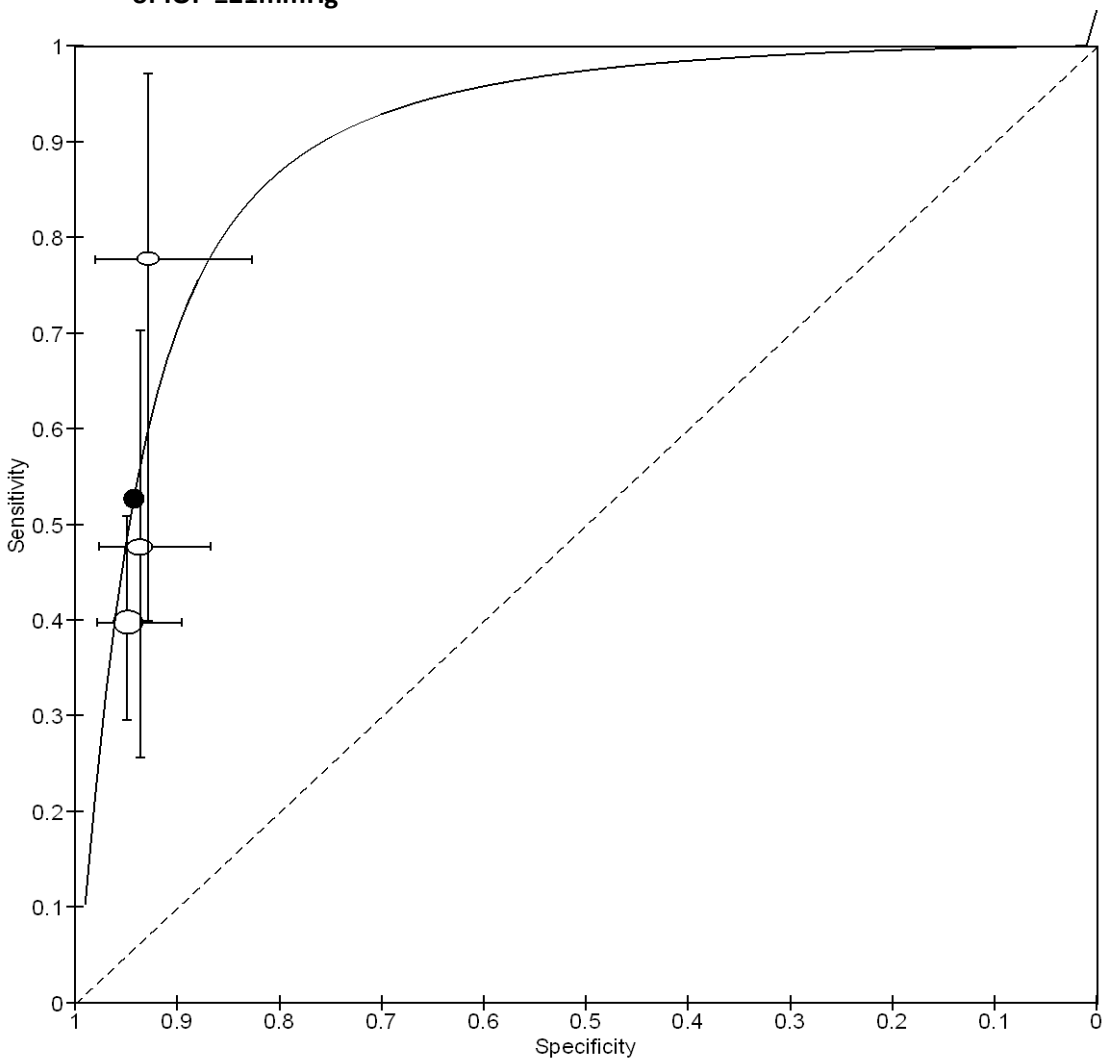


Figure 25: Sensitivity and specificity of Icare rebound tonometry for detection of IOP ≥21mmHg



K.2.2.2 ROC curve with study results by size

Figure 26: sROC plot of sensitivity and specificity of Pulsair non-contact tonometry for detection of IOP ≥21mmHg



K.2.3 Central corneal thickness measurement evidence

None.

2009

K.2.4 Visual field evidence

None.

K.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

K.2.5.1 SD-OCT

Figure 27: Sensitivity and specificity of SD-OCT for glaucoma diagnosis

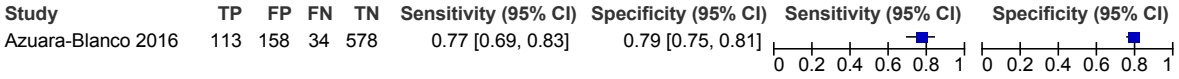


Figure 28: Sensitivity and specificity of SD-OCT cup diameter for glaucoma diagnosis

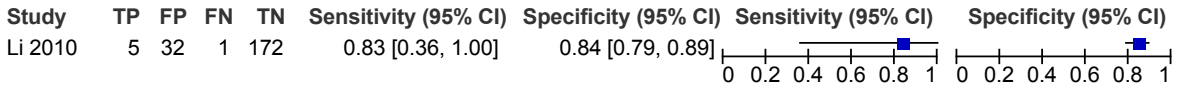


Figure 29: Sensitivity and specificity of SD-OCT cup and disc vertical ratio for glaucoma diagnosis

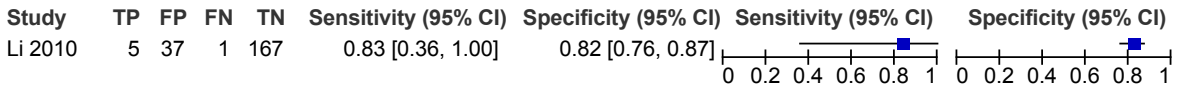


Figure 30: Sensitivity and specificity of SD-OCT cup area for glaucoma diagnosis

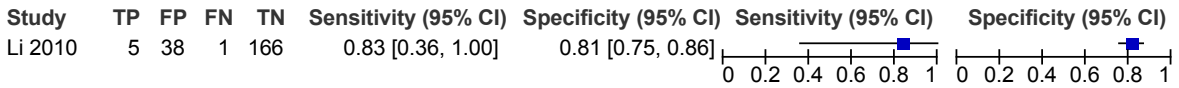


Figure 31: Sensitivity and specificity of Spectralis SD-OCT T-MRT for glaucoma diagnosis

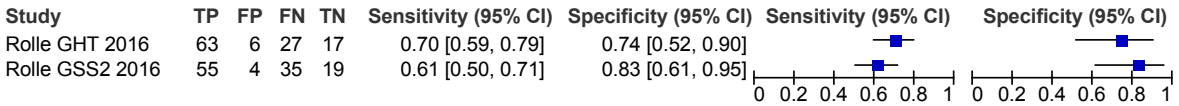


Figure 32: Sensitivity and specificity of Spectralis SD-OCT peripapillary retinal volume scan OCA1 for glaucoma diagnosis

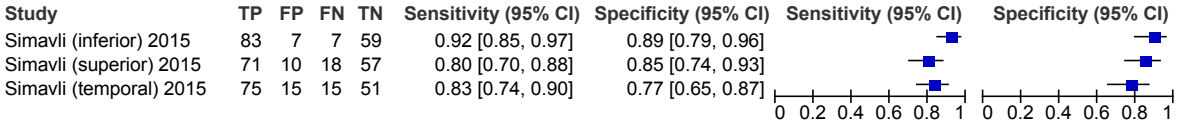


Figure 33: Sensitivity and specificity of Spectralis SD-OCT peripapillary retinal volume scan OCA2 for glaucoma diagnosis

K.2.5.2 Spectralis SD-OCT Peripapillary Nerve Fibre Layer at different thresholds

Figure 34: Sensitivity and specificity of Spectralis SD-OCT global RNFL thickness abnormal at <5% and <1%for glaucoma diagnosis

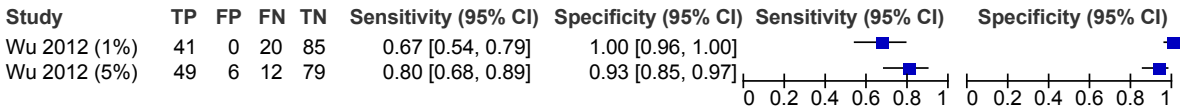


Figure 35: Sensitivity and specificity of Spectralis SD-OCT 1 quadrant with RNFL thickness abnormal at <5% and <1%for glaucoma diagnosis

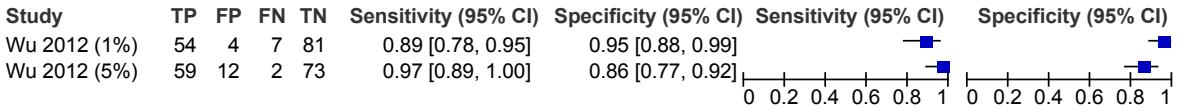
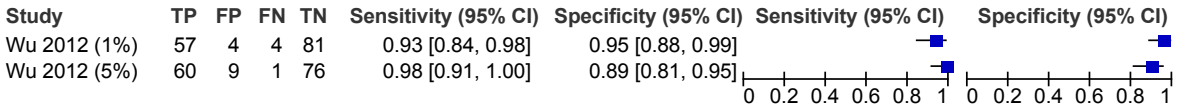


Figure 36: Sensitivity and specificity of Spectralis SD-OCT 1 sector of TS,TI,NS,NI with RNFL thickness abnormal at <5% and <1%for glaucoma diagnosis



K.2.5.3 HRT

Figure 37: Sensitivity and specificity of HRT-2 LDF1 for glaucoma diagnosis

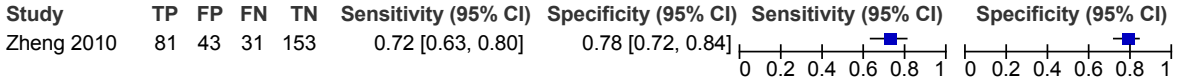


Figure 38: Sensitivity and specificity of HRT-2 LDF2 for glaucoma diagnosis

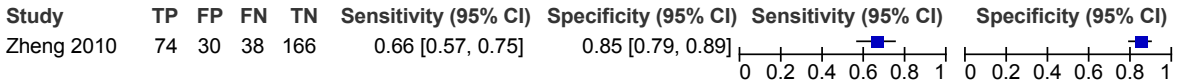


Figure 39: Sensitivity and specificity of HRT-2 LDF3 for glaucoma diagnosis

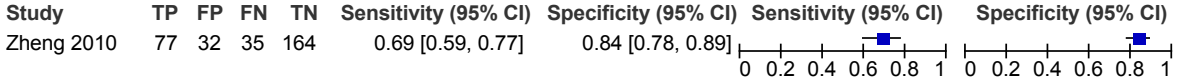


Figure 40: Sensitivity and specificity of HRT-3 MRA for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Azuara-Blanco 2016	120	256	18	453	0.87 [0.80, 0.92]	0.64 [0.60, 0.67]
Kamdeu Fansi 2011	4	21	0	196	1.00 [0.40, 1.00]	0.90 [0.86, 0.94]

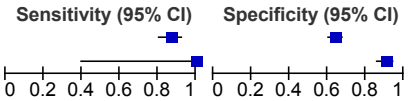
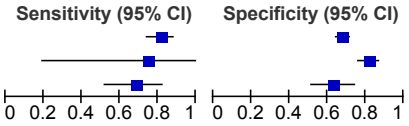


Figure 41: Sensitivity and specificity of HRT-3 GPS for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Azuara-Blanco 2016	110	229	25	481	0.81 [0.74, 0.88]	0.68 [0.64, 0.71]
Kamdeu Fansi 2011	3	40	1	177	0.75 [0.19, 0.99]	0.82 [0.76, 0.86]
Lee 2013	28	28	13	48	0.68 [0.52, 0.82]	0.63 [0.51, 0.74]



K.2.5.4 HRT-2 MRA at different thresholds

Figure 42: Sensitivity and specificity of HRT ('borderline' or more) for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zheng 2010	80	26	32	170	0.71 [0.62, 0.80]	0.87 [0.81, 0.91]

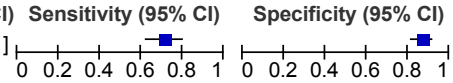
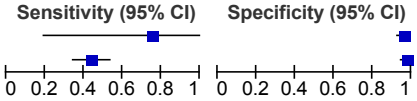


Figure 43: Sensitivity and specificity of HRT ('out' or more) for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kamdeu Fansi 2011	3	9	1	208	0.75 [0.19, 0.99]	0.96 [0.92, 0.98]
Zheng 2010	49	5	63	191	0.44 [0.34, 0.53]	0.97 [0.94, 0.99]



K.2.5.5 Combinations (of parameters or tests)

Figure 44: Sensitivity and specificity of HRT-3 MRA + HRT-3 GPS for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Azuara-Blanco 2016	122	329	12	367	0.91 [0.85, 0.95]	0.53 [0.49, 0.56]
Kamdeu Fansi 2011	4	58	0	159	1.00 [0.40, 1.00]	0.73 [0.67, 0.79]

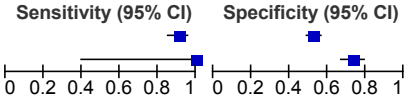


Figure 45: Sensitivity and specificity of HRT-3 MRA + SD-OCT for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Azuara-Blanco 2016	122	319	11	371	0.92 [0.86, 0.96]	0.54 [0.50, 0.58]

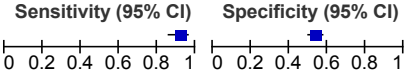
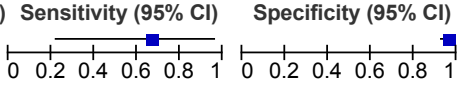


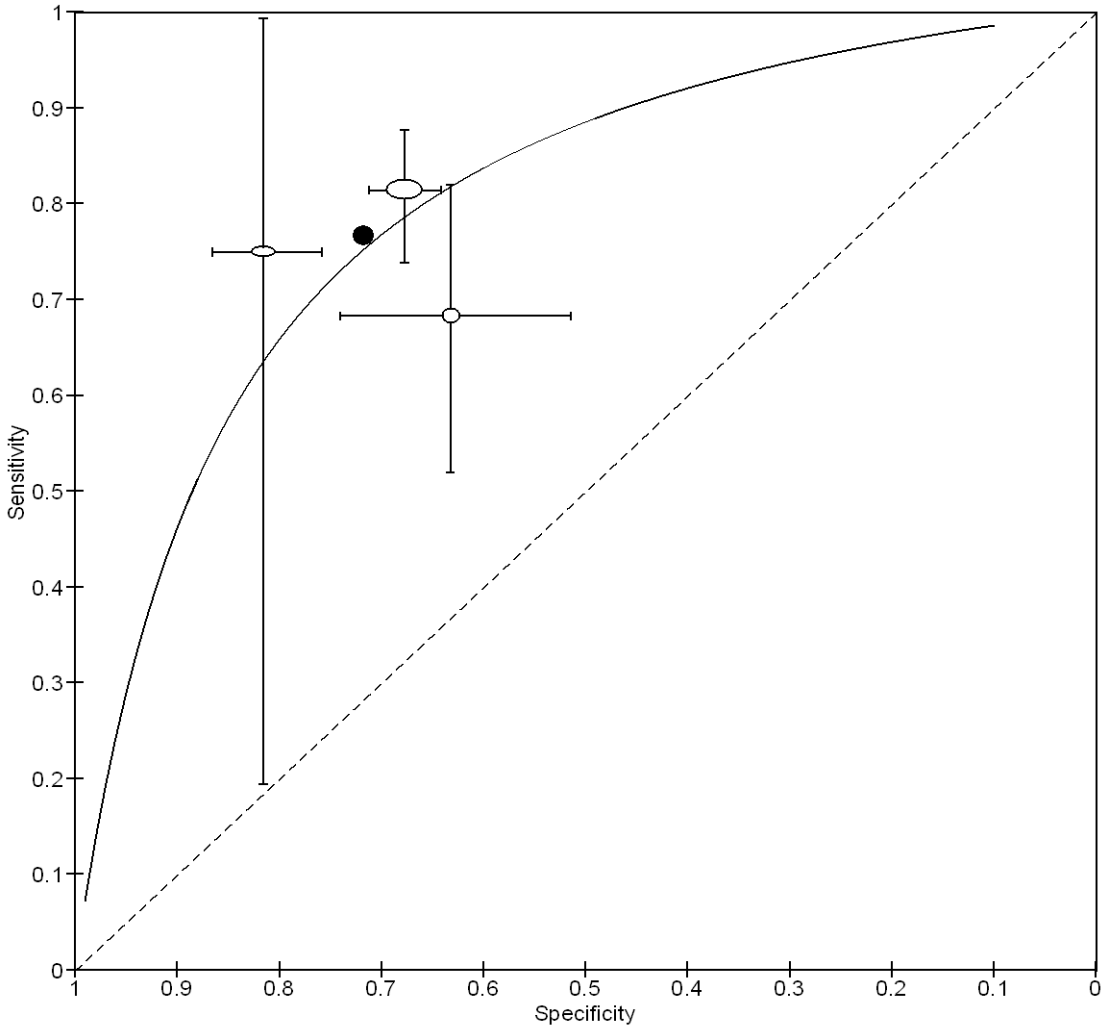
Figure 46: Sensitivity and specificity of SD-OCT ONH + RNFL parameters for glaucoma diagnosis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Li 2010	4	8	2	196	0.67 [0.22, 0.96]	0.96 [0.92, 0.98]



K.2.5.6 ROC curve with study results by size

Figure 47: sROC plot of sensitivity and specificity of HRT-3 GPS for detection of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)



K.3 Reassessment intervals

K.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

None.

K.3.2 Optimum intervals for chronic open-angle glaucoma

None.

K.4 Overview of Treatment

Figure 48 Any treatment vs. no treatment – OHT conversion to COAG & COAG progression

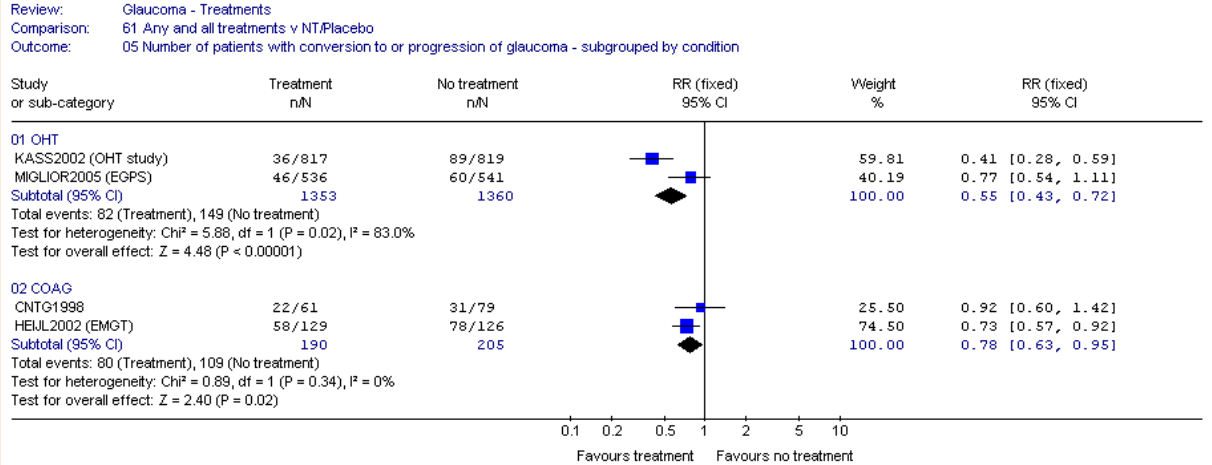


Figure 49 Any treatment vs. no treatment – visual field progression in OHT and COAG patients

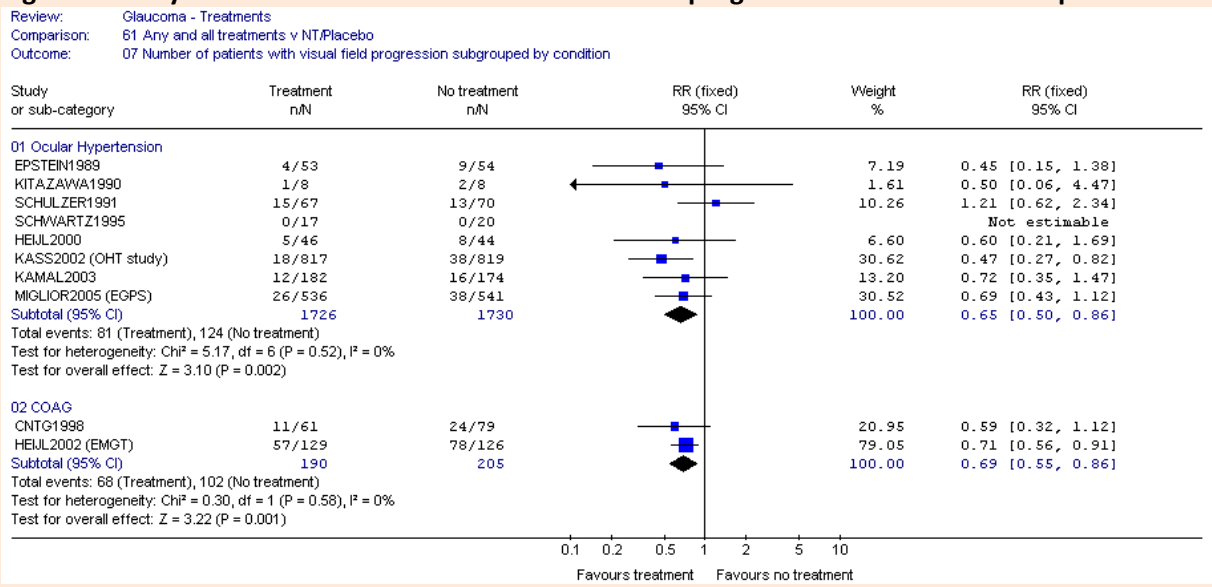
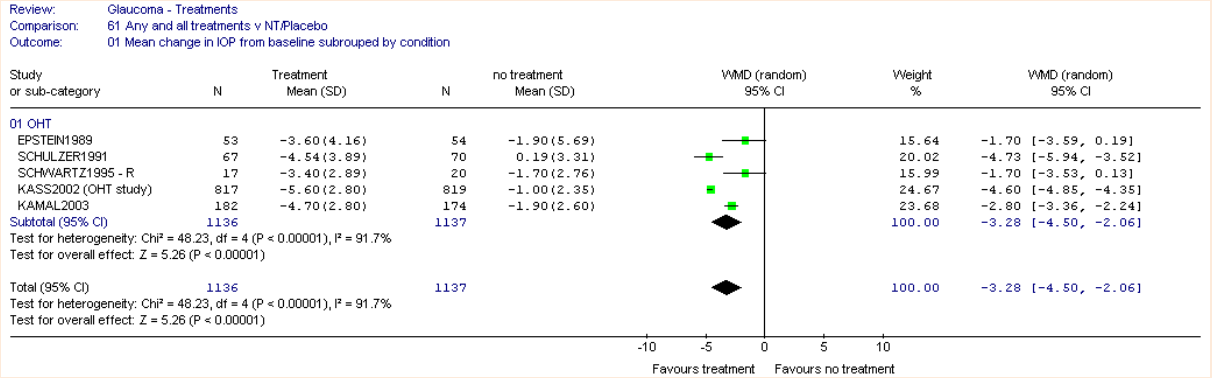


Figure 50 Any treatment vs. no treatment – change in IOP from baseline



2009

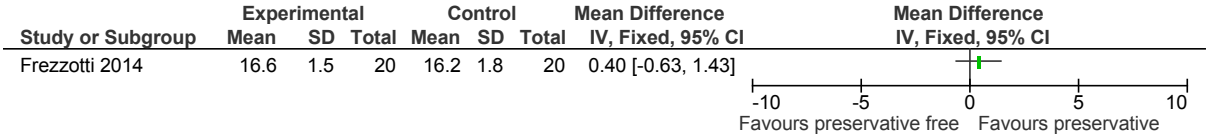
K.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

K.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

K.5.1.1 Preservative versus preservative-free solutions

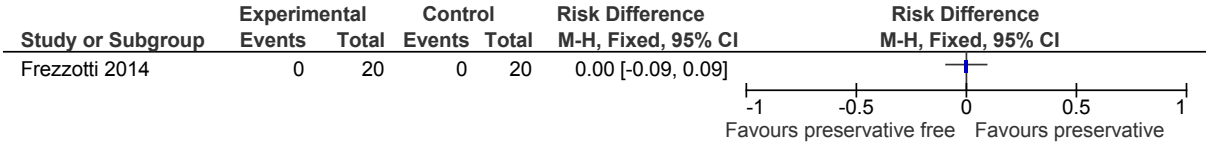
K.5.1.1.1 Change in IOP from baseline (follow-up 12 months)

Figure 51: Benzalkonium preserved beta-blocker versus preservative-free beta-blocker



K.5.1.1.2 Major adverse events (no definition; follow-up 12 months)

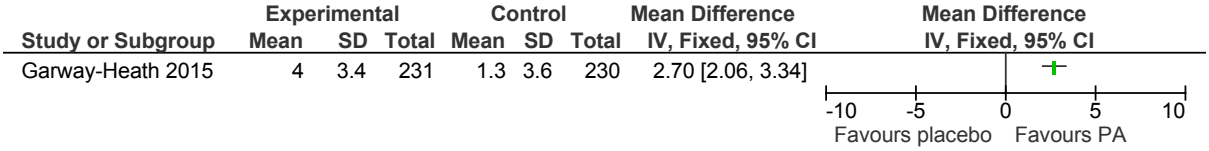
Figure 52: Benzalkonium preserved beta-blocker versus preservative-free beta-blocker



K.5.1.2 Prostaglandin analogues versus placebo or no treatment

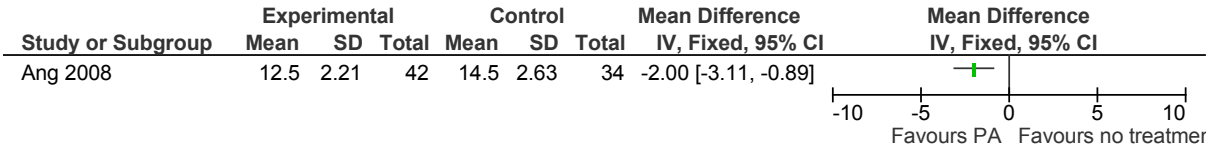
K.5.1.2.1 Change in IOP from baseline (follow-up 24 months)

Figure 53: Latanoprost versus placebo



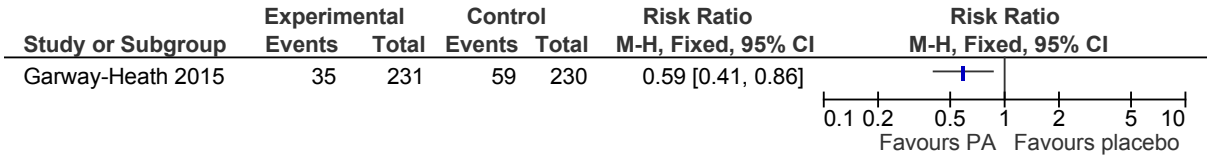
K.5.1.2.2 Final IOP (follow-up 6 months)

Figure 54: Travoprost versus no treatment



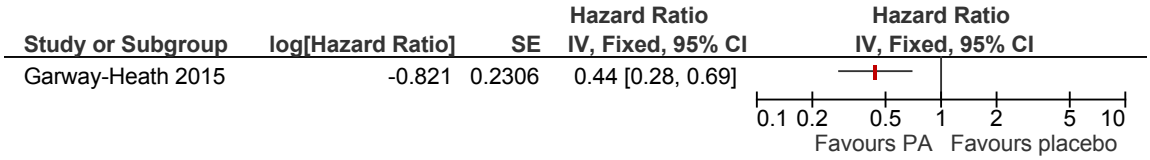
K.5.1.2.3 Number of people reaching deterioration end point at 24 months (deterioration defined as at least 3 visual field locations worse than baseline at the 5% levels in 2 consecutive reliable visual fields and at least 3 visual field locations worse than baseline at the 5% levels in the 2 subsequent consecutive reliable visual fields (follow-up 24 months)

Figure 55: Latanoprost versus placebo



K.5.1.2.4 Time to confirmed visual field deterioration (defined as time from baseline to the fourth visual field that confirmed progression; follow-up 24 months)

Figure 56: Latanoprost versus placebo



K.5.1.2.5 Adverse events: Allergic reaction (follow-up 6 months)

Figure 57: Travoprost versus no treatment

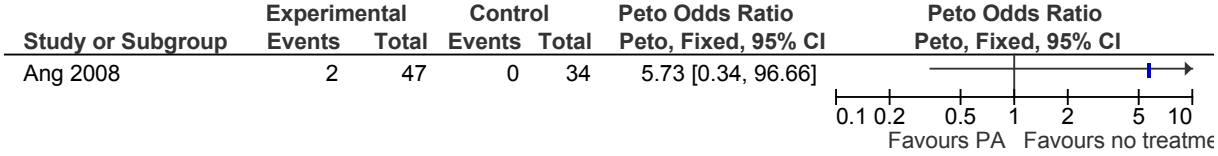
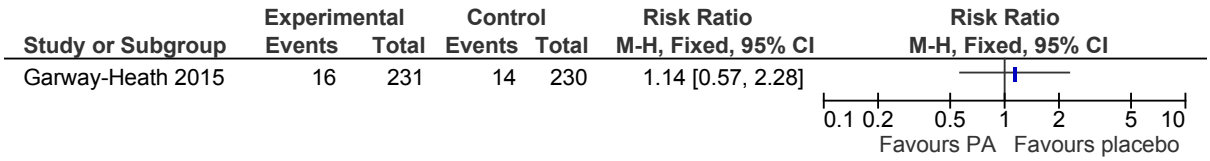
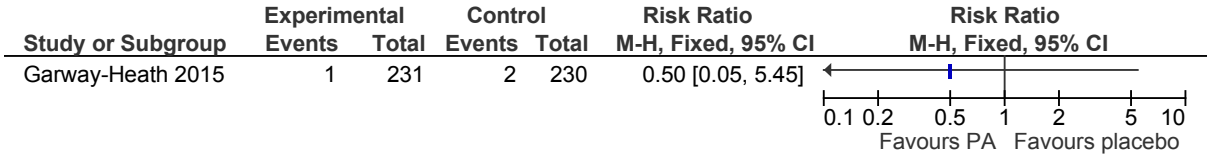


Figure 58: Latanoprost versus placebo



K.5.1.2.6 Adverse events: myocardial infarction (follow-up 24 months)

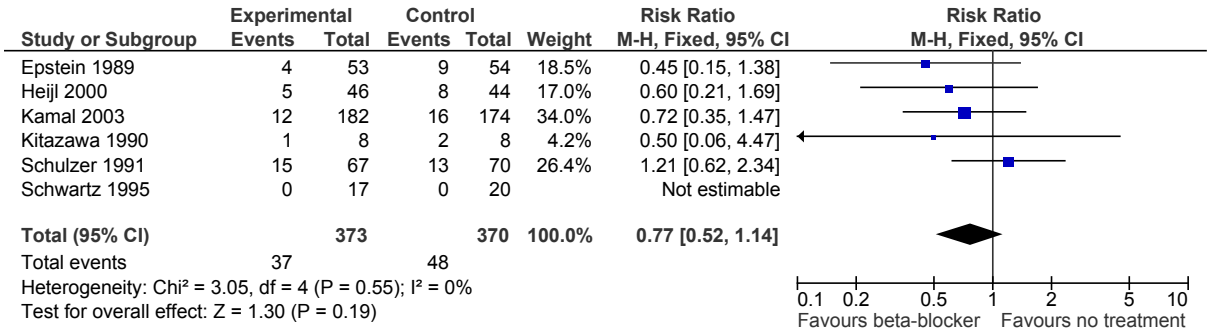
Figure 59: Latanoprost versus placebo



K.5.1.3 Beta-blockers versus no treatment

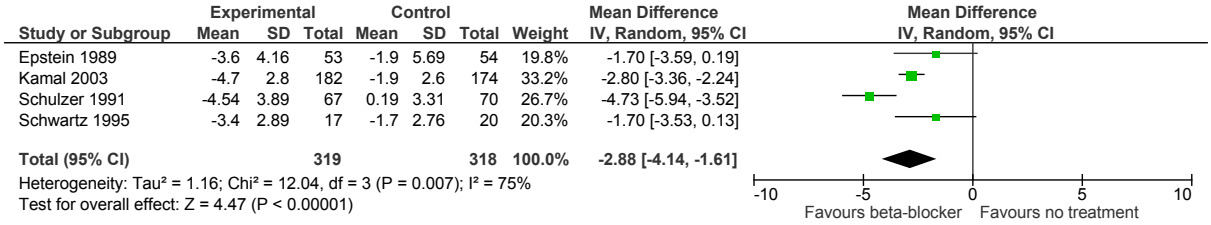
K.5.1.3.1 Visual field progression (follow-up 2-6 years)

Figure 60: Beta-blockers versus no treatment



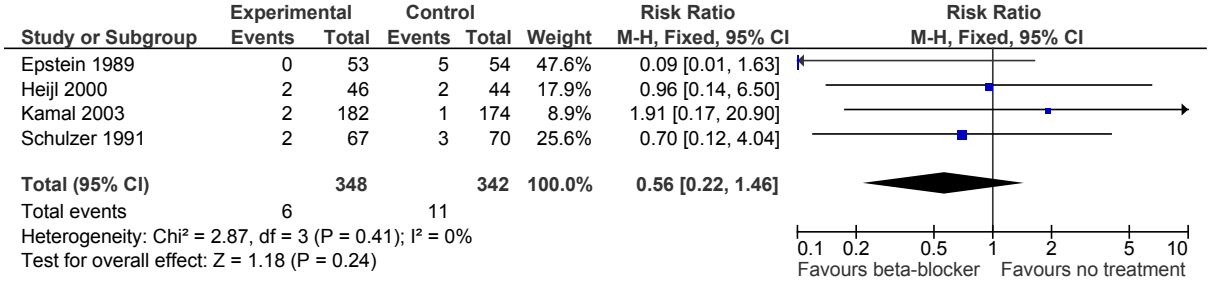
K.5.1.3.2 Mean change in IOP from baseline (follow-up 2-6 years)

Figure 61: Beta-blockers versus no treatment



K.5.1.3.3 Number of people with an IOP >30mmHg (follow-up 2-10 years)

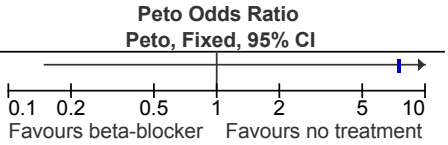
Figure 62: Beta-blockers versus no treatment



K.5.1.3.4 Adverse events: Respiratory (follow-up 5 years)

Figure 63: Beta-blockers versus no treatment

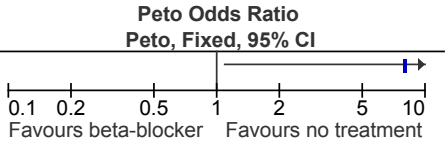
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Peto Odds Ratio Peto, Fixed, 95% CI
Epstein 1989	1	53	0	54	7.53 [0.15, 379.54]



K.5.1.3.5 Adverse events: Cardiovascular (follow-up 5 years)

Figure 64: Beta-blockers versus no treatment

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Peto Odds Ratio Peto, Fixed, 95% CI
Epstein 1989	4	53	0	54	7.99 [1.09, 58.33]

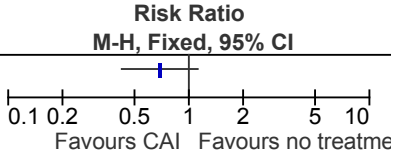


K.5.1.4 Carbonic anhydrase inhibitors versus no treatment

K.5.1.4.1 Visual field progression (follow-up 5 years)

Figure 65: Carbonic anhydrase inhibitors versus no treatment

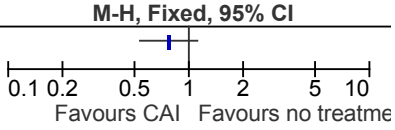
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Miglior 2005	26	536	38	541	0.69 [0.43, 1.12]



K.5.1.4.2 Conversion to COAG (follow-up 5 years)

Figure 66: Carbonic anhydrase inhibitors versus no treatment

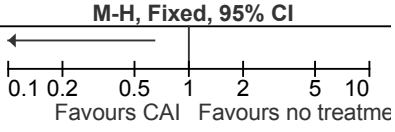
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Miglior 2005	46	536	60	541	0.77 [0.54, 1.11]



K.5.1.4.3 Number of people with an IOP >35mmHg (follow-up 5 years)

Figure 67: Carbonic anhydrase inhibitors versus no treatment

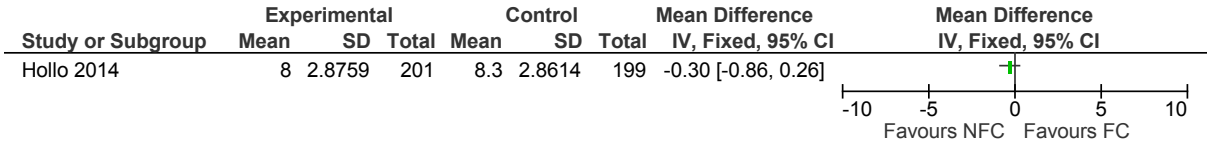
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Miglior 2005	1	536	12	541	0.08 [0.01, 0.64]



K.5.1.5 Fixed combination versus separate combination

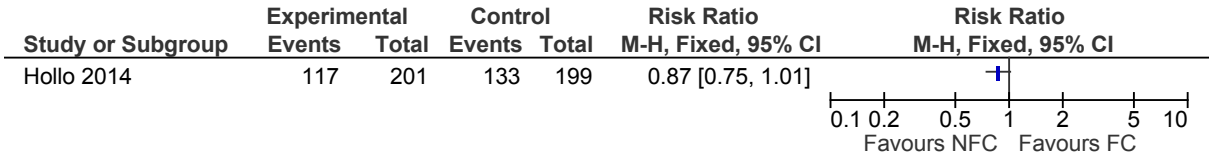
K.5.1.5.1 Change in IOP from baseline (follow-up 6 months)

Figure 68: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



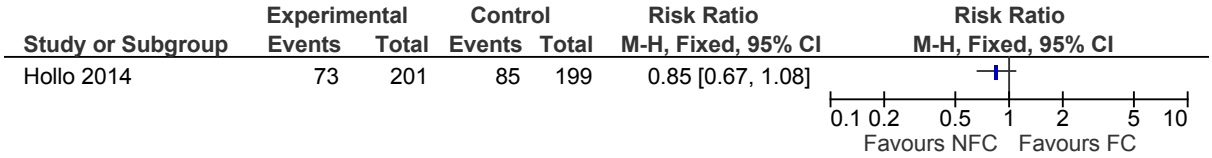
K.5.1.5.2 IOP reduction of ≥30% from baseline (follow-up 6 months)

Figure 69: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



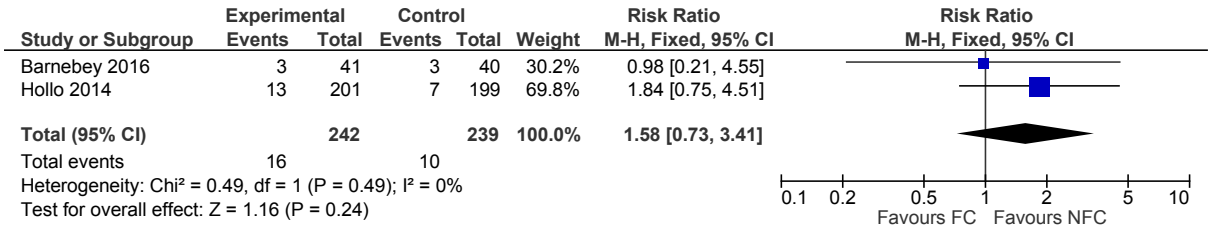
K.5.1.5.3 IOP reduction of ≥35% from baseline (follow -up 6 months)

Figure 70: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



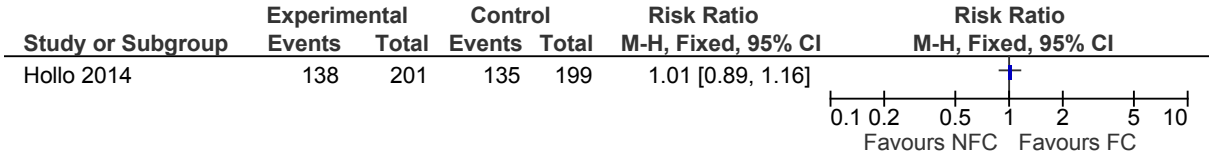
K.5.1.5.4 Adverse events: Hyperaemia (follow-up 6-12 months)

Figure 71: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



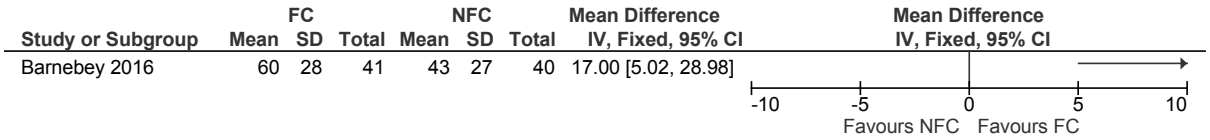
K.5.1.5.5 Mean IOP of ≤18 mmHg (follow-up 6 months)

Figure 72: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



K.5.1.5.6 Cumulative % of days that participants were adherent with dosing (follow-up 12 months)

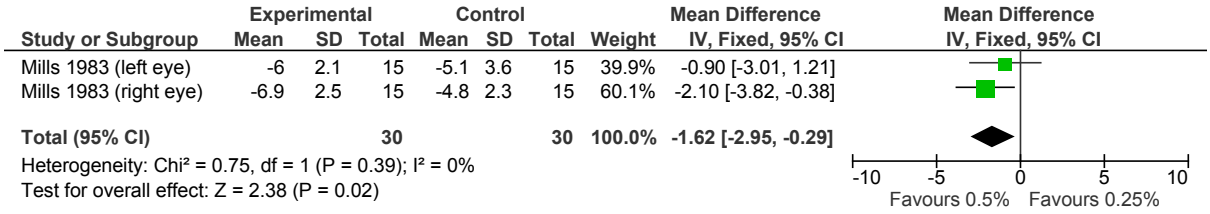
Figure 21: Prostaglandin analogue and beta-blocker versus the same medicines administered separately



K.5.1.6 Beta-blocker dosage

K.5.1.6.1 Mean change in IOP from baseline (follow-up 6 months)

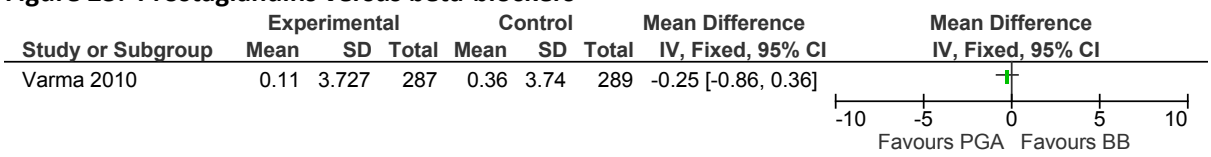
Figure 22: Timolol 0.5% versus Timolol 0.25%



K.5.1.7 Prostaglandins versus beta-blockers

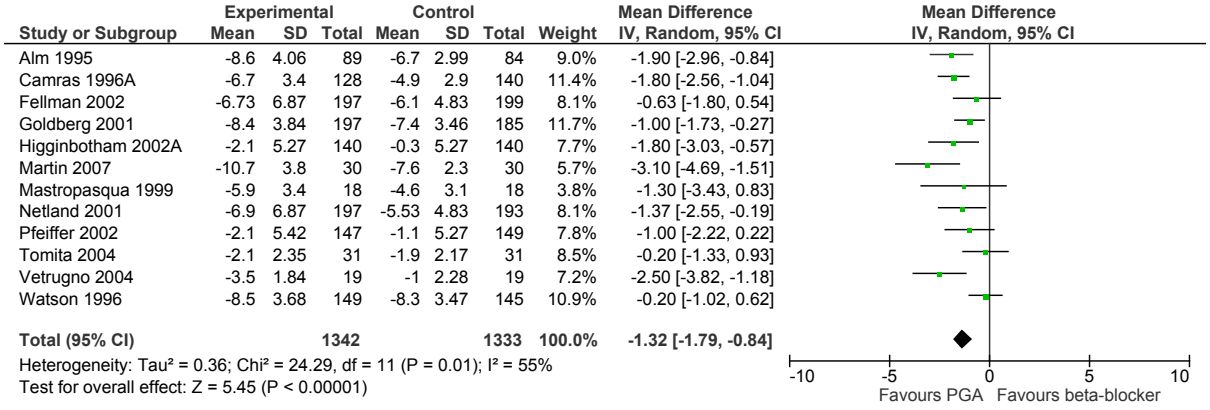
K.5.1.7.1 Change in diurnal IOP fluctuation from baseline (follow-up 26 weeks)

Figure 23: Prostaglandins versus beta-blockers



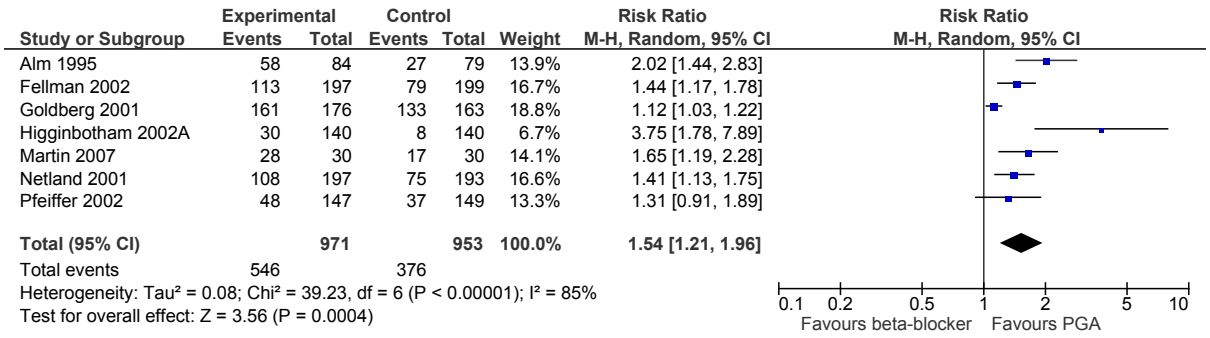
K.5.1.7.2 Mean change in IOP from baseline (follow-up 6-36 months)

Figure 24: Prostaglandins versus beta-blockers



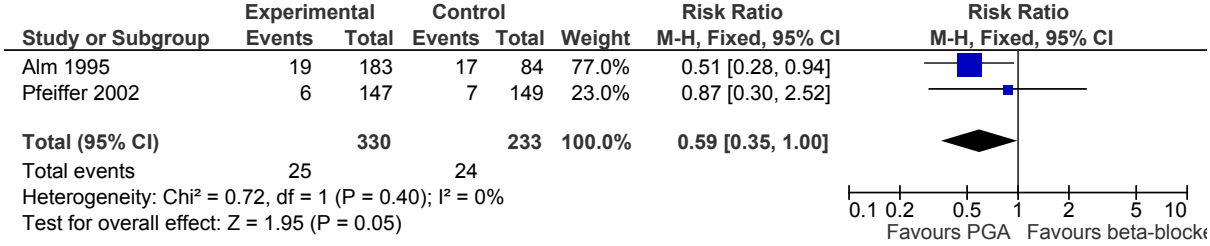
K.5.1.7.3 Number of people with acceptable IOP (follow -up 6-12 months)

Figure 25: Prostaglandins versus beta-blockers



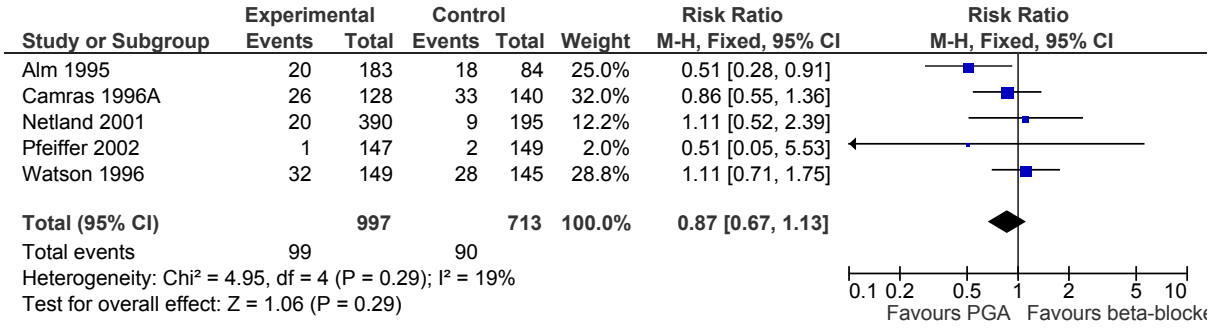
K.5.1.7.4 Adverse events: Respiratory (follow-up 6 months)

Figure 26: Prostaglandins versus beta-blockers



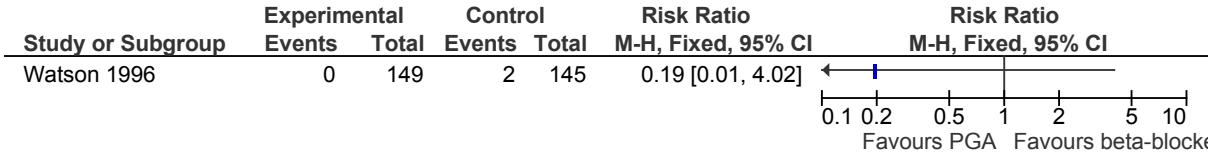
K.5.1.7.5 Adverse events: Cardiovascular (follow-up 6-12 months)

Figure 27: Prostaglandins versus beta-blockers



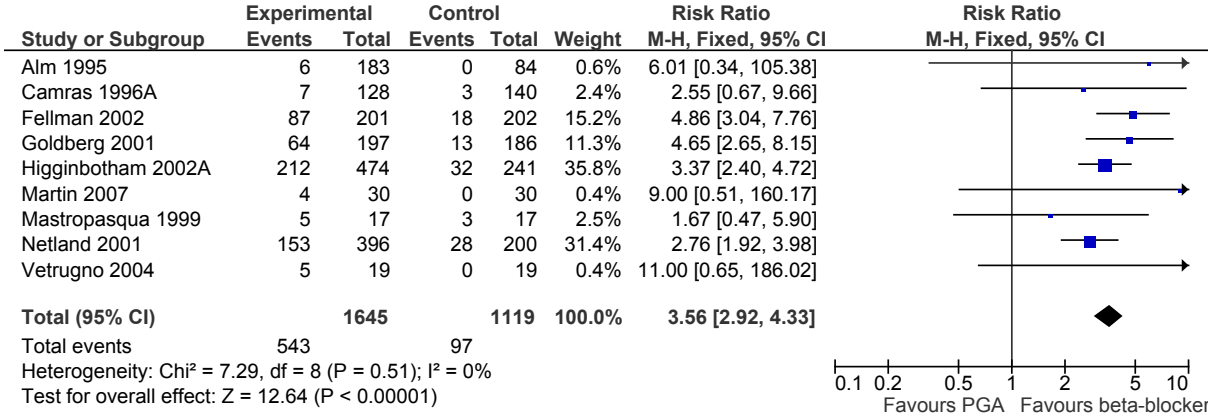
K.5.1.7.6 Adverse events: Allergic reaction (follow-up 6 months)

Figure 28: Prostaglandins versus beta-blockers



K.5.1.7.7 Adverse events: Hyperaemia (follow-up 6-12 months)

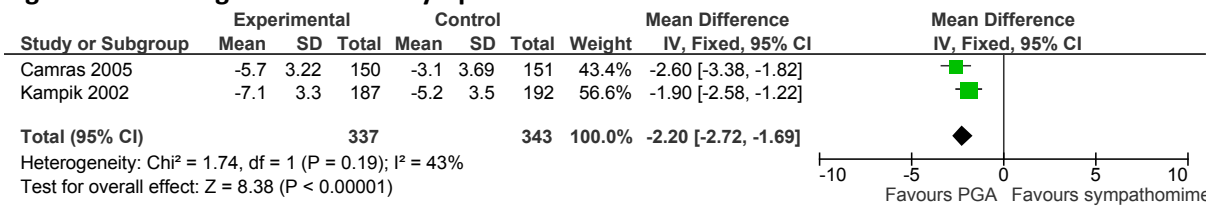
Figure 29: Prostaglandins versus beta-blockers



K.5.1.8 Prostaglandins versus sympathomimetics

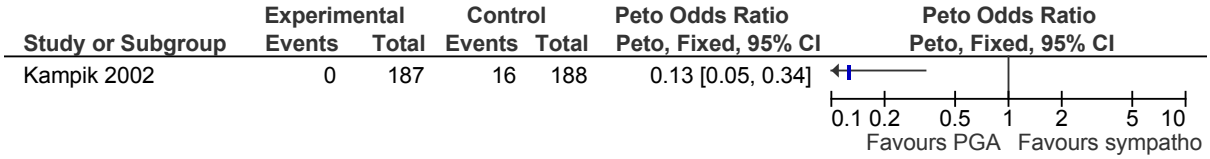
K.5.1.8.1 Change in IOP from baseline (follow-up 6-12 months)

Figure 30: Prostaglandins versus sympathomimetics



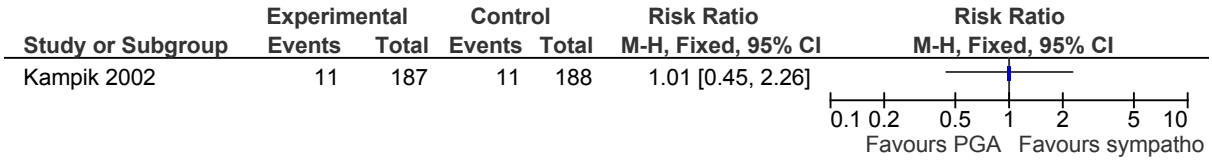
K.5.1.8.2 Adverse events: Allergic reaction (follow-up 6 months)

Figure 31: Prostaglandins versus sympathomimetics



K.5.1.8.3 Adverse events: Hyperaemia (follow-up 6 months)

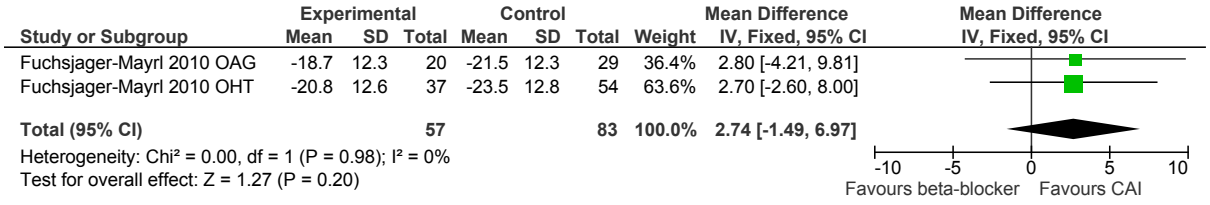
Figure 32: Prostaglandins versus sympathomimetics



K.5.1.9 Carbonic anhydrase inhibitors versus beta-blockers

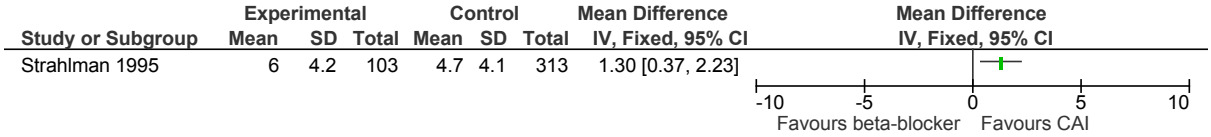
K.5.1.9.1 Change in IOP from baseline (% – follow-up 6 months)

Figure 33: Carbonic anhydrase inhibitors versus beta-blockers



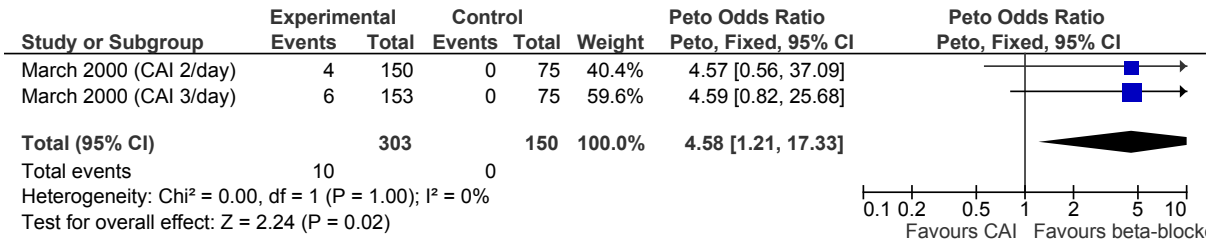
K.5.1.9.2 Change in IOP from baseline (mmHg – follow-up 12 months)

Figure 34: Carbonic anhydrase inhibitors versus beta-blockers



K.5.1.9.3 Adverse events: Hyperaemia (follow-up 18 months)

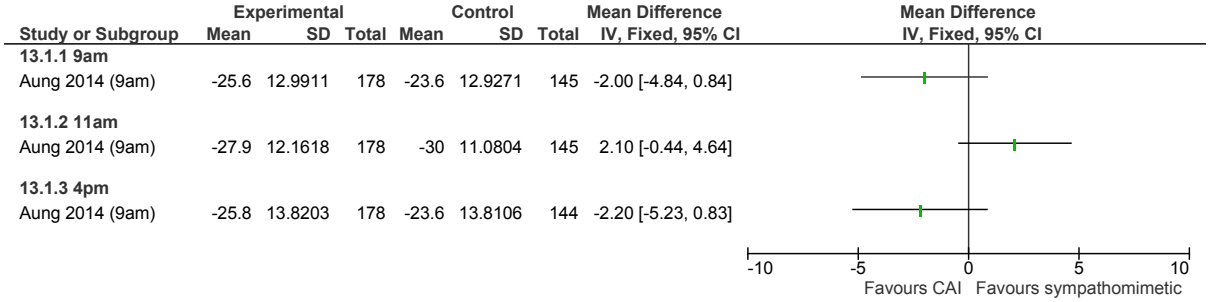
Figure 35: Carbonic anhydrase inhibitors versus beta-blockers



K.5.1.10 Carbonic anhydrase inhibitors versus sympathomimetics

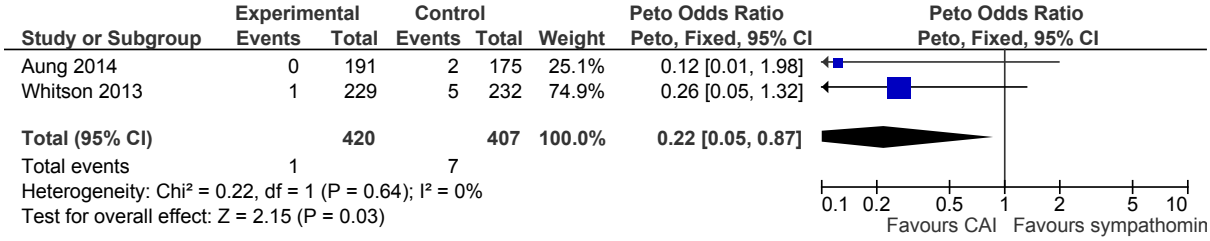
K.5.1.10.1 Mean change in IOP from baseline (% – follow-up 6 months)

Figure 36: Carbonic anhydrase inhibitors versus sympathomimetics



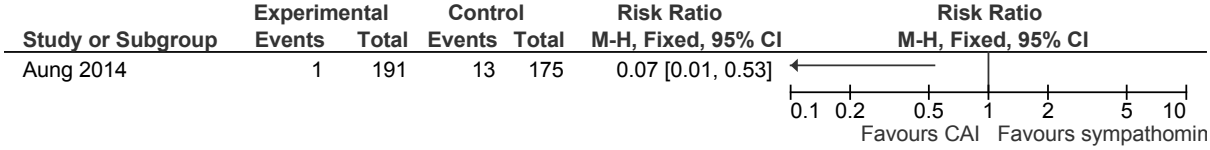
K.5.1.10.2 Adverse events: Allergic reaction (follow-up 6 months)

Figure 37: Carbonic anhydrase inhibitors versus sympathomimetics



K.5.1.10.3 Treatment discontinuation due to adverse events (follow-up 6 months)

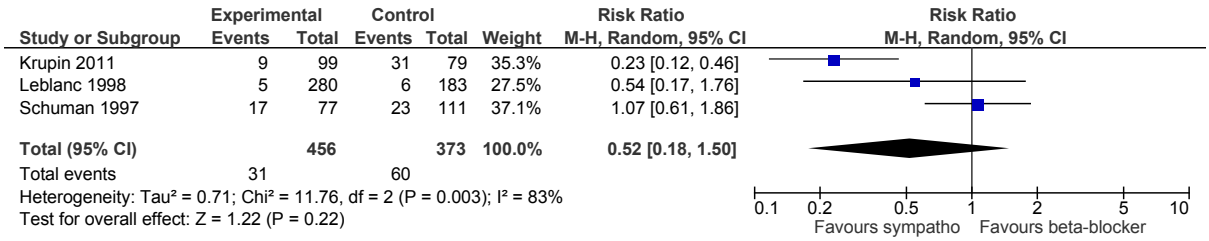
Figure 38: Carbonic anhydrase inhibitors versus sympathomimetics



K.5.1.11 Sympathomimetics versus beta-blockers

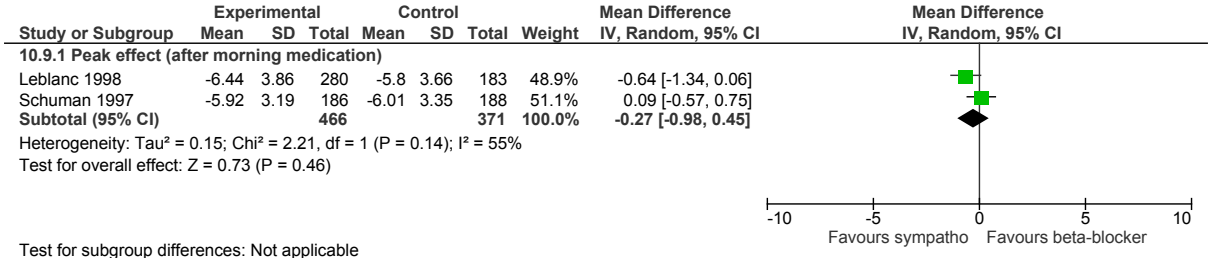
K.5.1.11.1 Visual field progression (follow-up 12 months)

Figure 39: Sympathomimetics versus beta-blockers



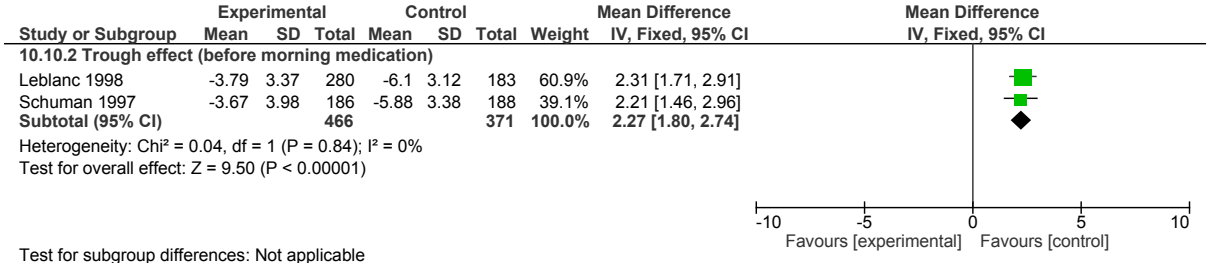
K.5.1.11.2 Change in IOP from baseline (peak effect – follow-up 12 months)

Figure 40: Sympathomimetics versus beta-blockers



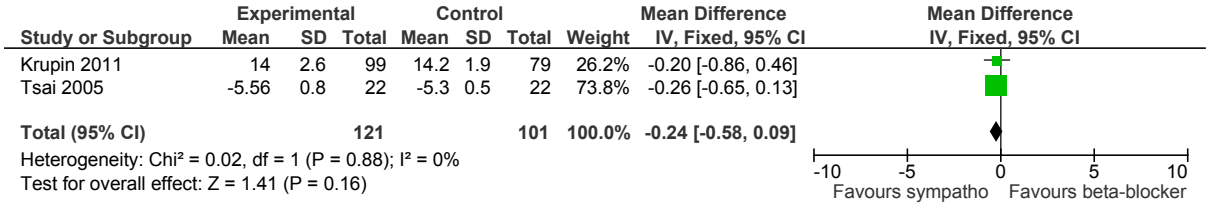
K.5.1.11.3 Change in IOP from baseline (trough effect-follow up 12 months

Figure 73: Sympathomimetics versus beta-blockers



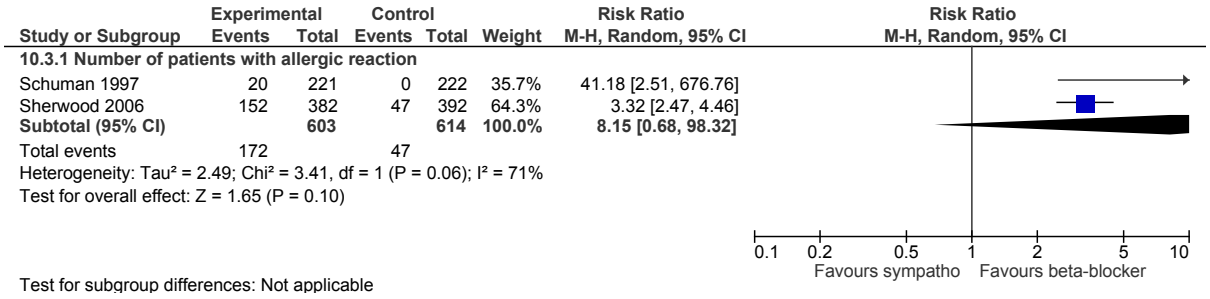
K.5.1.11.4 Change in IOP from baseline (mean diurnal – follow-up 12 months)

Figure 41: Sympathomimetics versus beta-blockers



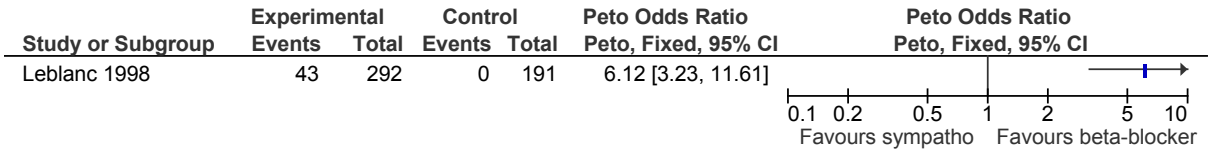
K.5.1.11.5 Adverse events: Allergic reaction (follow-up 12 months)

Figure 42: Sympathomimetics versus beta-blockers



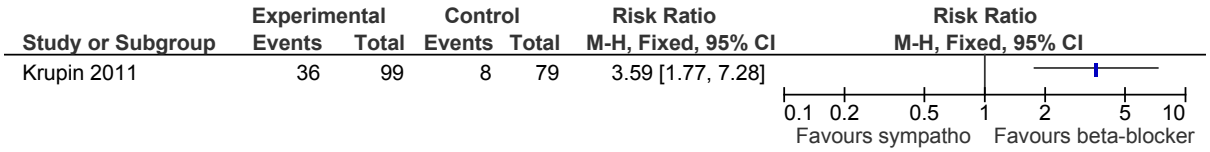
K.5.1.11.6 Treatment discontinuation due to allergic reaction (follow-up 12 months)

Figure 43: Sympathomimetic versus beta-blocker



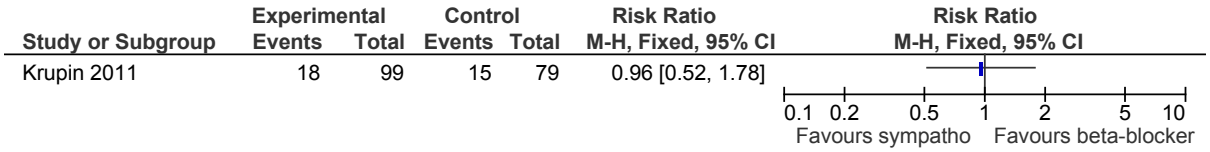
K.5.1.11.7 Treatment discontinuation prior to year 1

Figure 44: Sympathomimetics versus beta-blockers



K.5.1.11.8 Treatment discontinuation ≥ year 1

Figure 45: Sympathomimetics versus beta-blockers



K.5.1.12 Fixed combinations versus single medications

K.5.1.12.1 Change in diurnal IOP fluctuation (follow-up 26 weeks)

Figure 46: Prostaglandin and beta-blocker versus prostaglandin

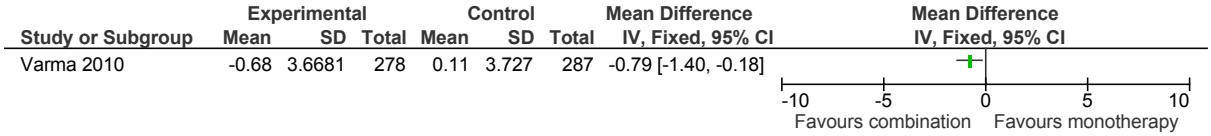
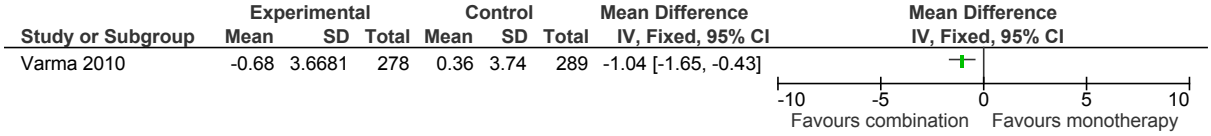


Figure 47: Prostaglandin and beta-blocker versus beta-blocker



K.5.1.12.2 Change in IOP from baseline (follow-up 6 months)

Figure 48: Prostaglandin and beta-blocker versus prostaglandin

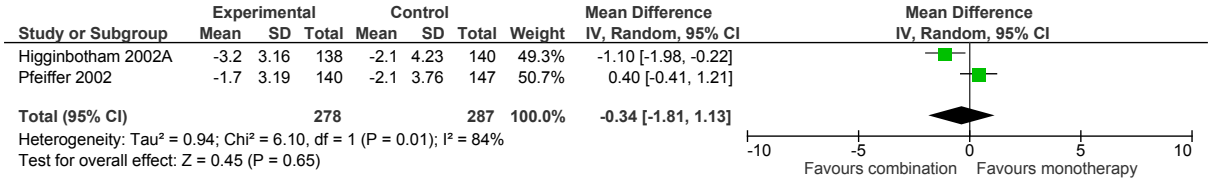


Figure 49: Prostaglandin and beta-blocker versus beta-blocker

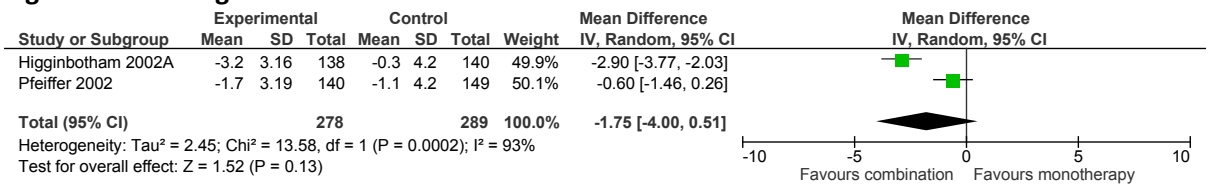
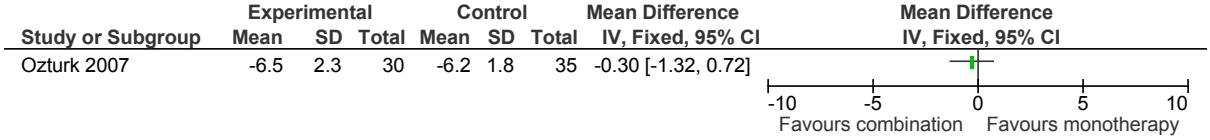


Figure 50: Carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue



K.5.1.12.3 Number of people with an acceptable IOP (follow-up 6 months)

Figure 51: Prostaglandin analogue and beta-blocker versus prostaglandin (<18mmHg)

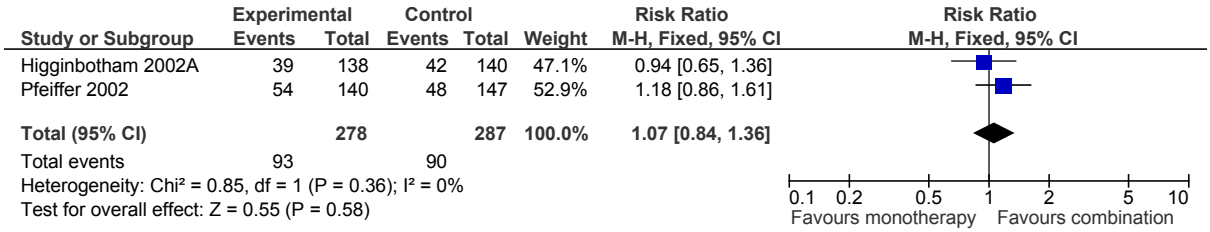


Figure 52: Prostaglandin and beta-blocker versus beta-blocker (<18mmHg)

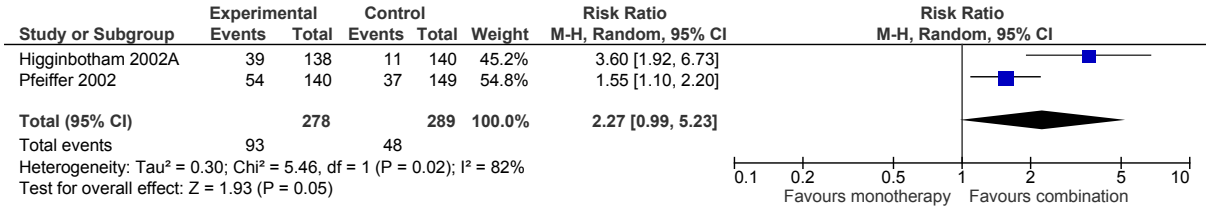
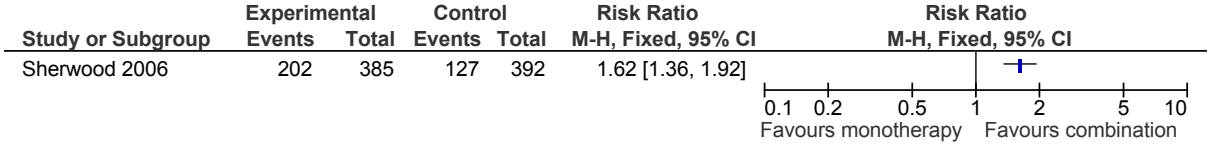


Figure 53: Sympathomimetic and beta-blocker versus beta-blocker (<17.5mmHg)



K.5.1.12.4 Adverse events: Respiratory (follow-up 6 months)

Figure 54: Prostaglandin analogue and beta-blocker versus beta-blocker

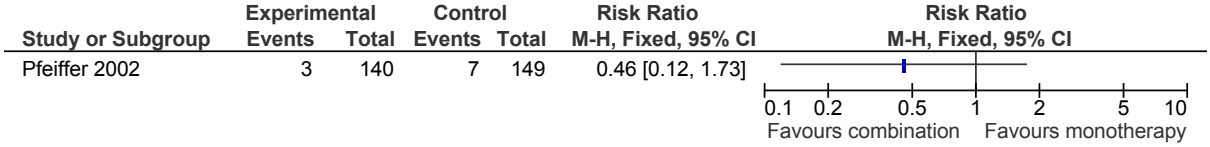


Figure 55: Prostaglandin analogue and beta-blocker versus prostaglandin analogue

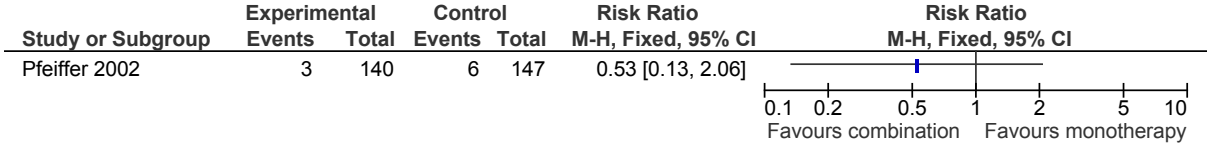
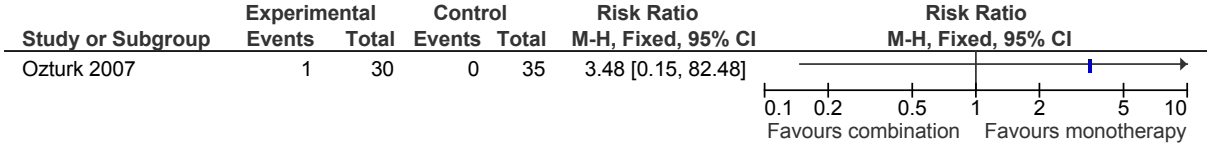


Figure 56: Carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue



K.5.1.12.5 Adverse events: Cardiovascular (follow-up 6 months)

Figure 57: Prostaglandin analogue and beta-blocker versus beta-blocker

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Pfeiffer 2002	5	140	2	149	2.66 [0.52, 13.49]

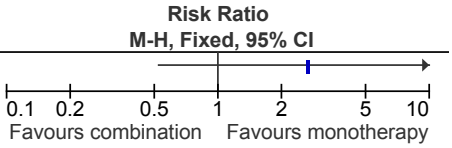
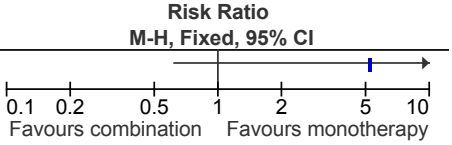


Figure 58: Prostaglandin analogue and beta-blocker versus prostaglandin analogue

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Pfeiffer 2002	5	140	1	147	5.25 [0.62, 44.38]



K.5.1.12.6 Adverse events: Allergic reaction (follow-up 6-12 months)

Figure 59: Sympathomimetic and beta-blocker versus beta-blocker

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Sherwood 2006	100	385	47	392	2.17 [1.58, 2.97]

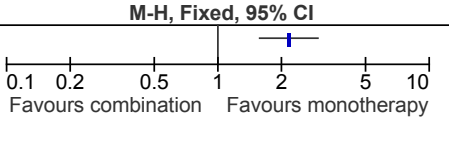


Figure 60: Carbonic anhydrase inhibitor and sympathomimetic versus sympathomimetic

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aung 2014	3	193	2	175	30.2%	1.36 [0.23, 8.04]
Whitson 2013	14	218	5	232	69.8%	2.98 [1.09, 8.13]
Total (95% CI)		**411**		**407**	**100.0%**	**2.49 [1.05, 5.90]**
Total events	17		7			

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)

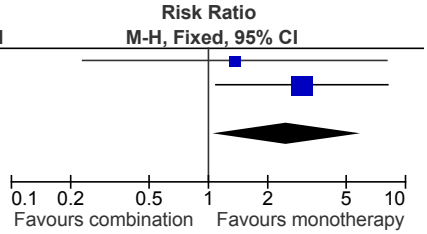
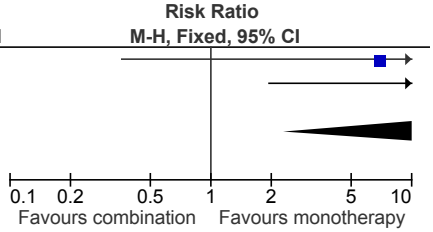


Figure 61: Carbonic anhydrase inhibitor and sympathomimetic versus carbonic anhydrase inhibitor

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aung 2014	3	193	0	191	34.0%	6.93 [0.36, 133.22]
Whitson 2013	14	218	1	229	66.0%	14.71 [1.95, 110.89]
Total (95% CI)		**411**		**420**	**100.0%**	**12.06 [2.30, 63.29]**
Total events	17		1			

Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)



K.5.1.12.7 Adverse events: Hyperaemia (follow-up 6 to 12 months)

Figure 62: Prostaglandin and beta-blocker versus beta-blocker

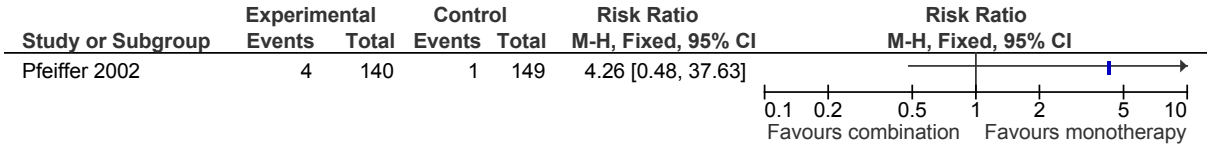


Figure 63: Prostaglandin and beta-blocker versus prostaglandin

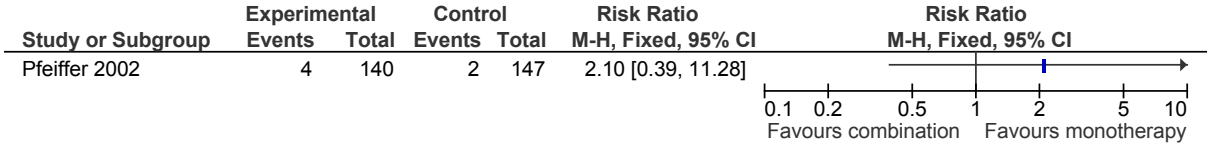
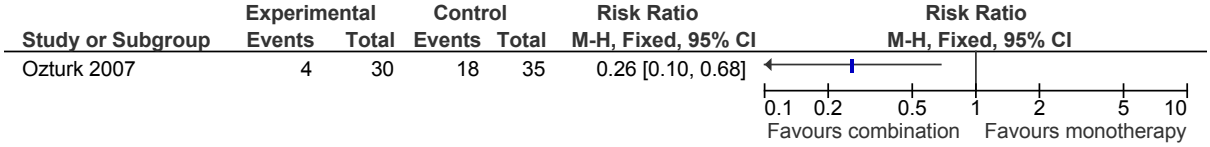


Figure 64: Carbonic anhydrase inhibitor and beta-blocker versus prostaglandin



K.5.1.12.8 Treatment discontinuation due to adverse events (follow-up 6 months)

Figure 65: Carbonic anhydrase inhibitor and sympathomimetic versus sympathomimetic

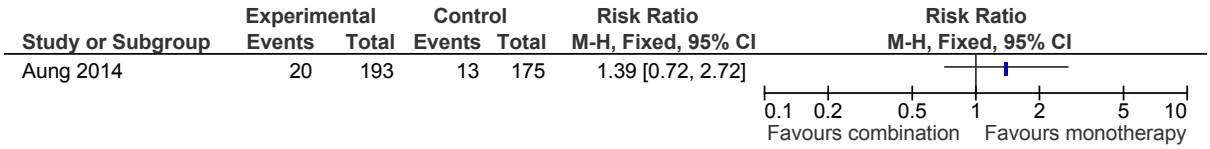
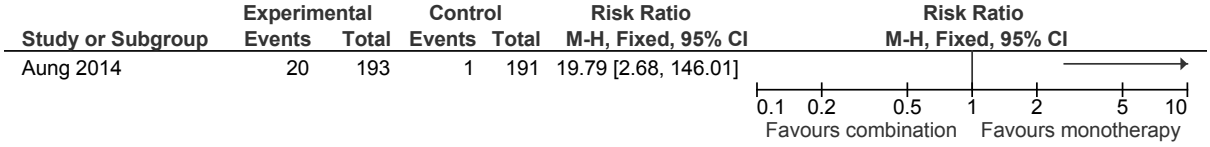


Figure 66: Carbonic anhydrase inhibitors and sympathomimetics versus carbonic anhydrase inhibitors



K.5.1.12.9 Change in IOP from baseline (% – follow-up 6 months)

Figure 67: Carbonic anhydrase inhibitors and sympathomimetic versus sympathomimetic

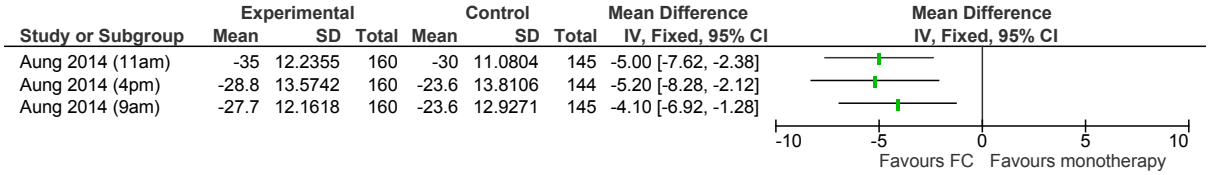


Figure 68: Carbonic anhydrase inhibitors and sympathomimetic versus carbonic anhydrase inhibitors

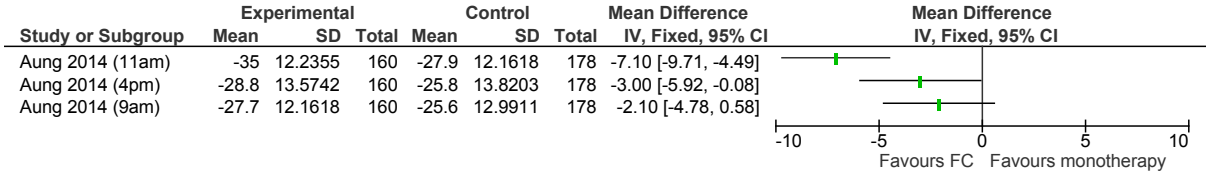
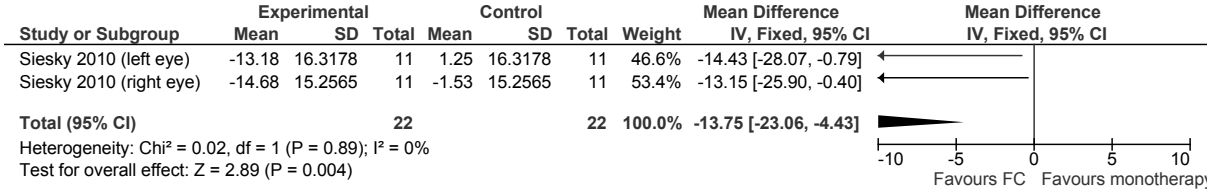


Figure 69: Carbonic anhydrase inhibitors and beta-blockers versus beta-blockers



K.5.1.13 Separate combination versus single medications

K.5.1.13.1 Change in IOP from baseline (follow-up 6 months)

Figure 70: Prostaglandin analogues and beta-blockers versus prostaglandin analogues

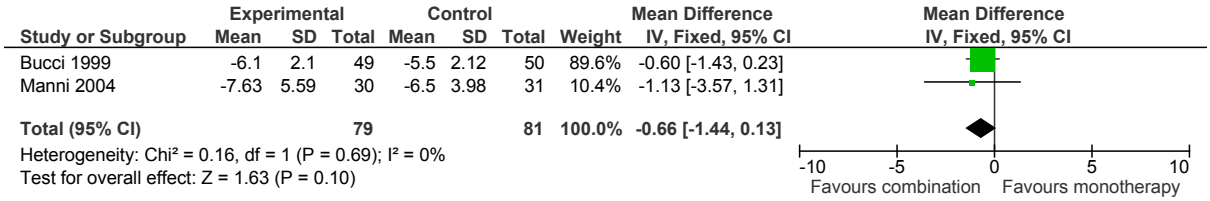
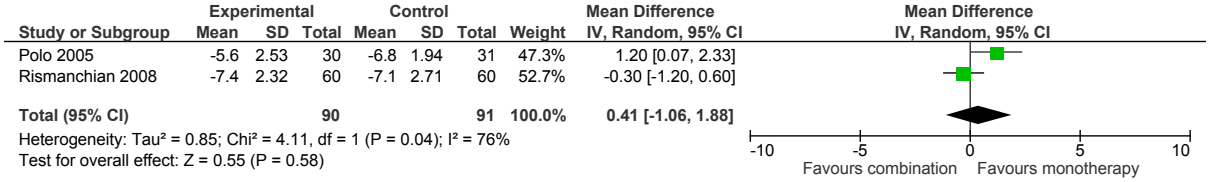


Figure 71: Carbonic anhydrase inhibitors and beta-blockers versus prostaglandin analogues



K.5.1.13.2 Number of people with an acceptable IOP (follow-up 24 months)

Figure 72: Prostaglandin and beta-blocker versus prostaglandin

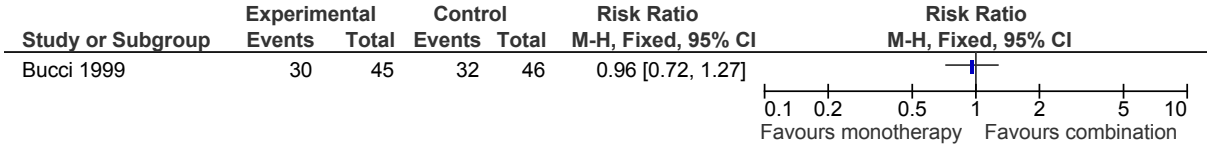


Figure 73: Prostaglandin and beta-blocker versus beta-blocker

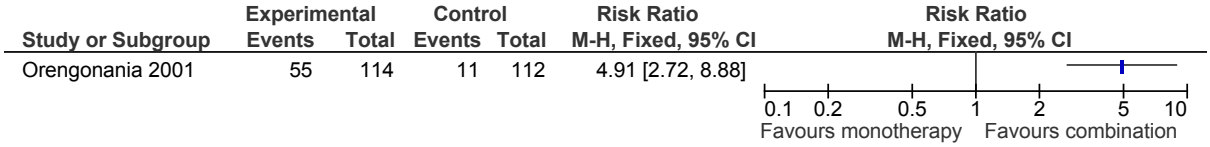
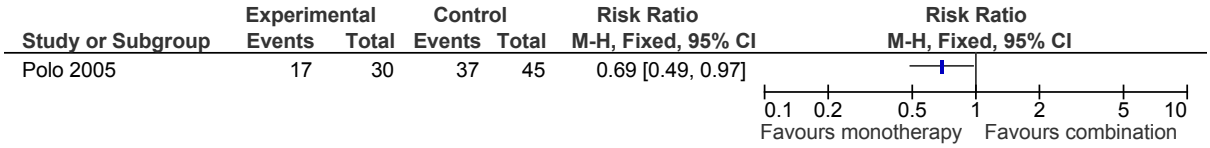
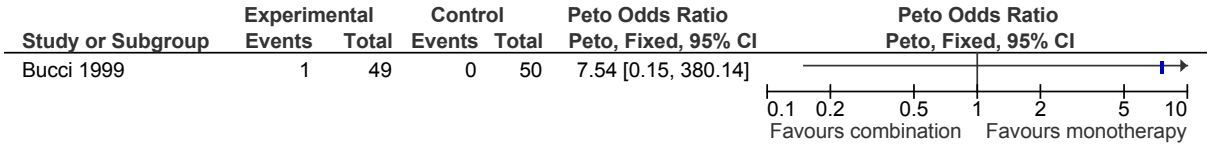


Figure 74: Carbonic anhydrase inhibitor and beta-blocker versus prostaglandin



K.5.1.13.3 Adverse events: Respiratory (follow-up 6 months)

Figure 75: Prostaglandin and beta-blocker versus prostaglandin



K.5.1.13.4 Adverse events: Hyperaemia (follow-up 6 months)

Figure 76: Prostaglandin and beta-blocker versus prostaglandin

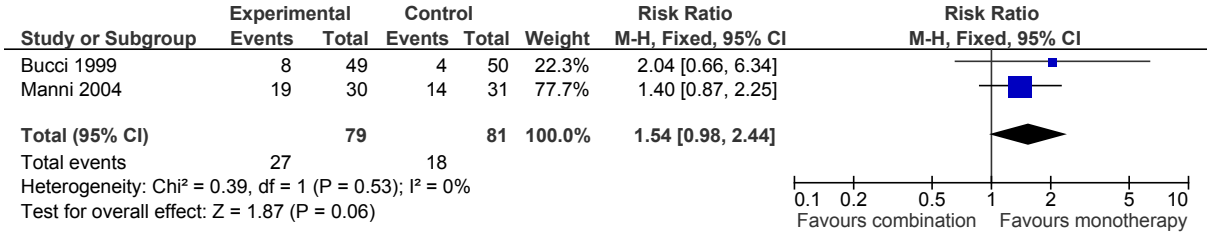
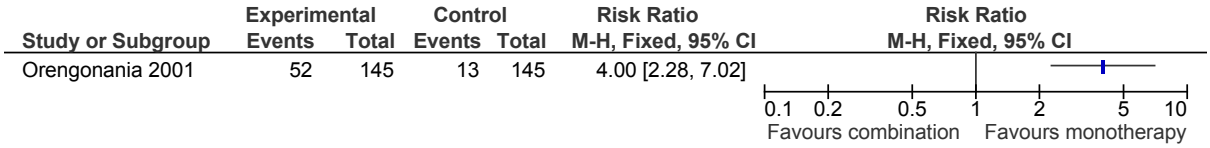


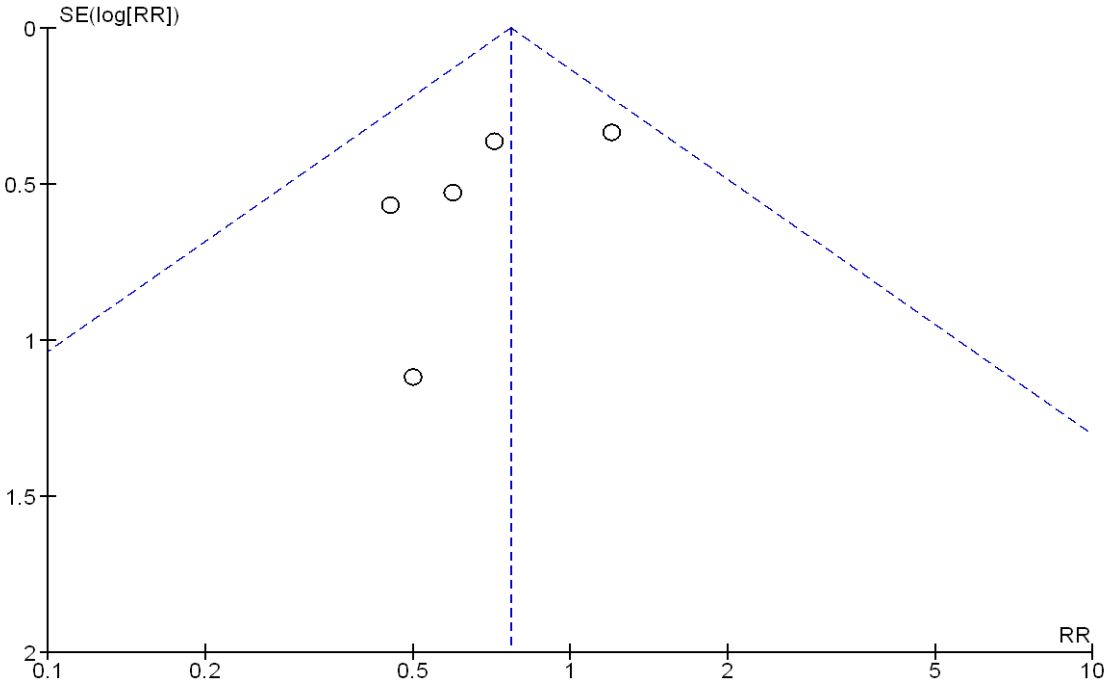
Figure 77: Prostaglandin and beta-blocker versus beta-blocker



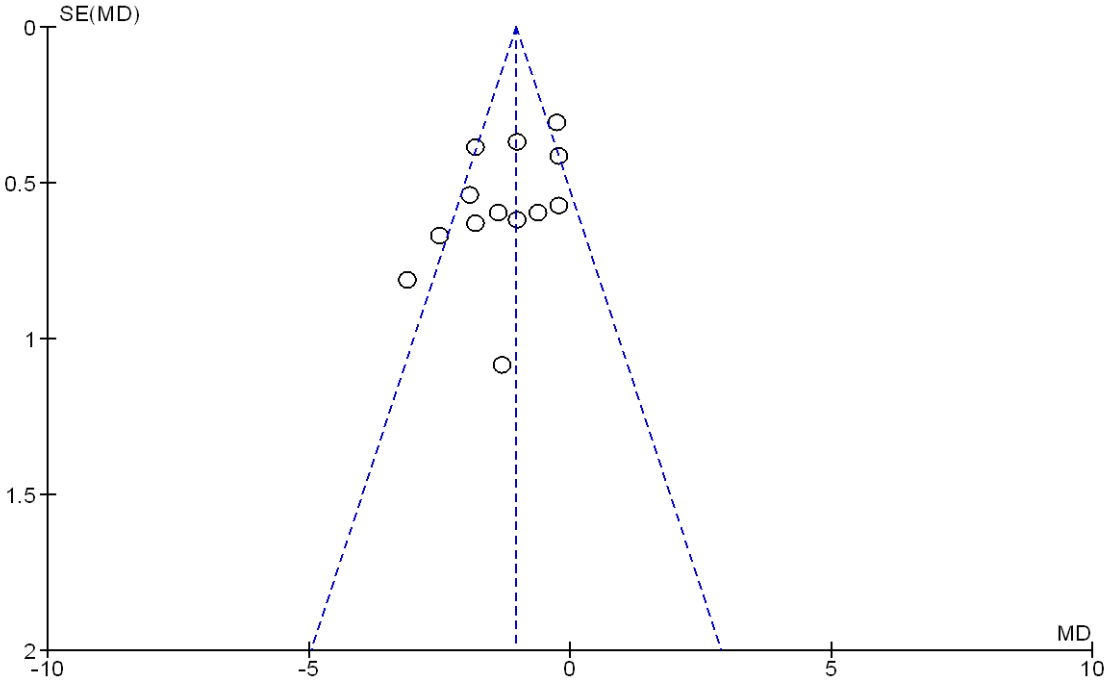
K.5.1.14 Funnel plots

Funnel plots were constructed for outcomes of comparisons containing 5 or more studies in order to assess for publication bias.

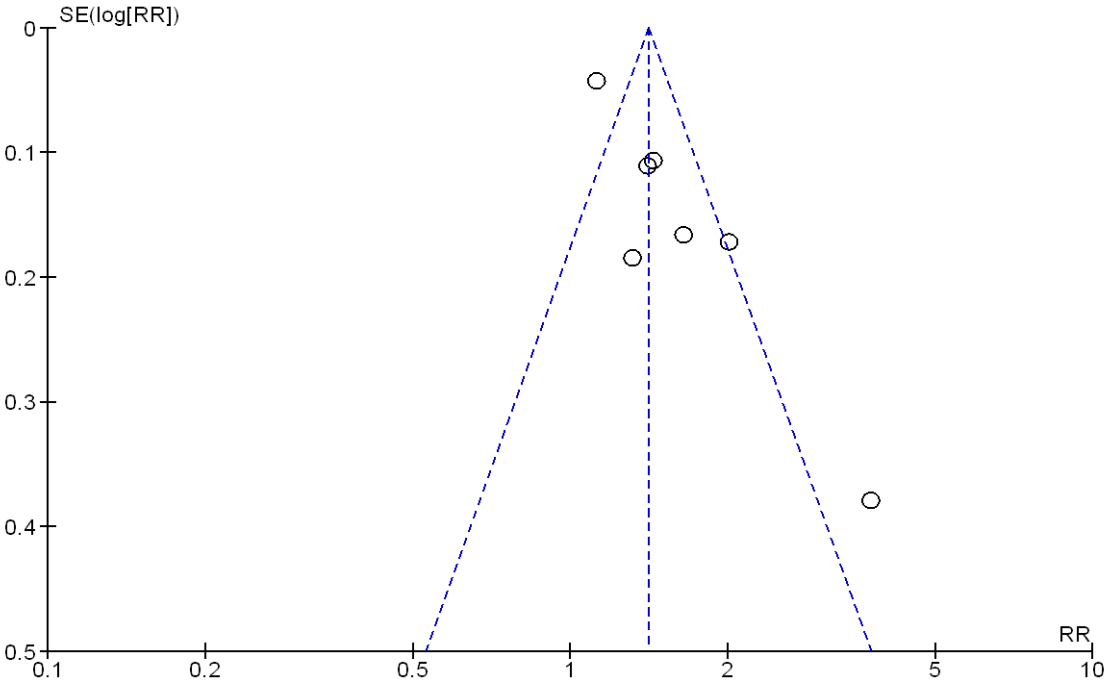
K.5.1.14.1 Beta-blockers versus no treatment: Visual field progression (follow-up 2-6 years)



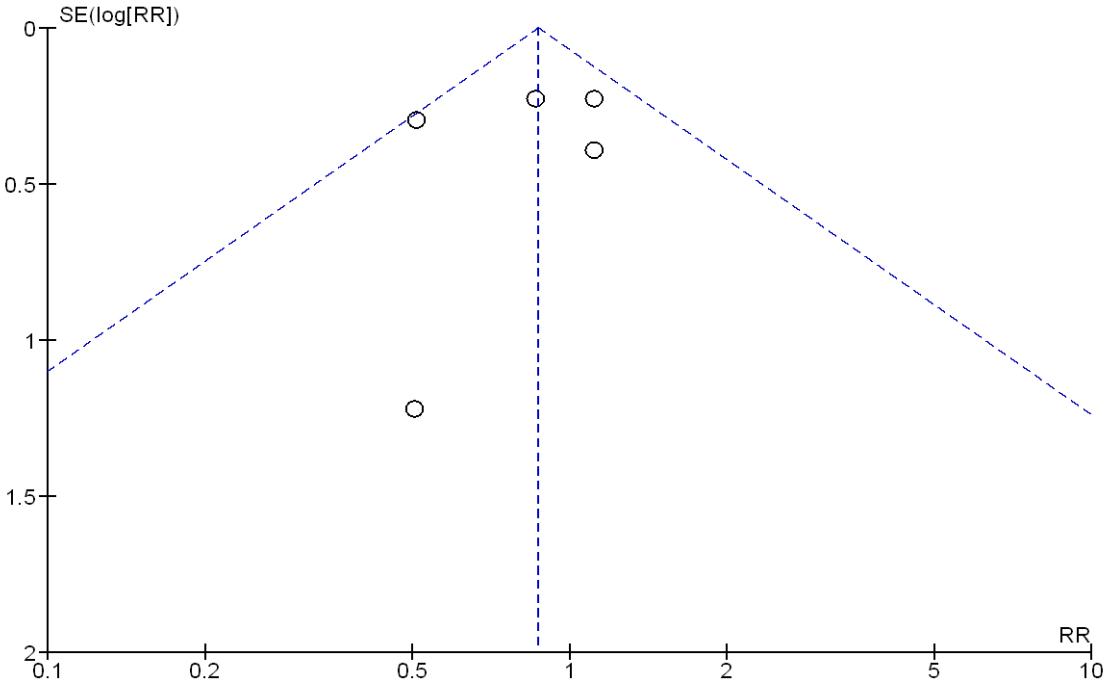
K.5.1.14.2 Prostaglandins versus beta-blockers: Mean change in IOP from baseline (follow-up 6-36 months)



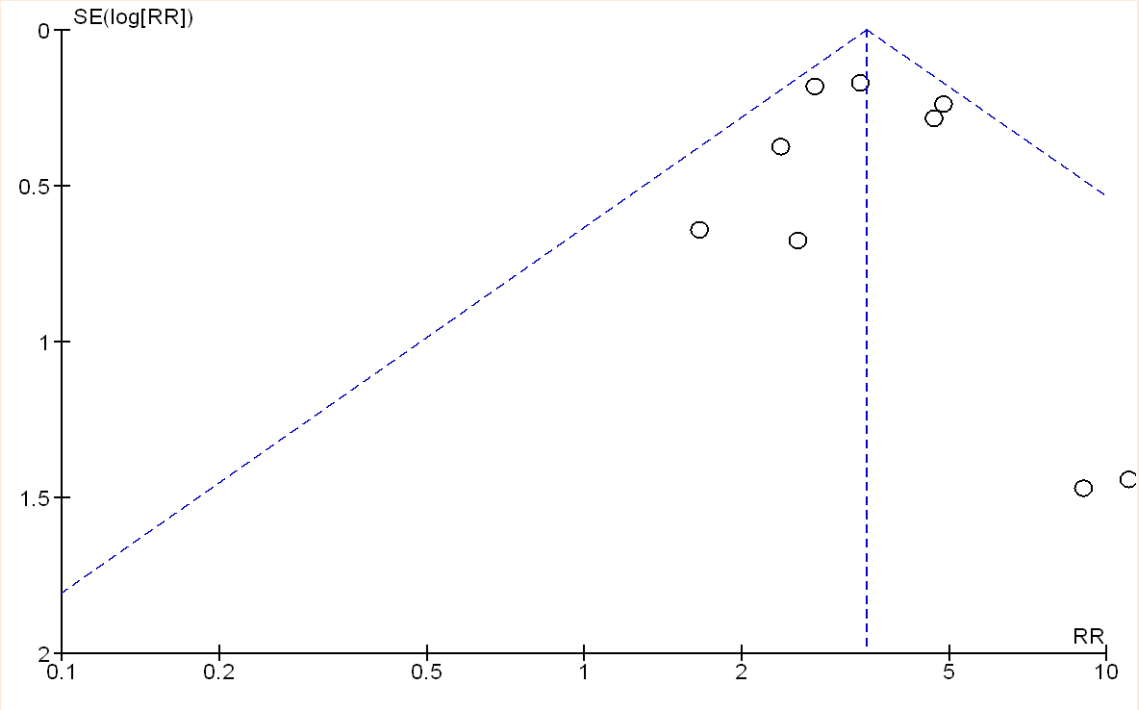
K.5.1.14.3 Prostaglandins versus beta-blockers: Number of people with an acceptable IOP (follow-up 6-12 months)



K.5.1.14.4 Prostaglandins versus beta-blockers: Adverse events: Cardiovascular (follow-up 6-12 months)



K.5.1.14.5 Prostaglandins versus beta-blockers: Adverse events: Hyperaemia (follow-up 6-12 months)



2009

K.5.2 Laser treatment for COAG

Figure 74 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – change in IOP from baseline

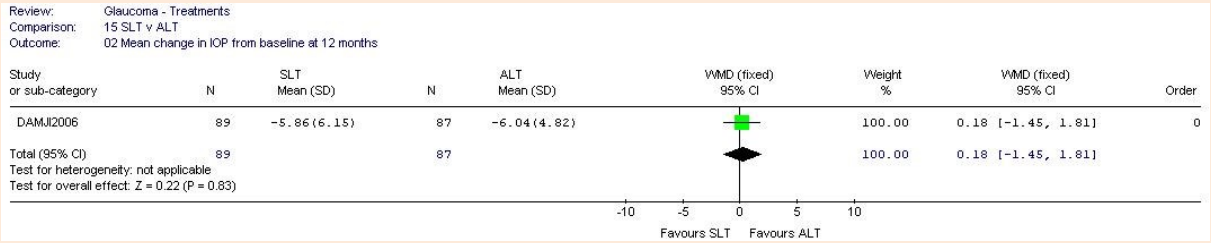


Figure 75 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – unacceptable IOP

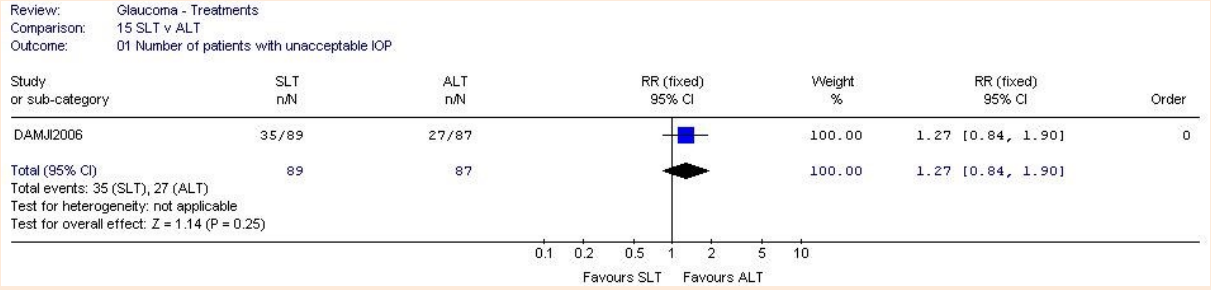


Figure 76 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – complications: PAS formation

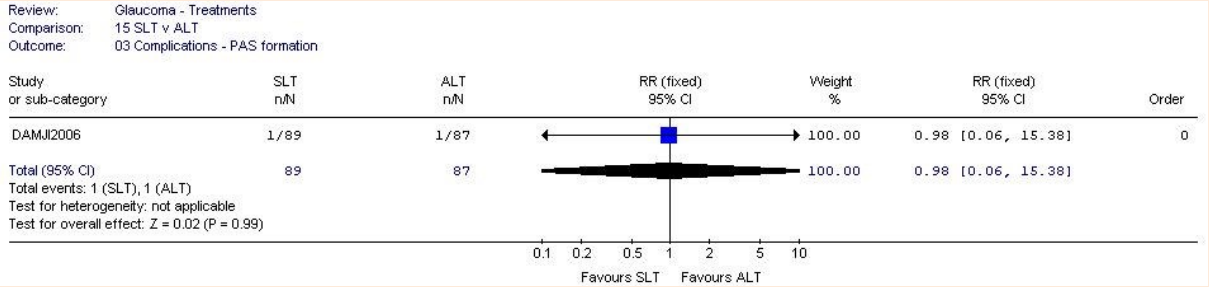


Figure 77 Laser vs. pharmacological treatment – unacceptable IOP

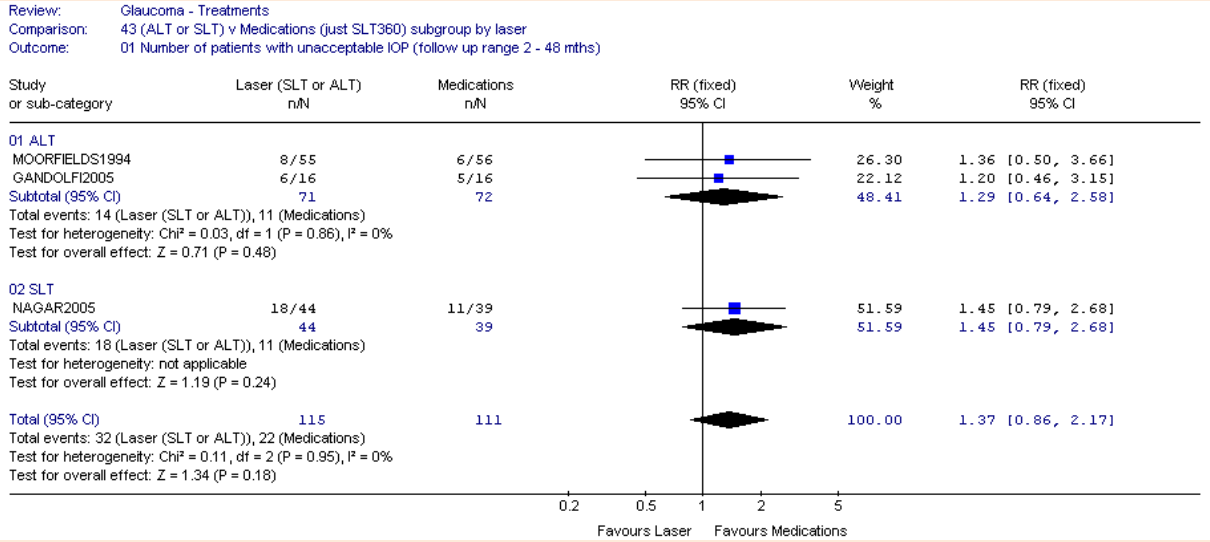
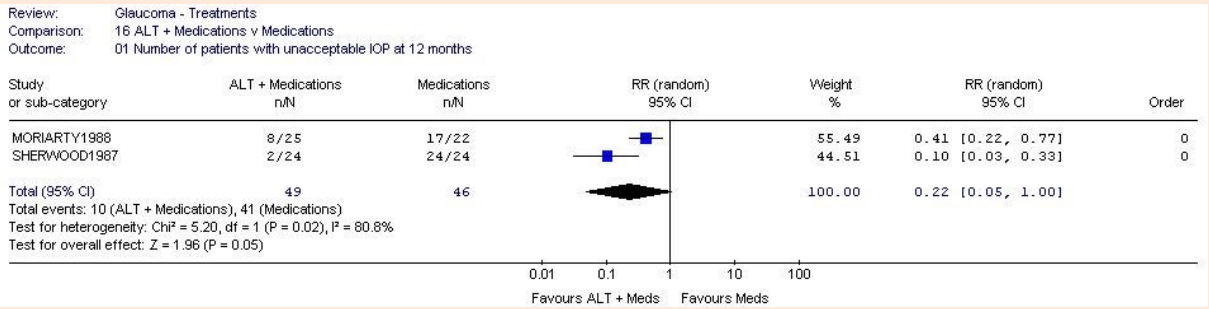
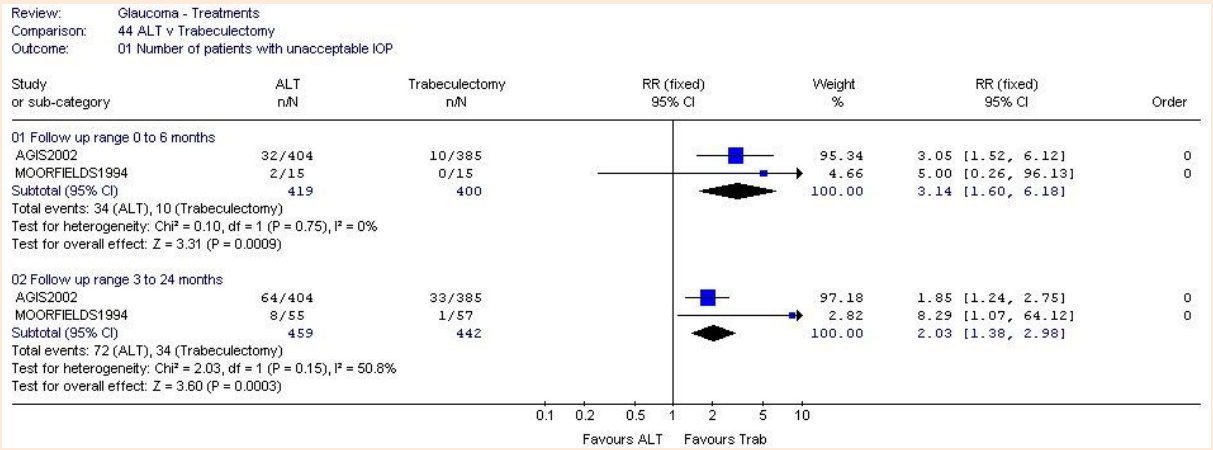


Figure 78 Laser plus pharmacological treatment vs. pharmacological treatment – unacceptable IOP



2009

Figure 79 Laser vs. trabeculectomy – unacceptable IOP



K.5.3 Surgical treatment for COAG

Figure 80 Trabeculectomy vs. pharmacological treatment – visual field progression at 1-5 years

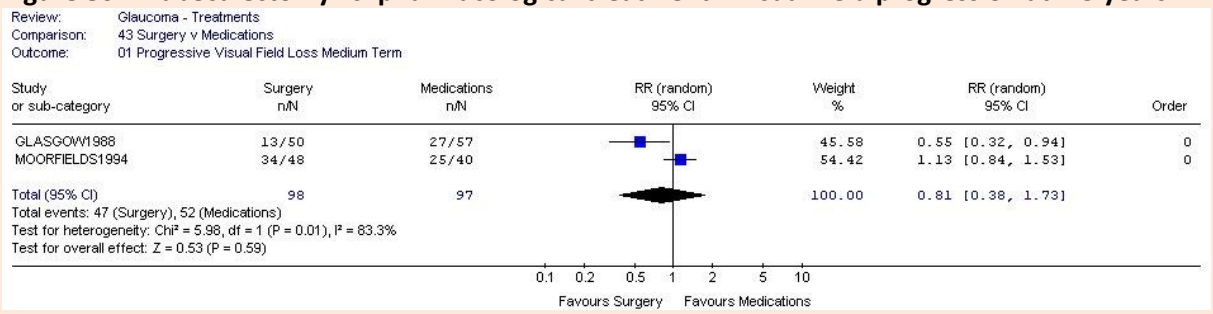
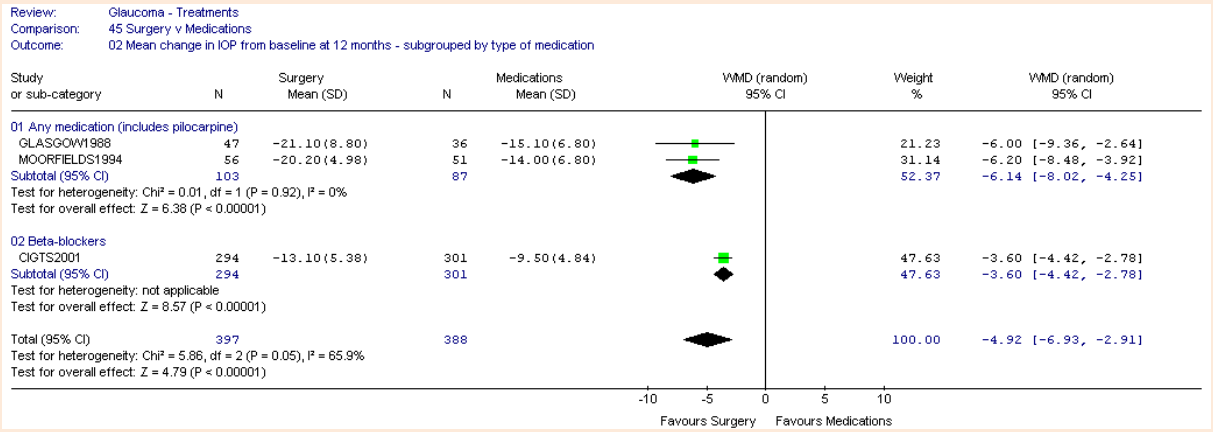


Figure 81 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 12 months



2009

Figure 82 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 1-5 years

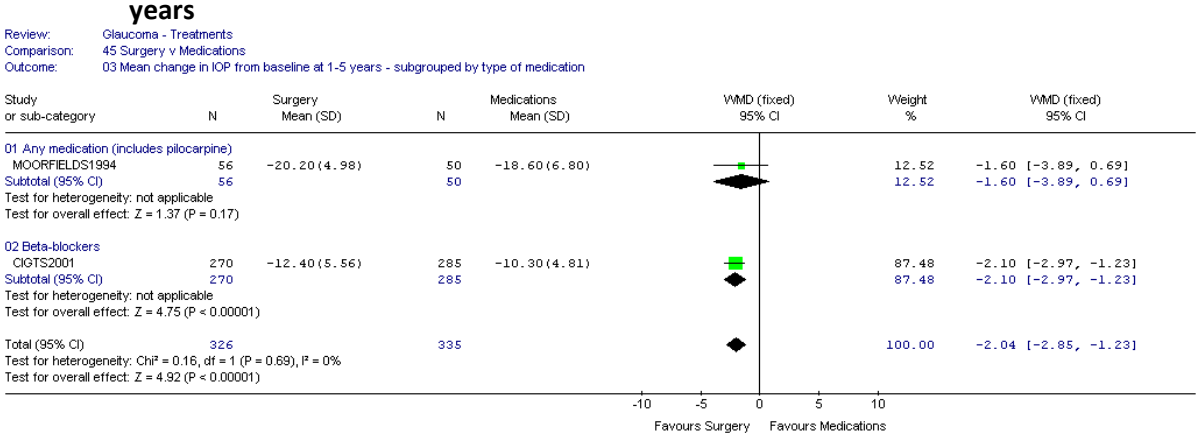


Figure 83 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at >5 years

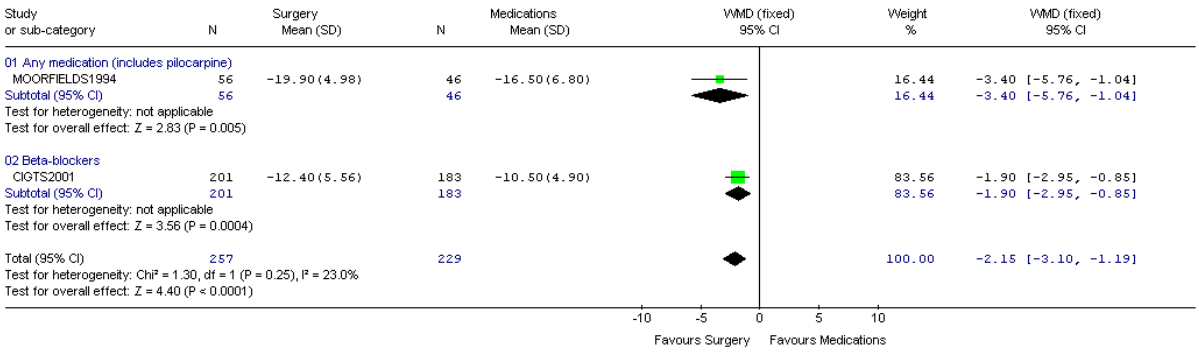


Figure 84 Trabeculectomy vs. pharmacological treatment – unacceptable IOP at 12 months

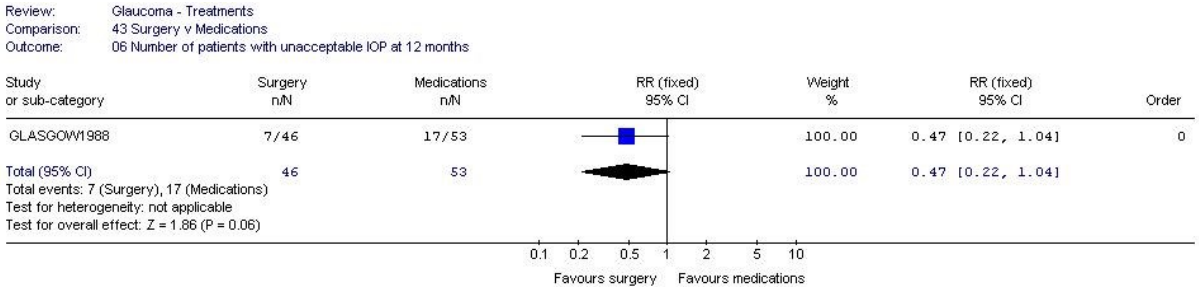


Figure 85 Trabeculectomy plus augmentation vs. trabeculectomy – unacceptable IOP

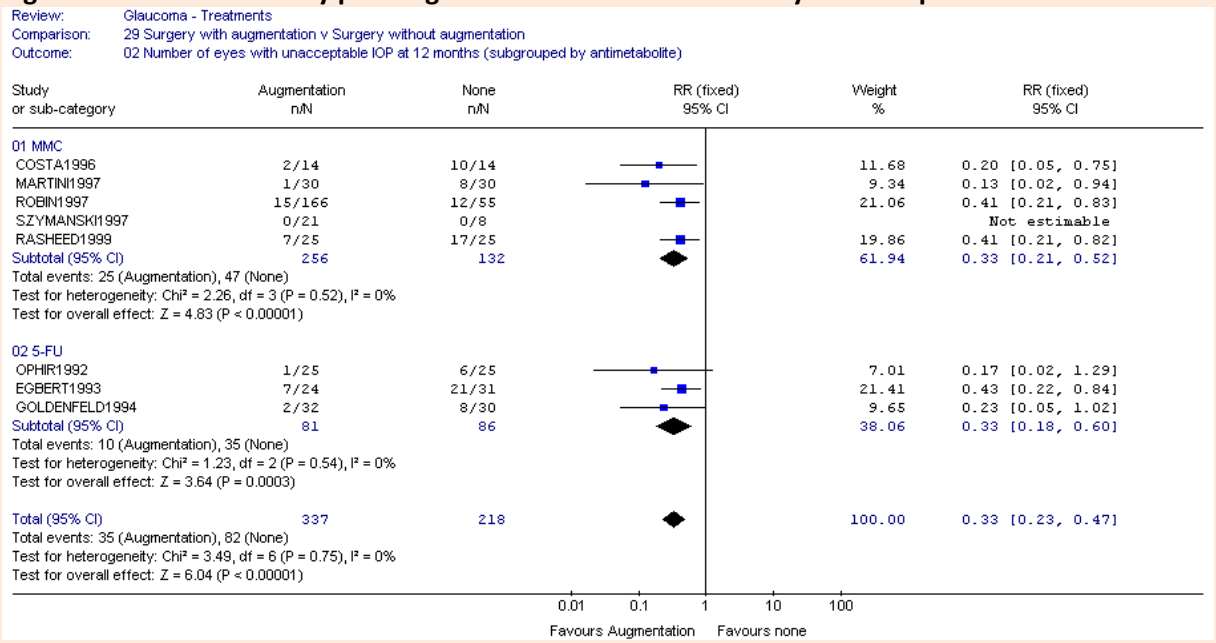


Figure 86 Trabeculectomy plus augmentation vs. trabeculectomy – complications: cataract formation

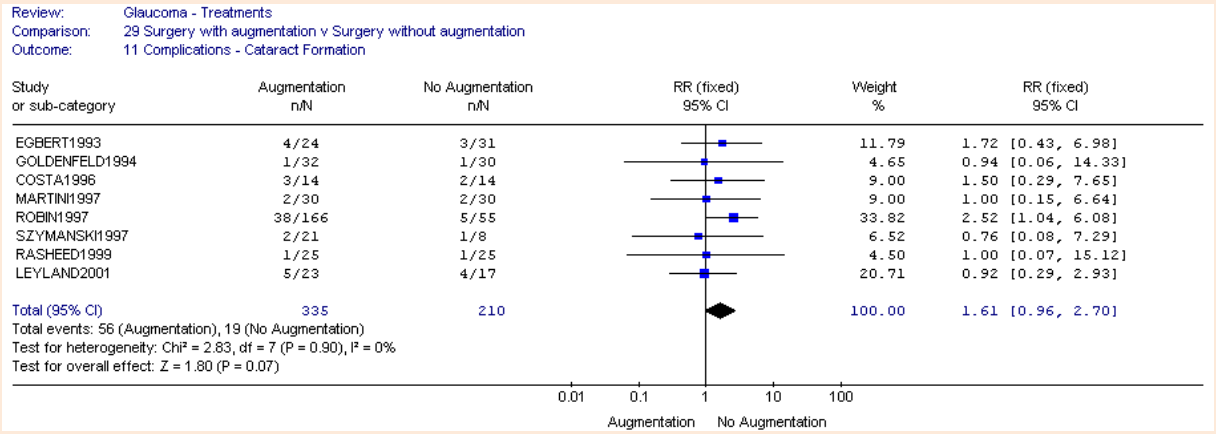
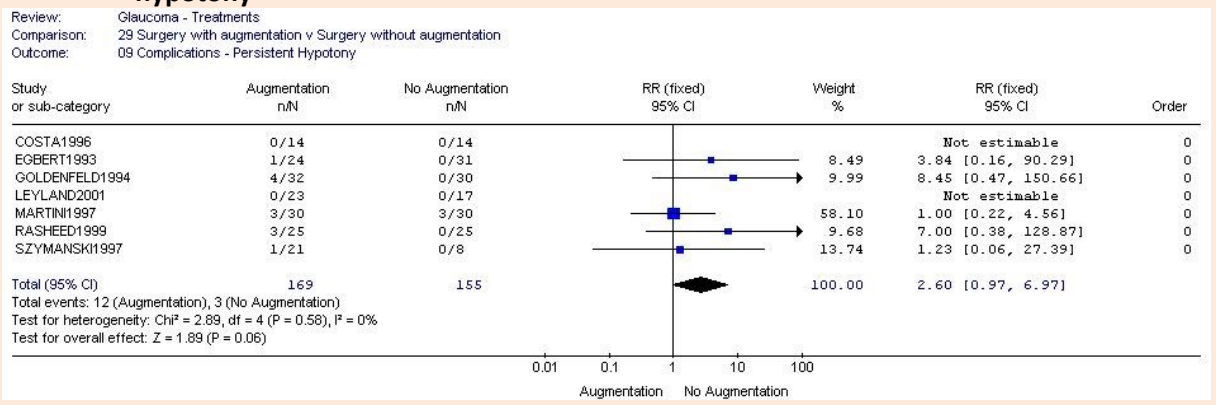


Figure 87 Trabeculectomy plus augmentation vs. trabeculectomy – complications: persistent hypotony



2009

Figure 88 Trabeculectomy plus augmentation vs. trabeculectomy – complications: wound leaks

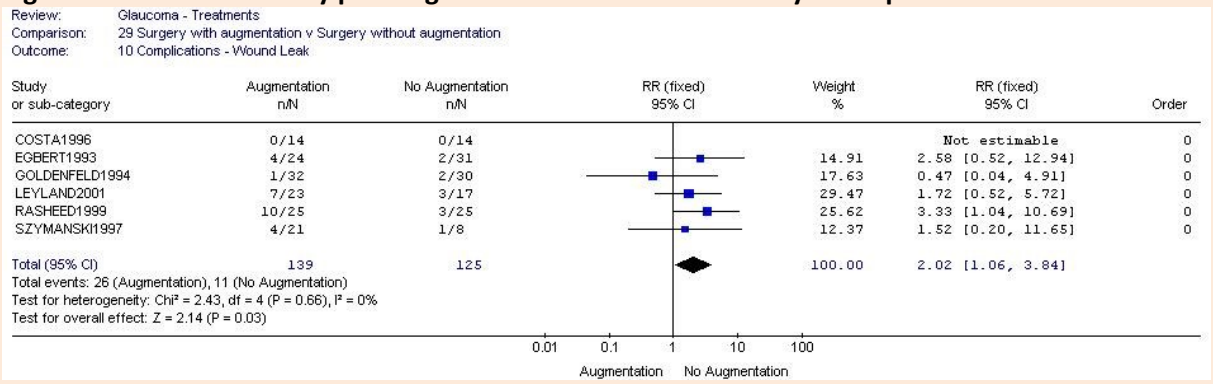


Figure 89 Trabeculectomy plus augmentation vs. trabeculectomy – complications: corneal epithelial defects

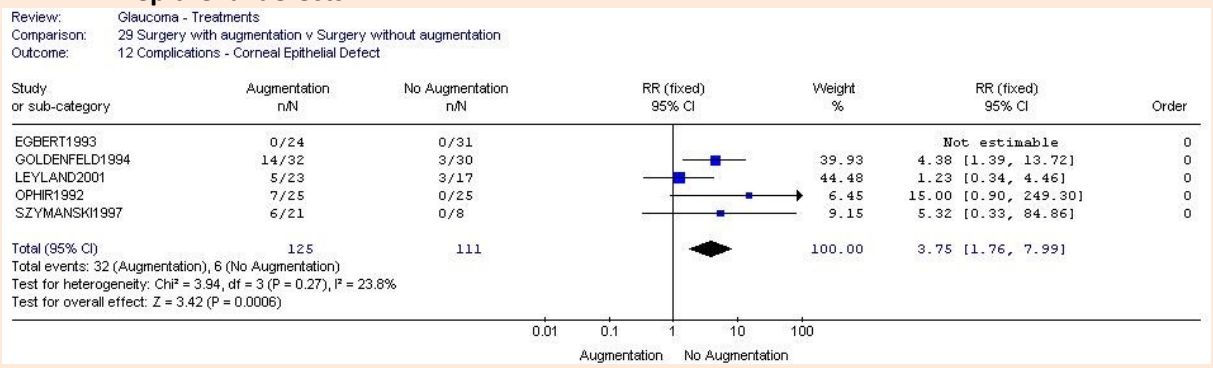


Figure 90 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – unacceptable IOP

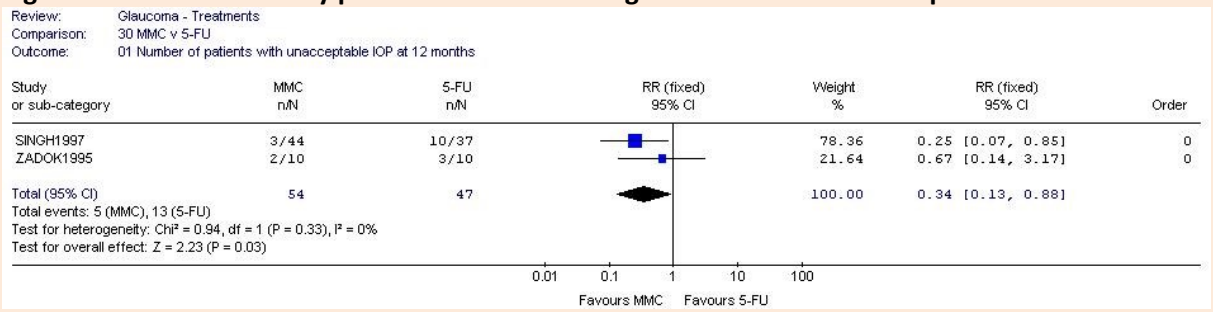
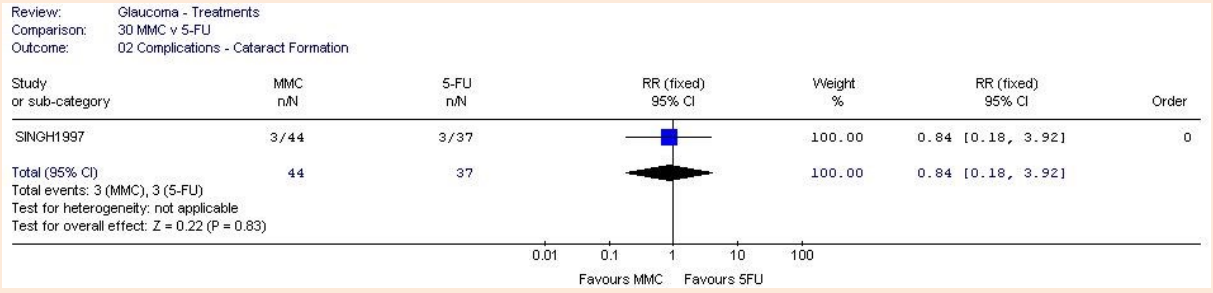


Figure 91 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: cataract formation



2009

Figure 92 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: persistent hypotony

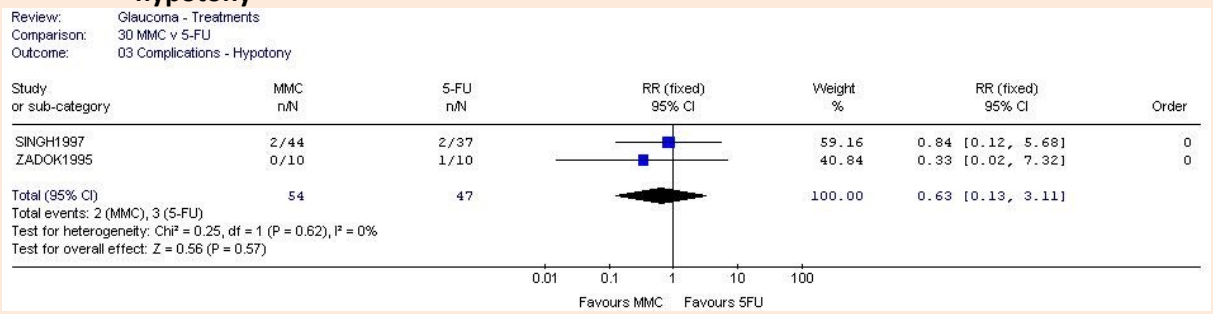


Figure 93 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: wound leaks

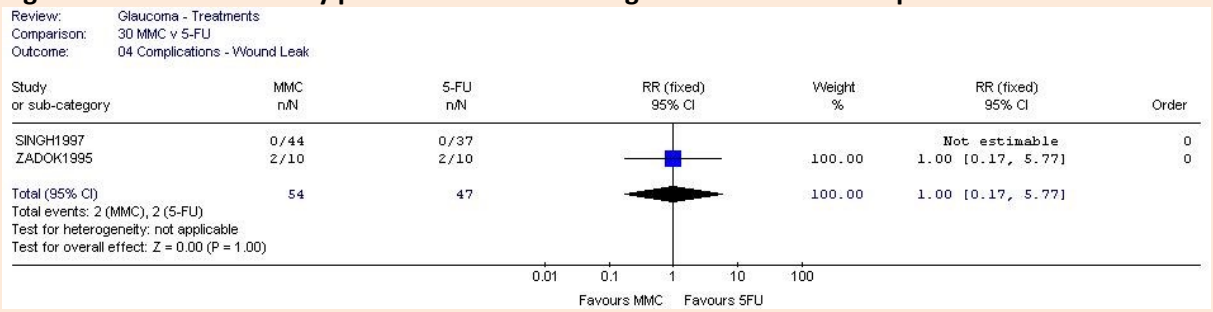


Figure 94 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: corneal defects

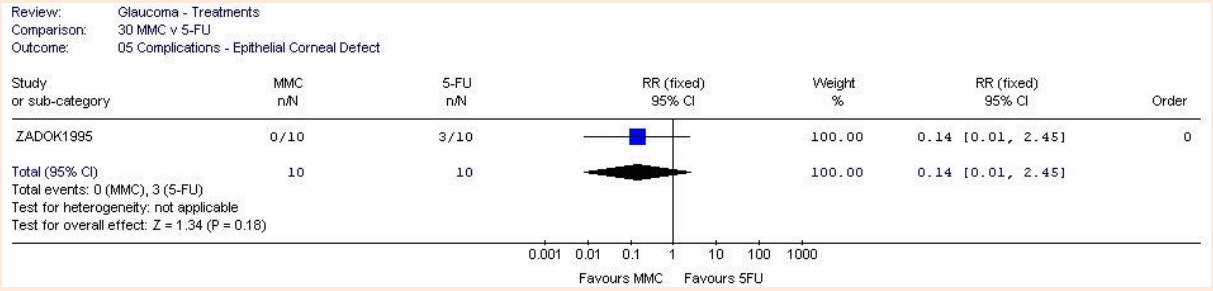
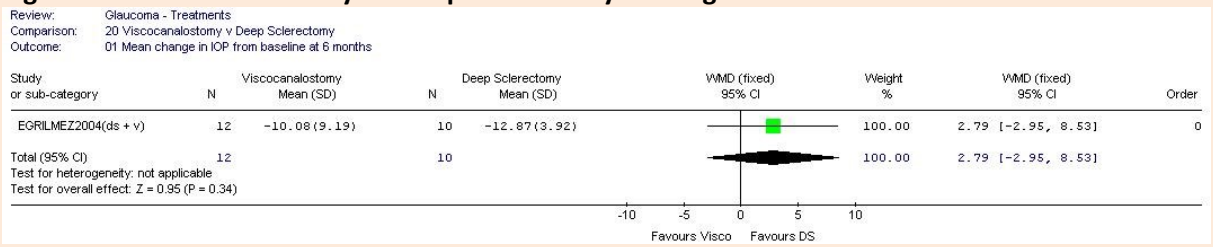


Figure 95 Viscocanalostomy vs. deep sclerectomy – change in IOP from baseline at 6 months



2009

Figure 96 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 6 months

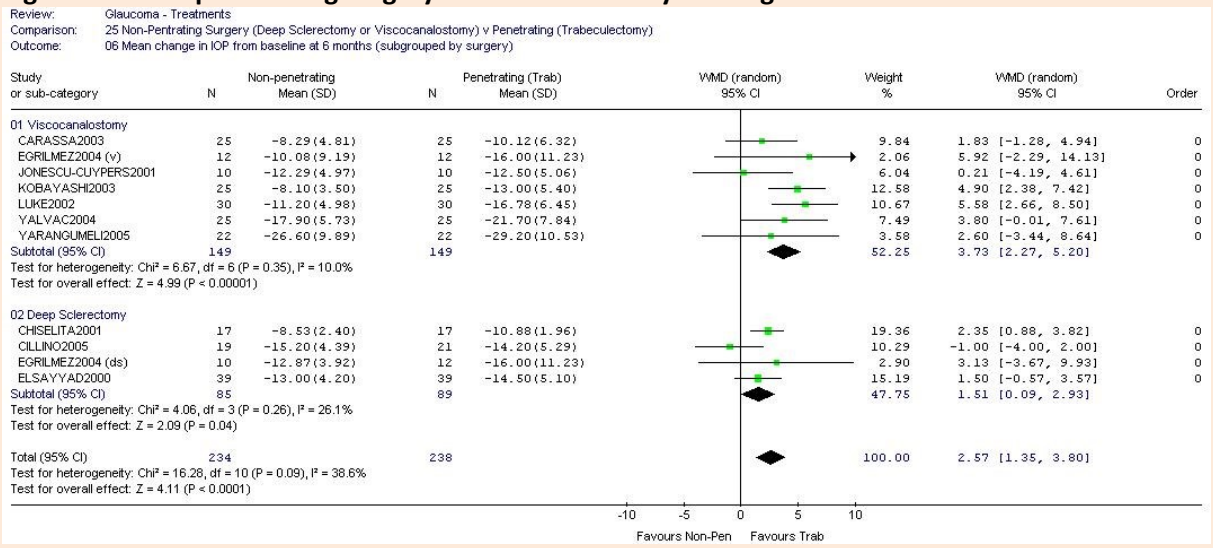


Figure 97 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 12 months

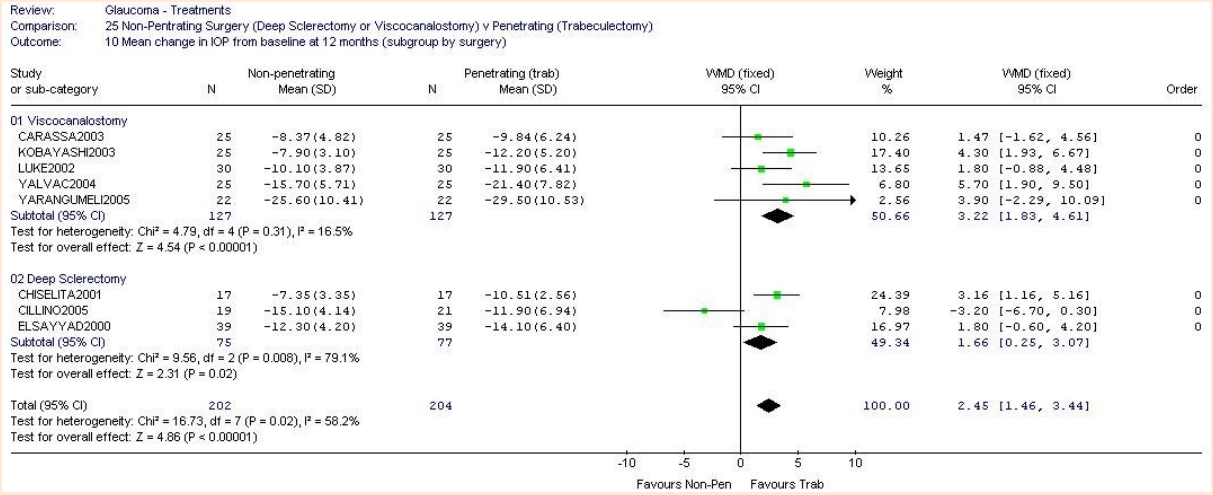
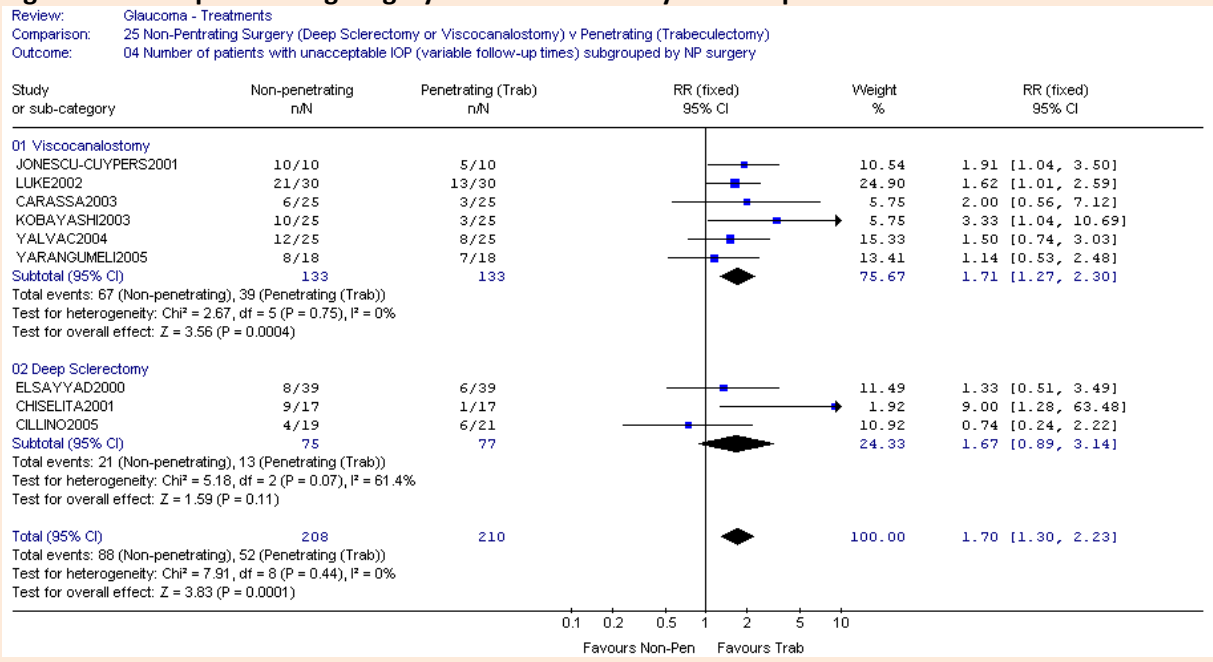


Figure 98 Non-penetrating surgery vs. trabeculectomy - unacceptable IOP



2009

Figure 99 Non-penetrating surgery vs. trabeculectomy – complications: cataract formation

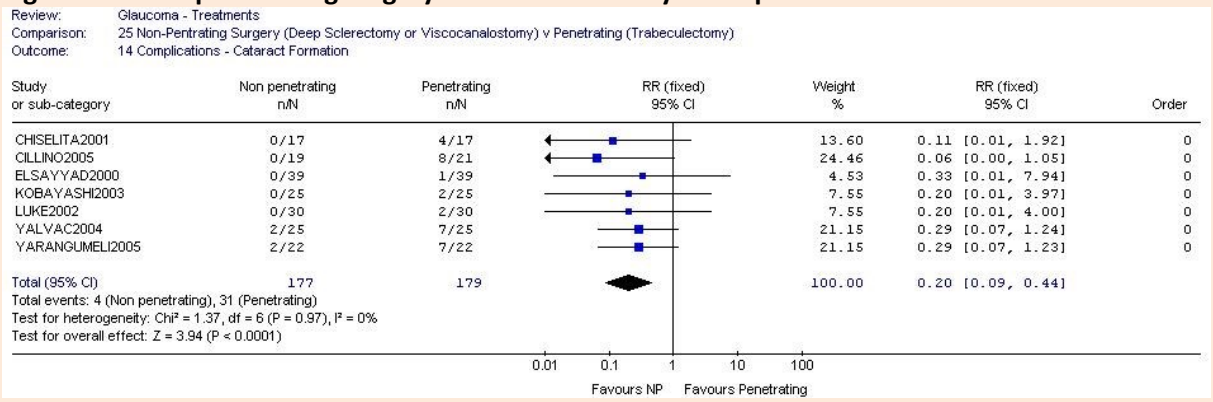


Figure 100 Non-penetrating surgery vs. trabeculectomy – complications: persistent hypotony

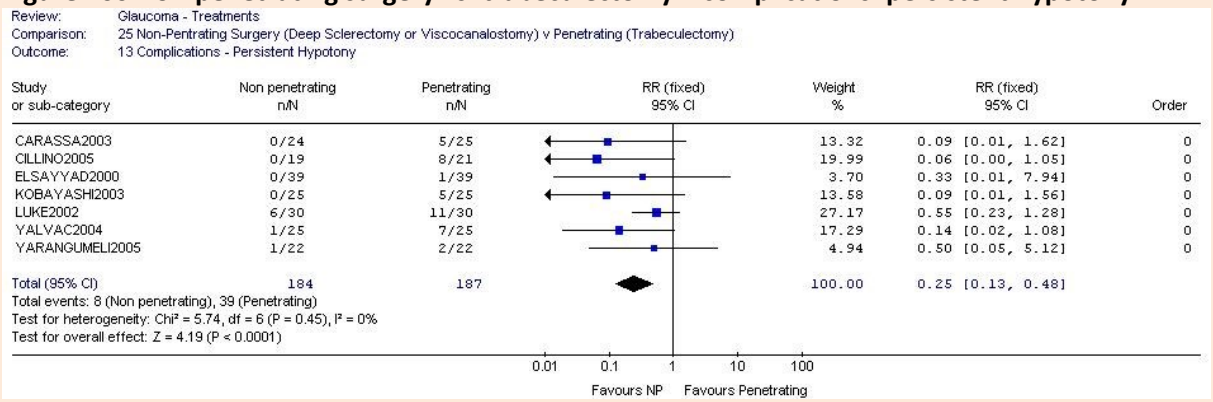


Figure 101 Non-penetrating surgery vs. trabeculectomy – complications: wound leaks

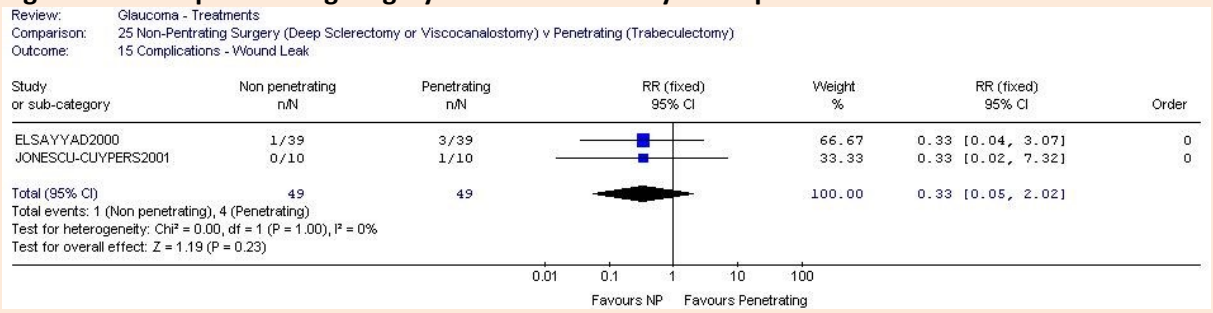
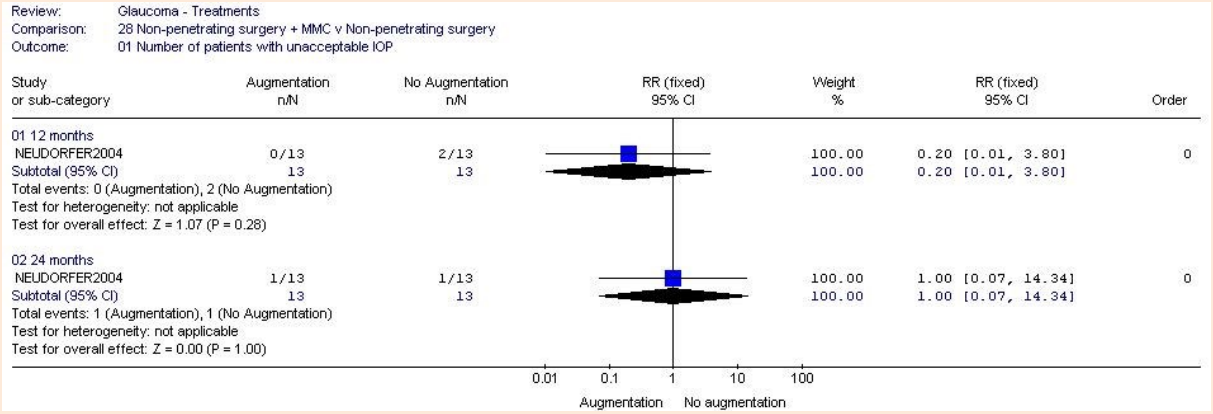


Figure 102 Non-penetrating surgery plus augmentation vs. non-penetrating surgery – unacceptable IOP



2009

K.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

2009

K.6 Complementary and alternative interventions

None.

K.7 Organisation of care

K.7.1 Service models for case finding, referral filtering and diagnosis

None.

K.7.2 Skills required by healthcare professionals

None.

2009

K.8 Provision of information for patients

None.

Appendix L: Excluded clinical studies

L.1 Prognostic risk tools

L.1.1 Increased risk of conversion to COAG

Reference	Reason for exclusion
Alencar 2008[10]	Inappropriate population
Alencar 2010[11]	Inappropriate population
Ameen 2016[16]	Inappropriate study design
Anonymous 1994[2]	Inappropriate study design
Anton 2013 [24]	Incorrect population
Ariyasu 1996[32]	Inappropriate population
Asaoka 2014[33]	Internal validation
Azarbod 2012[38]	Inappropriate outcome
Belghith 2016[58]	No extractable data
Bengtsson 2009[65]	Inappropriate outcome
Bock 2010[72]	Internal validation
Bowd 2004[76]	No extractable data
Bowd 2009[74]	Inappropriate study design
Bowd 2012[75]	Internal validation
Brandt 2012[79]	Not validated
Bryan 2013[85]	No extractable data
Burgansky-Eliash 2007[88]	Inappropriate study design
Burr 2012[91]	Systematic review, screened for relevant references
Caprioli 2011[102]	Derivation study
Casas-Llera 2009[105]	Derivation study
Charalel 2014[114]	Inappropriate study design
Chen 2000[118]	Inappropriate study design
Chung 2016[131]	Inappropriate study design
Cohen 2003[134]	Not validated
Coleman 2004[136]	No extractable data
Crabb 1997[146]	No extractable data
Cristini 1997[150]	Inappropriate study design
Danias 2015[159]	Inappropriate study design
De Moraes 2009[164]	Inappropriate study design
De Moraes 2011[166]	No extractable data
De Moraes 2012[165]	Inappropriate outcome
Demirel 2009[168]	No extractable data
Ederer 1994[176]	Inappropriate study design
Ernest 2016[188]	Inappropriate outcome
Essock 2007[190]	Inappropriate population
Ferreras 2007[205]	Inappropriate study design
Fitzgerald 2013[206]	Incorrect study design

Reference	Reason for exclusion
Fitzke 1996[207]	Inappropriate study design
Fujino 2015[215]	No extractable data
Galassi 2003[216]	Inappropriate study design
Ganekal 2012[220]	Inappropriate study design
Gao 2011[222]	No extractable data
Gao 2015[221]	Validation undergoing, not yet published
Garcia-Martin 2010[226]	Unable to obtain paper
Gardiner 2016[227]	No extractable data
Golubnitschaja 2013[239]	Not relevant
Gordon 2002[240]	Derivation study
Gordon 2008[241]	Not validated
Hatanaka 2012[260]	Not validated
Heeg 2009[263]	Inappropriate study design
Heijl 1989[268]	Inappropriate study design
Heijl 2003[266]	Inappropriate study design
Heijl 2008[265]	Derivation study
Higginbotham 2004[271]	Inappropriate study design
Hirasawa 2014[273]	No extractable data
Hirasawa 2015[274]	No extractable data
Hitzl 2003[276]	Internal validation
Hu 2014[284]	No extractable data
Jimenez-Aragon 2013[301]	Not validated
Johnson 1995[303]	Inappropriate study design
Junoy Montolio 2012[308]	Inappropriate study design
Katz 1999[321]	No extractable data
Klemetti 1990[339]	No extractable data
Kourkoutas 2012[353]	Not validated
Kummet 2013[357]	Inappropriate population
Kymes 2012[361]	Inappropriate outcome
Lachkar 2006[363]	Unable to obtain paper
Lalezary 2006[365]	Inappropriate study design
Larrosa 2012[369]	Inappropriate study design
Leung 2011[389]	Not validated
Lewis 1988[390]	No extractable data
Mansberger 2006[420]	Inappropriate study design
Mansberger 2008[421]	Inappropriate study design
Maslin 2015[431]	Inappropriate study design
Medeiros 2005[442]	Inappropriate population
Medeiros 2008[439]	Narrative review
Medeiros 2008[439]	Inappropriate study design
Medeiros 2008[440]	Inappropriate study design
Medeiros 2009[434]	Inappropriate study design
Medeiros 2009[441]	Inappropriate study design

Reference	Reason for exclusion
Medeiros 2012[444]	Not appropriately validated
Medeiros 2012[445]	No extractable data
Medeiros 2014[436]	Inappropriate tool
Meira-Freitas 2013[446]	Not validated
Meira-Freitas 2014[447]	Inappropriate tool
Miglior 2003[452]	Inappropriate study design
Moreno-Montanes 2008[460]	Inappropriate study design
Mwanza 2013[473]	Internal validation
Nakagami 2006[478]	Inappropriate study design
Nouri-Mahdavi 2004[499]	Inappropriate study design
Nouri-Mahdavi 2007[500]	Not validated
Ocular Hypertension Treatment Study 2007[504]	Inappropriate population
Ocular Hypertension Treatment Study 2008[241]	Not validated
O'Leary 2012[503]	Derivation study
Pensyl 2012[536]	Inappropriate study design
Polo Llorens 2000[543]	Unable to obtain paper
Sacchi 2014[586]	Not validated
Scuderi 2008[601]	Inappropriate study design
Song 2014[625]	No extractable data
Stephen 2013[630]	Internal validation
Strouthidis 2008[640]	No extractable data
Strouthidis 2010[639]	Inappropriate population
Stroux 2003[641]	Not validated
Swift 2002[646]	Not validated
Swindale 2000[647]	Internal validation
Takwoingi 2014[650]	Inappropriate population
Tokuda 2012[656]	Internal validated
Vernon 1990[673]	Not validated
Wahl 2016[677]	Inappropriate population
Walland 2008[678]	Letter to the editor
Weinreb 2010[685]	Inappropriate population
Wesselink 2009[687]	Inappropriate outcome
Zangwill 2005[712]	Inappropriate study design
Zenker 1989[713]	Not validated
Zhang 2016[714]	Inappropriate study design
Zhu 2014[721]	Derivation study
Zhu 2015 [720]	Incorrect population

L.1.2 Increased risk of COAG progression

Reference	Reason for exclusion
Alencar 2008[10]	Inappropriate population
Alencar 2010[11]	Inappropriate population
Ameen 2016[16]	Inappropriate study design

Reference	Reason for exclusion
Anonymous 1994[2]	Inappropriate study design
Ariyasu 1996[32]	Inappropriate population
Asaoka 2014[33]	Internal validation
Azarbod 2012[38]	Inappropriate outcome
Belghith 2016[58]	No extractable data
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Bowd 2012[75]	Internal validation
Brandt 2012[79]	Not validated
Bryan 2013[85]	No extractable data
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Burr 2012[91]	Systematic review, screened for relevant references
Caprioli 2011[102]	Derivation study
Casas-Llera 2009[105]	Derivation study
Charalel 2014[114]	Inappropriate study design
Chen 2000[118]	Inappropriate study design
Chung 2016[131]	Inappropriate study design
Cohen 2003[134]	Not validated
Coleman 2004[136]	No extractable data
Crabb 1997[146]	No extractable data
Cristini 1997[150]	Inappropriate study design
Danias 2015[159]	Inappropriate study design
De Moraes 2009[164]	Inappropriate study design
De Moraes 2011[166]	No extractable data
De Moraes 2012[165]	Inappropriate outcome
Demirel 2009[168]	No extractable data
Ederer 1994[176]	Inappropriate study design
Ernest 2016[188]	Inappropriate outcome
Essock 2007[190]	Inappropriate population
Ferreras 2007[205]	Inappropriate study design
Fitzgerald 2013[206]	Incorrect study design
Fitzke 1996[207]	Inappropriate study design
Fujino 2015[215]	No extractable data
Galassi 2003[216]	Inappropriate study design
Ganekal 2012[220]	Inappropriate study design
Gao 2011[222]	No extractable data
Gao 2015[221]	Validation undergoing, not yet published
Garcia-Martin 2010[226]	Unable to obtain paper
Gardiner 2016[227]	No extractable data
Golubnitschaja 2013[239]	Not relevant
Gordon 2002[240]	Derivation study

Reference	Reason for exclusion
Gordon 2008[241]	Not validated
Hatanaka 2012[260]	Not validated
Heeg 2009[263]	Inappropriate study design
Heijl 1989[268]	Inappropriate study design
Heijl 2003[266]	Inappropriate study design
Heijl 2008[265]	Derivation study
Higginbotham 2004[271]	Inappropriate study design
Hirasawa 2014[273]	No extractable data
Hirasawa 2015[274]	No extractable data
Hitzl 2003[276]	Internal validation
Hu 2014[284]	No extractable data
Jimenez-Aragon 2013[301]	Not validated
Johnson 1995[303]	Inappropriate study design
Junoy Montolio 2012[308]	Inappropriate study design
Katz 1999[321]	No extractable data
Klemetti 1990[339]	No extractable data
Kourkoutas 2012[353]	Not validated
Kummet 2013[357]	Inappropriate population
Kymes 2012[361]	Inappropriate outcome
Lachkar 2006[363]	Unable to obtain paper
Lalezary 2006[365]	Inappropriate study design
Larrosa 2012[369]	Inappropriate study design
Leung 2011[389]	Not validated
Lewis 1988[390]	No extractable data
Mansberger 2006[420]	Inappropriate study design
Mansberger 2008[421]	Inappropriate study design
Maslin 2015[431]	Inappropriate study design
Medeiros 2005[442]	Inappropriate population
Medeiros 2008[439]	Narrative review
Medeiros 2008[439]	Inappropriate study design
Medeiros 2008[440]	Inappropriate study design
Medeiros 2009[434]	Inappropriate study design
Medeiros 2009[441]	Inappropriate study design
Medeiros 2012[444]	Not appropriately validated
Medeiros 2012[445]	No extractable data
Medeiros 2014[436]	Inappropriate tool
Meira-Freitas 2013[446]	Not validated
Meira-Freitas 2014[447]	Inappropriate tool
Miglior 2003[452]	Inappropriate study design
Moreno-Montanes 2008[460]	Inappropriate study design
Mwanza 2013[473]	Internal validation
Nakagami 2006[478]	Inappropriate study design
Nouri-Mahdavi 2004[499]	Inappropriate study design

Reference	Reason for exclusion
Nouri-Mahdavi 2007[500]	Not validated
Ocular Hypertension Treatment Study 2007[504]	Inappropriate population
Ocular Hypertension Treatment Study 2008[241]	Not validated
O'Leary 2012[503]	Derivation study
Pensyl 2012[536]	Inappropriate study design
Polo Llorens 2000[543]	Unable to obtain paper
Sacchi 2014[586]	Not validated
Scuderi 2008[601]	Inappropriate study design
Song 2014[625]	No extractable data
Stephen 2013[630]	Internal validation
Strouthidis 2008[640]	No extractable data
Strouthidis 2010[639]	Inappropriate population
Stroux 2003[641]	Not validated
Swift 2002[646]	Not validated
Swindale 2000[647]	Internal validation
Takwoingi 2014[650]	Inappropriate population
Tokuda 2012[656]	Internal validated
Vernon 1990[673]	Not validated
Wahl 2016[677]	Inappropriate population
Walland 2008[678]	Letter to the editor
Weinreb 2010[685]	Inappropriate population
Wesselink 2009[687]	Inappropriate outcome
Zangwill 2005[712]	Inappropriate study design
Zenker 1989[713]	Not validated
Zhang 2016[714]	Inappropriate study design
Zhu 2014[721]	Derivation study
Zhu 2015[720]	Inappropriate length of follow-up

L.2 Tests used in case finding, diagnosis and reassessment

L.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

Reference	Reason for exclusion
Alencar 2010[11]	Incorrect target condition
Alonso 2010[14]	Incorrect target condition
Andrews 2012[19]	Incorrect intervention
Azad 2014[37]	Incorrect intervention
Bald 2012[46]	Incorrect study design
Devereux 2000 [173]	Incorrect intervention
Foster 2000 [209]	Incorrect intervention
Gispets 2014[232]	Incorrect intervention
Halkiadakis 2008[253]	Incorrect target condition
Kochupurakal 2016[342]	Incorrect target condition
Mowatt 2008[468]	Systematic review checked for references
Nolan 2007 [497]	Incorrect target condition – previously included in CG85
Park 2011[529]	Incorrect target condition
Pekmezci 2009[535]	Incorrect target condition

Reference	Reason for exclusion
Perera 2010[537]	Incorrect intervention
Qin 2013[550]	Incorrect study design
Quek 2012[553]	No relevant outcomes reported
Thomas 1996 [655]	Incorrect target condition

L.2.2 Accuracy of IOP tests

Reference	Reason for exclusion
Anand 2010[17]	Inappropriate reference standard and target condition
Andreanos 2016[18]	Inappropriate outcomes
Azuara-Blanco 2016[39]	Inappropriate index test
Bali 2012[47]	Inappropriate index test
Carbonaro 2010[104]	No appropriate statistical outcomes
Costin 2014[142]	Inappropriate study design
de la Rosa 2013[163]	Inappropriate index and reference tests
Ehrlich 2010[182]	No appropriate statistical outcomes
Ehrlich 2012[183]	Inappropriate reference standard
Farrell 2013[196]	No appropriate statistical outcomes
Geimer 2013[231]	Inappropriate index and reference tests
Grewal 2008[244]	Inappropriate index and reference tests
Hong 2016[281]	No appropriate statistical outcomes
Li 2015[398]	Inappropriate reference test
Moreno 2011[464]	Inappropriate index and reference tests
Moreno-Montanes 2010[463]	Inappropriate index and reference tests
Mori 2010[465]	Inappropriate index and reference tests
Nouri-Mahdavi 2008[501]	Inappropriate index and reference tests
Ogbuehi 2008[509]	No appropriate statistical outcomes
Onochie 2016[512]	Inappropriate outcomes
Park 2009[530]	Inappropriate index and reference tests
Prata 2014[546]	Inappropriate index and reference tests
Renier 2010[567]	No appropriate statistical outcomes
Richter 2016[570]	Inappropriate index and reference tests
Touboul 2008[659]	No appropriate statistical outcomes
Yavin 2014[706]	Inappropriate target condition
Zheng 2010[718]	Inappropriate index and reference tests

L.2.3 Central corneal thickness measurement evidence

None.

2009

L.2.4 Visual field evidence

None.

L.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

Reference	Reason for exclusion

Reference	Reason for exclusion
Akashi 2013[7]	Inappropriate study design
Arintawati 2013[31]	Inappropriate study design
Bae 2015[42]	Inappropriate reference standard
Barua 2016[54]	Inappropriate study design
Baskaran 2012[56]	Inappropriate study design
Begum 2016[57]	Inappropriate reference standard
Benitez-del-Castillo 2011[66]	Inappropriate study design
Bertuzzi 2014[67]	Inappropriate study design
Bowd 2009[74]	Inappropriate study design
Bozkurt 2010[77]	Inappropriate study design
Brusini 2011[84]	Inappropriate index test
Calvo 2014[96]	Inappropriate study design
Cellini 2012[107]	Inappropriate study design
Chang 2009[113]	Inappropriate study design
Chauhan 2009[116]	Inappropriate reference standard
Cho 2011[129]	Inappropriate study design
Dascalu 2014[160]	Inappropriate reference standard
Ferreras 2008[203]	Inappropriate target condition
Ferreras 2008[204]	Inappropriate study design
Garas 2011[223]	Duplicate of included study
Garas 2011[224]	Target condition does not match protocol
Grewal 2008[244]	Inappropriate study design
Halkiadakis 2008[253]	No extractable outcomes
Healey 2010[262]	Inappropriate study design
Hewitt 2009[269]	Inappropriate population
Hirasawa 2015[272]	Inappropriate study design
Hirashima 2013[275]	Inappropriate study design
Horn 2011[283]	Inappropriate study design
Huang 2011[285]	Inappropriate study design
Huang 2011[286]	Article not in English
Hwang 2012[288]	Inappropriate study design
Hwang 2015[287]	Inappropriate study design
Jeoung 2010[299]	Inappropriate study design
Jeoung 2011[297]	Inappropriate study design
Jeoung 2014[298]	Inappropriate study design
Jia 2014[300]	Inappropriate statistical outcomes
Jindal 2010[302]	Inappropriate study design
Kasumovic 2014[317]	Reference standard unclear
Khanal 2016[324]	Inappropriate study design
Khanal 2016[325]	Inappropriate study design
Kiddee 2013[327]	Inappropriate reference standard
Kim 2010[332]	Inappropriate study design
Kim 2010[333]	Inappropriate study design

Reference	Reason for exclusion
Kim 2013[329]	Inappropriate study design
Kim 2013[330]	Inappropriate study design
Kim 2014[331]	Inappropriate study design
Kita 2013[336]	Inappropriate study design
Koh 2014[344]	Inappropriate study design
Kotowski 2012[352]	Inappropriate study design
Kratz 2014[354]	Inappropriate study design
Kurysheva 2016[358]	Inappropriate study design
Larrosa 2015[367]	Inappropriate study design
Larrosa 2015[368]	Inappropriate index test
Leal-Fonseca 2014[371]	Inappropriate reference standard
Lee 2010[382]	Inappropriate study design
Lee 2013[375]	Inappropriate study design
Lee 2015[379]	Inappropriate population
Lee 2016[374]	Inappropriate study design
Leite 2011[383]	Inappropriate target condition
Lester 2013[289]	Inappropriate study design
Leung 2009[387]	Inappropriate reference standard
Leung 2010[388]	Inappropriate reference standard
Lindbohm 2012[401]	Inappropriate study design
Lisboa 2012[403]	Inappropriate reference standard
Lisboa 2013[404]	Inappropriate study design
Loewen 2015[408]	Inappropriate study design
Lu 2008[412]	Inappropriate study design
Malik 2016[416]	Inappropriate reference standard
Mansoori 2011[422]	Inappropriate study design
Martinez-de-la-Casa 2014[427]	Inappropriate study design
Medeiros 2008[438]	Inappropriate reference standard
Medeiros 2009[443]	Inappropriate reference standard
Medeiros 2011[435]	Inappropriate study design
Michelessi 2015[448]	Cochrane review scanned for references
Moon 2012[459]	Target condition does not match protocol
Moreno 2011[464]	Inappropriate study design
Moreno-Montanes 2009[461]	Inappropriate target condition
Moreno-Montanes 2010[463]	Inappropriate study design
Mori 2010[465]	Inappropriate study design
Mwanza 2012[472]	Inappropriate study design
Mwanza 2014[471]	Reference standard unclear
Na 2011[477]	Inappropriate study design
Na 2012[475]	Inappropriate study design
Na 2013[474]	Inappropriate study design
Na 2013[476]	Inappropriate reference standard
Nakanishi 2015[481]	Inappropriate study design

Reference	Reason for exclusion
Nakatani 2011[482]	Inappropriate study design
Nouri-Mahdavi 2008[501]	Inappropriate study design
Nukada 2011[502]	Unclear if control group received same reference standard
Oddone 2008[505]	Inappropriate study design
Oddone 2011[506]	Inappropriate study design
Ong 2013[511]	Inappropriate index test
Pablo 2010[519]	Inappropriate study design
Pablo 2010[521]	Inappropriate study design
Pablo 2011[520]	Inappropriate study design
Parikh 2008[526]	Inappropriate reference test
Parikh 2010[527]	Inappropriate study design
Park 2009[530]	Inappropriate reference standard
Park 2013[528]	Inappropriate study design
Pomorska 2012[545]	Inappropriate study design
Prata 2014[546]	Inappropriate population
Pueyo 2009[548]	Reference standard does not match protocol
Rajan 2016[554]	Inappropriate study design
Rao 2012[556]	Inappropriate study design
Rao 2013[555]	Inappropriate study design
Rao 2014[560]	Inappropriate reference standard
Rao 2014[561]	Inappropriate reference standard
Rao 2015[557]	Inappropriate reference standard
Rao 2015[558]	Inappropriate outcomes
Rao 2015[559]	Inappropriate reference standard
Reus 2010[568]	Inappropriate index test
Richter 2016[570]	Unclear if all participants received reference standard
Roberti 2014[573]	Inappropriate study design
Rolle 2011[576]	Inappropriate study design
Saarela 2008[584]	Inappropriate study design
Saarela 2010[585]	Inappropriate reference standard
Saito 2009[587]	Inappropriate study design
Saito 2009[588]	Reference standard unclear
Schulze 2011[595]	Inappropriate study design
Schuman 2008[598]	Reference standard unclear
Seo 2012[602]	Inappropriate study design
Seol 2015[603]	Inappropriate study design
Seong 2010[604]	Inappropriate study design
Sevim 2013[605]	Inappropriate reference standard
Shin 2013[614]	Target condition does not match protocol
Shin 2013[616]	Inappropriate study design
Shin 2014[615]	Inappropriate reference standard

Reference	Reason for exclusion
Silverman 2016[620]	Inappropriate study design
Springelkamp 2014[627]	Inappropriate study design
Suh 2014[643]	Inappropriate reference standard
Sullivan-Mee 2013[644]	Inappropriate study design
Sung 2012[645]	Inappropriate study design
Toth 2008[658]	Inappropriate reference standard
Wang 2011[679]	Inappropriate study design
Xu 2013[698]	Inappropriate index test
Yaghoubi 2015[699]	Systematic review scanned for references
Yang 2015[702]	Inappropriate study design
Yang 2015[703]	Inappropriate study design
Yuksel 2009[710]	Inappropriate comparison
Zheng 2008[717]	Inappropriate index test
Zheng 2010[718]	Inappropriate study design

L.3 Reassessment intervals

L.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

No relevant studies were identified for full-text assessment.

L.3.2 Optimum intervals for chronic open-angle glaucoma

No relevant clinical studies were identified for full-text assessment.

L.4 Overview of Treatment

2009

None.

L.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

L.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

Reference	Reason for exclusion
Aihara 2013[5]	No extractable outcomes
Aihara 2016[4]	Inappropriate length of follow up
Alagoz 2008[8]	Inappropriate comparator
Alagoz 2008[9]	Inappropriate comparator
Alm 2011[12]	No comparator
Altafini 2015[15]	Inappropriate comparator
Ang 2015[22]	Inappropriate study design
Anonymous 2012[23]	Inappropriate study design
Aptel 2008[25]	Unable to obtain paper

Reference	Reason for exclusion
Aptel 2011[27]	Inappropriate study design
Aptel 2012[26]	Meta-analysis inappropriate comparator
Araie 2008[29]	Inappropriate comparator
Araie 2010[30]	Inappropriate comparator
Aydin Kurna 2014[36]	Inappropriate outcomes
Babic 2013[41]	Inappropriate length of follow up
Bafa 2011[43]	No extractable outcomes
Baiza-Duran 2009[44]	Inappropriate comparator
Baiza-Duran 2012[45]	Inappropriate comparator
Bengtsson 2016[64]	Inappropriate length of follow up
Bhagat 2014[68]	Inappropriate length of follow up
Bhorade 2010[69]	Inappropriate comparator
Birt 2010[71]	Inappropriate comparator
Bournias 2009[73]	Inappropriate comparator
Brandt 2008[78]	Inappropriate population
Brandt 2016[80]	Inappropriate intervention
Budengeri 2013[87]	Meta-analysis inappropriate population
Cankaya 2011[99]	Inappropriate study design
Cantor 2008[101]	Inappropriate comparator
Cantor 2009[100]	Meta-analysis inappropriate comparator
Casson 2009[106]	Inappropriate study design
Centofanti 2009[109]	Inappropriate comparator
Centofanti 2010[108]	Inappropriate comparator
Chabi 2012[111]	Inappropriate length of follow up
Chabi 2016[110]	Inappropriate length of follow up
Chander 2013[112]	Inappropriate comparator
Chen 2013[117]	Inappropriate population
Chen 2016[119]	Meta-analysis inappropriate population
Cheng 2009[124]	Meta-analysis inappropriate comparator
Cheng 2009[120]	Meta-analysis inappropriate population
Cheng 2009[125]	Meta-analysis scanned for references
Cheng 2009[121]	Meta-analysis inappropriate length of follow up
Cheng 2012[123]	Meta-analysis inappropriate length of follow up
Cheng 2012[122]	Meta-analysis scanned for references
Chew 2014[126]	Systematic review scanned for references
Chi 2013[127]	Unable to obtain paper
Colak 2014[135]	Inappropriate comparator
Costagliola 2008[141]	Inappropriate length of follow up
Cox 2008[144]	Systematic review scanned for references
Craven 2010[148]	Inappropriate length of follow up
Crichton 2013[149]	Inappropriate comparator
Cucherat 2014[151]	Meta-analysis inappropriate length of

Reference	Reason for exclusion
	follow up
Cvenkel 2008[154]	Inappropriate length of follow up
Daka 2014[157]	Systematic review scanned for references
Day 2008[161]	Inappropriate comparator
Day 2013[162]	Inappropriate population
Delval 2013[167]	Unable to obtain paper
Denis 2008[171]	Inappropriate study design
Denis 2010[169]	Inappropriate comparator
Dirks 2008[174]	Inappropriate study design
DuBiner 2014[175]	Inappropriate comparator
Egorov 2009[180]	Inappropriate comparator
Eren 2012[187]	Length of follow up not appropriate
Evans 2008[191]	Inappropriate outcomes
Eyawo 2009[192]	Meta-analysis all papers published before 2008
Facio 2009[193]	Inappropriate comparator
Fan 2014[194]	No extractable data
Faridi 2010[195]	Inappropriate comparator
Fechtner 2011[197]	Inappropriate comparator
Fechtner 2016[198]	Inappropriate length of follow up
Feke 2013[199]	Unable to obtain paper
Feldman 2008[201]	Inappropriate length of follow up
Feldman 2016[200]	Inappropriate length of follow up
Fogagnolo 2015[208]	Inappropriate comparator
Fristrom 2008[212]	Inappropriate study design
Fristrom 2010[211]	Inappropriate comparator
Fuchsjager-Mayrl 2005 [214]	No extractable data. Used for baseline data
Galose 2016[217]	Inappropriate comparison
Gandolfi 2012[218]	Inappropriate comparator
Garcia-Feijoo 2010[225]	Inappropriate study design
Garway-Heath 2013[229]	Inappropriate study design
Gatchev 2016[230]	Inappropriate intervention
Godfrey 2009[233]	Inappropriate length of follow up
Goldberg 2008[237]	Inappropriate comparator
Goldberg 2012[234]	Inappropriate length of follow up
Goldberg 2014[236]	Inappropriate length of follow up
Gross 2008[245]	Unable to obtain paper
Grueb 2011[246]	Inappropriate study design
Grueb 2013[247]	Inappropriate length of follow up
Gugleta 2010[248]	Systematic review scanned for references
Gulati 2012[249]	Inappropriate outcomes
Gulkilik 2011[250]	Inappropriate study design
Gutierrez-Diaz 2014[252]	Inappropriate comparator
Hamacher 2008[254]	Inappropriate study design

Reference	Reason for exclusion
Harvey 2013[258]	Inappropriate study design
Hatanaka 2008[259]	Inappropriate length of follow up
Hodge 2008[277]	Systematic review scanned for references
Hommer 2012[279]	Inappropriate study design
Honrubia 2009[282]	Meta-analysis inappropriate comparator
Ikeda 2016[290]	Inappropriate study design
Ilechie 2016[291]	Inappropriate length of follow up
Inoue 2011[292]	Inappropriate study design
Januleviciene 2012[295]	Inappropriate study design
Johnson 2010[304]	No extractable data
Joshi 2013[306]	Inappropriate length of follow up
Jothi 2010[307]	Inappropriate length of follow up
Kaarniranta 2016[309]	Inappropriate length of follow up
Kammer 2010[312]	Inappropriate comparator
Kanamoto 2015[314]	Inappropriate comparator
Kapoor 2013[315]	Inappropriate length of follow up
Katsanos 2011[318]	Inappropriate comparator
Katz 2010[320]	Inappropriate length of follow up
Katz 2012[322]	Inappropriate population
Katz 2013[319]	Inappropriate length of follow up
Kim 2016[328]	Inappropriate length of follow up
Kitazawa 2011[338]	Inappropriate length of follow up
Kocluk 2011[343]	Unable to obtain paper
Konstas 2008[347]	Inappropriate study design
Konstas 2009[348]	Inappropriate comparator
Konstas 2012[350]	Inappropriate study design
Konstas 2013[349]	Inappropriate study design
Konstas 2013[346]	Inappropriate length of follow up
Konstas 2014[351]	Inappropriate study design
Konstas 2017[345]	Inappropriate study design
Krupin 2011[355]	Inappropriate study design
Lanzl 2013[366]	Inappropriate study design
Lee 2010[381]	Meta-analysis inappropriate study design
Lee 2012[376]	Unable to obtain paper
Lee 2016[378]	Inappropriate length of follow up
Lewis 2016[391]	Inappropriate intervention
Li 2014[396]	Meta-analysis inappropriate population
Li 2015[395]	Meta-analysis inappropriate population
Li 2016[397]	Systematic review scanned for references
Lin 2014[400]	Meta-analysis inappropriate comparator
Ling 2014[402]	Inappropriate comparator
Liu 2009[405]	Inappropriate study design
Liu 2016[406]	Inappropriate length of follow up

Reference	Reason for exclusion
Loon 2008[409]	Meta-analysis inappropriate length of follow up
Lou 2014[411]	Meta-analysis inappropriate population
Lou 2015[410]	Meta-analysis inappropriate comparator
Macky 2010[414]	Inappropriate comparator
Macky 2014[415]	Inappropriate comparator
Manni 2008[419]	Inappropriate study design
Manni 2009[418]	Inappropriate comparator
Mansouri 2008[424]	Inappropriate comparator
Mansouri 2015[423]	Inappropriate outcomes
Martinez 2009[428]	Inappropriate comparator
Martinez 2010[429]	Inappropriate comparator
Medeiros 2016[437]	Inappropriate length of follow up
Miglior 2010[451]	Inappropriate length of follow up
Mishra 2014[456]	Inappropriate length of follow up
Miura 2008[457]	Unable to obtain paper
Mizoguchi 2012[458]	Inappropriate comparison
Mulaney 2008[469]	Inappropriate length of follow up
Mundorf 2008[470]	Inappropriate comparator
Nakakura 2012[479]	Inappropriate comparator
Nakamura 2009[480]	Inappropriate comparator
Nguyen 2013[492]	Inappropriate length of follow up
Ni 2016[493]	Paper not in English
Nixon 2009[496]	Inappropriate length of follow up
Nixon 2013[495]	Unable to obtain paper
Oddone 2015[507]	Inappropriate study design
Orme 2010[516]	Meta-analysis inappropriate comparator
Ozkurt 2009[517]	Inappropriate comparator
Pacella 2010[522]	Inappropriate study design
Pachimkul 2011[523]	Unable to obtain paper
Pajic 2010[524]	Inappropriate study design
Palmberg 2010[525]	Inappropriate length of follow up
Pfeiffer 2011[539]	Inappropriate comparator
Pfeiffer 2014[541]	Unable to extract data
Pfennigsdorf 2012[542]	Inappropriate study design
Qian 2011[549]	Unable to obtain paper
Quaranta 2008[552]	Inappropriate comparator
Quaranta 2013[551]	Meta-analysis inappropriate study design
Rao 2016[562]	Length of follow up not appropriate
Realini 2009[565]	Inappropriate length of follow up
Realini 2013[564]	Inappropriate length of follow up
Rhee 2008[569]	Inappropriate comparator
Rigollet 2011[571]	Inappropriate comparator

Reference	Reason for exclusion
Rolle 2008[578]	Inappropriate comparator
Rossetti 2015[579]	Inappropriate comparator
Rouland 2013[582]	Inappropriate length of follow up
Russ 2013[583]	Inappropriate comparator
Sakata 2016[589]	Inappropriate length of follow up
Sanseau 2013[590]	Inappropriate comparator
Schnober 2010[594]	Inappropriate comparator
Sezgin Akcay 2013[606]	Inappropriate comparator
Sharpe 2008[608]	Inappropriate length of follow up
Sharpe 2013[609]	Systematic review screened for references
Shedden 2010[610]	Inappropriate length of follow up
Shen 2016[611]	Systematic review scanned for references
Shoji 2013[617]	Inappropriate comparator
Siesky 2012[618]	Outcomes not matching protocol
Simmons 2008[622]	Inappropriate comparator
Smith 2012[624]	Inappropriate population
Spaeth 2011[626]	No extractable data
Stankiewicz 2011[629]	Inappropriate study design
Stevens 2012[631]	Inappropriate length of follow up
Stewart 2008[633]	Meta-analysis inappropriate study design
Stewart 2010[632]	Meta-analysis inappropriate study design
Sugiyama 2009[642]	Inappropriate study design
Tanna 2010[651]	Meta-analysis inappropriate study design
Teus 2009[652]	Inappropriate length of follow up
Traverso 2010[660]	Inappropriate comparator
Trocme 2010[663]	Meta-analysis scanned for references
Tsumura 2012[665]	Inappropriate study design
Uusitalo 2010[668]	Inappropriate comparator
Uusitalo 2016[667]	Inappropriate length of follow up
Vinuesa 2009[675]	Inappropriate study design
Vold 2008[676]	Inappropriate comparator
Wang 2013[680]	Meta-analysis inappropriate study design
Webers 2010[683]	Meta-analysis inappropriate length of follow up
Weinreb 2016[684]	Inappropriate length of follow up
Whitson 2010[689]	Inappropriate comparator
Williams 2008[691]	Inappropriate population
Wirta 2011[692]	Meta-analysis inappropriate comparator
Wu 2011[696]	Inappropriate population
Xing 2014[697]	Meta-analysis inappropriate study design
Yamamoto 2016[701]	Inappropriate length of follow up
Yao 2014[704]	Inappropriate comparator
Yildirim 2008[707]	Inappropriate comparator

Reference	Reason for exclusion
Yoshikawa 2014[708]	Inappropriate length of follow up
Yuce 2012[709]	Study not in English
Zhao 2011[716]	Inappropriate comparator
Zhao 2013[715]	Inappropriate population

L.5.2 Laser treatment for COAG

None.

L.5.3 Surgical treatment for COAG

None.

2009

L.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

L.6 Complementary and alternative interventions

L.7 Organisation of care

L.7.1 Service models for case finding, referral filtering and diagnosis

Reference	Reason for exclusion
Ahmed 2016[3]	Incorrect study design
Ang 2009[21]	Incorrect study design
Banegas 2016[48]	Incorrect study design
Barleon 2014[52]	Incorrect study design
Bell 1997[59]	Incorrect study design
Bell 1997[60]	Incorrect study design
Bengtsson 1991[63]	Incorrect study design
Bengtsson 1981[61]	Incorrect study design
Bengtsson 1988[62]	Incorrect study design
Briesen 2013[81]	Not in English
Buys 2012[94]	Incorrect study design
Chauhan 1999[115]	Incorrect study design
Christoffersen 1993 [130]	Incorrect study design
Cooper 1986[139]	Incorrect study design
Dabasia 2015[156]	Incorrect study design
Detry-Morel 2004[172]	Incorrect study design
El-Assal 2015[184]	Incorrect study design
Gray 2000[242]	Incorrect intervention
Harasymowycz 2005[255]	Incorrect study design
Jampel 2006[294]	Incorrect study design
Khan 2012[323]	Incorrect study design
Kwartz 2005[359]	Incorrect study design

Reference	Reason for exclusion
Lenake 2014[384]	Incorrect study design
Li 2013[394]	Incorrect study design
Lockwood 2010[407]	Incorrect study design
Morrison 1990[467]	Literature review
Newman 1998[491]	Incorrect study design
Niessen 1997[494]	Incorrect study design
Norskov 1970[498]	Incorrect study design
Olawoye 2013[510]	Incorrect study design
Patel 1995[532]	Incorrect study design
Peeters 2008[534]	Health economics
Perkins 1973[538]	Incorrect study design
Pomorska 2012[545]	Incorrect study design
Savini 2011[591]	Literature review
Schiefer 2003[593]	Incorrect study design
Shah 2006[607]	Incorrect study design
Shin 2014[615]	Incorrect study design
Stoutenbeek 2008[637]	Incorrect study design

L.7.2 Skills required by healthcare professionals

None.

L.8 Provision of information for patients

None.

2009

Appendix M: Excluded health economic studies

M.1 Prognostic risk tools

M.1.1 Increased risk of conversion to COAG

None.

M.1.2 Increased risk of COAG progression

None.

M.2 Tests used in case finding, diagnosis and reassessment

M.2.1 Accuracy of tests for identifying closed or occludable anterior chamber angle

None.

M.2.2 Accuracy of IOP tests

None.

M.2.3 Central corneal thickness measurement evidence

None.

2009

M.2.4 Visual field evidence

None.

M.2.5 Accuracy of structural tests for identifying and monitoring the progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer)

None.

M.3 Reassessment intervals

M.3.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

None.

M.3.2 Optimum intervals for chronic open-angle glaucoma

None.

M.4 Overview of Treatment

None.

2009

M.5 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

M.5.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

Reference	Reason for exclusion
Cottle 1988[143]	This study was assessed as not applicable as it was too old (published over 15 years before the beginning of development of the guideline update)
de Natale 2009[484]	This study was assessed as not applicable, as it was not a cost-utility analysis (only costs).
Denis 2008[170]	This study was assessed as not applicable, as it was not a cost-utility analysis (only costs).
Hommer 2008[280]	This study was assessed as not applicable, as it was on a mixed population of OHT and COAG; outcome was % on target; only 1 year time horizon.
Kymes 2006[360]	This study was assessed as not applicable as it was a US study
Lachaine 2008[362]	This study was assessed as not applicable, as it was not a cost-utility analysis (outcome is IOP reduction), with a Canadian perspective.
Lafuma 2008[364]	This study was assessed as not applicable, as it was not a cost-utility analysis (only costs).
Le Pen 2005[370]	This study was assessed as partially applicable with very serious limitations as it had a short time horizon (5 years) and did not include the cost of blindness.
Peeters 2012[533]	This study was assessed as not applicable, as it was not a cost-utility analysis (outcome was years of blindness). Study from the Netherlands; discount rate 4%; did not include no treatment.
Rouland 2003[581]	This study was assessed as not applicable as it was not a cost utility analysis (outcome is IOP reduction), French perspective.
Rouland 2005[580].	This study was assessed as not applicable as it was not a cost utility analysis (outcome is IOP reduction), French perspective.
Stewart 2002[634]	This study was assessed as not applicable as it was a US study
Stewart 2006[636]	This study was assessed as not applicable as it was a US study
Stewart 2009[635]	This study was assessed as partially applicable with very serious limitations, as it did not report the discount rate; it had a short time horizon (5 years), data on resource use from expert opinion, assumptions on IOP for controlled and uncontrolled, rate of blindness was used for early stages of the model, blindness assumed only in the uncontrolled IOP group, costs were the same independently from severity (no cost of blindness).
Thelen 2013[653]	This study was assessed as not applicable as it was not a cost-utility analysis (outcome is IOP reduction), German perspective.
van Gestel 2012[670]	This study was assessed as not applicable, as it included indirect costs, productivity loss; the discount rate was different from reference case and different rates were used for effects and costs. Study conducted in the Netherlands.
van Gestel 2014[669]	This study was assessed as not applicable as it included indirect costs, productivity loss; the discount rate was different from the reference case and different rates were used for effects and costs. Study conducted in the Netherlands. Interventions were not defined (any treatment versus no treatment).

M.5.2 Laser treatment for COAG

None.

M.5.3 Surgical treatment for COAG

None.

2009

M.5.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

None.

M.6 Complementary and alternative interventions

M.7 Organisation of care

M.7.1 Service models for case finding, referral filtering and diagnosis

Reference	Reason for exclusion
Crane 2013[147]	This study was assessed as not applicable as the interventions being compared in the study were not appropriate for the review.

M.7.2 Skills required by healthcare professionals

None.

2009

M.8 Provision of information for patients

None.

Appendix N: Cost-effectiveness analysis: treatment for ocular hypertension

N.1 Introduction

In the original guideline, a cost–utility analysis on different first-line treatment strategies was carried out for the ocular hypertension (OHT) and chronic open-angle glaucoma (COAG) populations. The aim was to determine the most cost-effective first-line treatment strategy in managing OHT and COAG patients from the point of diagnosis.

In the OHT treatment model, prostaglandin analogues (PGA) were identified as the most effective medical treatment in the original guideline; however, they were not cost effective in all the OHT risk groups because of their higher costs compared to beta-blockers (BB). The generic version of one of the PGA products is now available at a lower cost; therefore, previous conclusions based on their high cost may not be applicable anymore. This does not apply to the COAG population for whom PGA were cost effective even when their cost was high. Therefore, only the OHT model was updated.

Compared to the original guideline, the new OHT model incorporates more questions:

- for the OHT population, is treatment cost effective at all, considering that if people need treatment they would usually be referred to the Hospital Eye Service (HES) and require more frequent reassessment?
- is treatment based on central corneal thickness (CCT) together with intraocular pressure (IOP) cost effective compared to IOP only, considering that CCT assessment requires additional cost?
- what is the most cost-effective treatment strategy among those licenced for first-line use?

We identified a number of economic evaluations in the published literature (see Chapter 8) but it was considered necessary to develop our own analysis to determine the most cost-effective treatment strategy for different subgroups of patients. We took this approach because we found limited applicability in the published economic evaluations, mainly because the important long-term consequences (that is, development of blindness) were ignored, or drugs were aggregated together in a single medical treatment. Furthermore, most of the published studies did not evaluate cost-effectiveness using the NICE reference case.

N.2 Methods

N.2.1 Model overview

N.2.1.1 Comparators

The main comparators in terms of treatment:

- no treatment
- BB
- PGA.

Other strategies compared in the model are:

- deciding treatment strategy based on IOP only
- deciding treatment strategy based on both IOP and CCT.

N.2.1.2 Population

The population of the model was people with a confirmed diagnosis of OHT. The current threshold (embedded in clinical practice) of IOP at which people are considered to have OHT is IOP>21 mmHg. Two subgroups were evaluated separately: those with an IOP≥25 mmHg and those with IOP between 21–25 mmHg. The aim of stratifying the population into these2 subgroups was to see if the cost effectiveness results differed between the 2 populations considering people with higher baseline IOP have a higher baseline risk of progression prior to treatment and to explore whether it would be cost effective not to treat people with an IOP below 25 mmHg. The a priori choice of ≥25 mmHg (25 or more) was made in order to acknowledge the threshold used in the CG85 OHT treatment table (>25, that is, ≥26 equivalent in words as 26 or more) and the OHTS entry criterion (≥24; equivalent 24 or more), the a priori value of ≥25 chosen (that is, 25 mmHg or more) being midway between these 2.

N.2.1.3 Time horizon, perspective, discount rates used

The analysis followed the standard assumptions of the reference case including discounting at 3.5% for costs and health effects, lifetime horizon and conducting an incremental analysis. A sensitivity analysis using a discount rate of 1.5% for costs and health effects was also conducted.

N.2.1.4 Deviations from NICE reference case

Some studies[189] have shown a poor correlation between visual function and EQ-5D based utilities; for this reason, another generic preference-based instrument (HUI3), which was shown to have larger and more significant correlations with tests of visual function, was used. A sensitivity analysis using utilities generated using the EQ-5D preference based instrument was also conducted.

N.2.1.5 Key assumptions

The following assumptions were made:

- The initial age of people diagnosed with OHT was 60.
- The model population was 50% men and 50% women.
- In the absence of treatment, the change in IOP was equal to 0.
- A patient starting with a prostaglandin analogue who demonstrated intolerance to this drug was switched to a beta-blocker.
- A patient starting with a beta-blocker who demonstrated intolerance to this drug (including development of asthma) was switched to a prostaglandin analogue.
- A patient could only switch in their first year of treatment.
- The adverse event of asthma from BBs lasted for 1 year (on the assumption that asthma due to commencement of BB would be identified within a year of starting this treatment).
- After a first switch in treatment, a second one could occur only after conversion and thus its cost was included in the downstream cost of the stage.
- An intention to treat analysis was assumed for drug effectiveness; therefore, the overall change in IOP already incorporated possible changes in treatment, and when a treatment switch occurred, the same effectiveness of the initial treatment was kept in the model.
- The severity of the condition was similar in both eyes of a patient.
- The cost of switching treatment was the cost of an additional monitoring visit.
- The relationship between reduction in IOP and corresponding decrease in probability of conversion to COAG was linear.
- Goldmann Applanation Tonometry has 100% sensitivity and 100% specificity and patients' IOP were accurately measured prior to entering the model.

- Patients' CCT were accurately measured.
- The relationship between baseline IOP and probability of conversion to COAG was identical to the extent to which treatment-related reduction in IOP modified probability of conversion.

N.2.2 Approach to modelling

Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover. The model was thus represented by a Markov model where patients could not return to previous stages. The cycle length was set at 1 year. Therefore all the probabilities, costs and health utilities were set to reflect annual values.

When defining the COAG stages, an adapted version of the Hodapp, Parrish and Anderson classification (Table 30) was used. This staging system was chosen as it allowed the use of costs and utility values associated with different severity levels of COAG already present in the literature. It has also been used in previous glaucoma economic models[360,93] and in the selected sources of probability of progression.[93]

Compared to the original staging system, the last 2 stages (severe COAG and blindness) were collapsed as there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe COAG to blindness.

Table 30: COAG staging classification in the model

COAG stage	Mean defect (MD) score
No COAG (a)	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00
Severe Visual Impairment (SVI)	-20.01 or worse

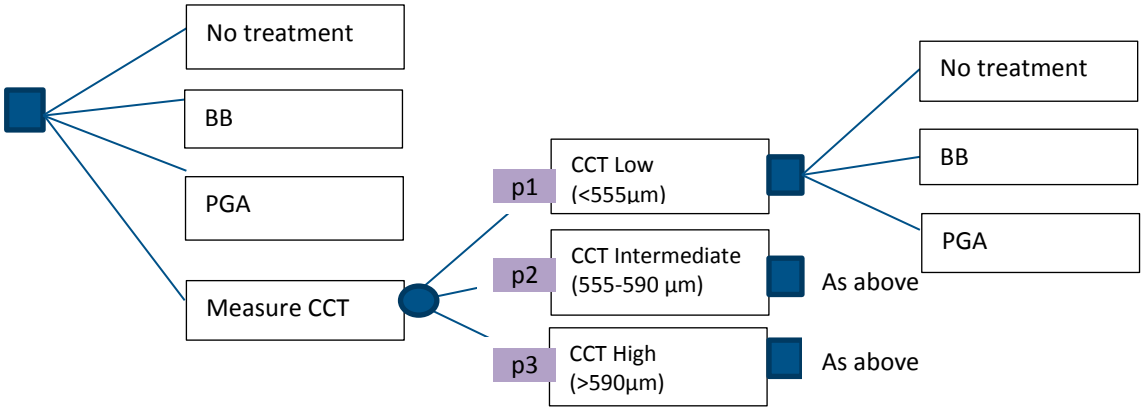
(a) Includes OHT patients

N.2.2.1 Model structure

The decision analysis for the treatment question started once patients have had full clinical eye examinations including having their IOP measured using Goldmann Applanation Tonometry. It would have also been established that they had no optic nerve head damage or any glaucomatous visual field loss. The patients were then classified into categories corresponding to their IOP: IOP≤21 mmHg, IOP between 22–24 mmHg and IOP≥25 mmHg. People diagnosed with OHT (IOP >21 mmHg) could fall into 2 IOP categories (IOP 22–24 mmHg and IOP≥25 mmHg) and these 2 IOP subgroups were evaluated separately.

The model represented in Figure 103 and Figure 104 below was run separately for each IOP subgroup; therefore, the results and conclusions could differ between the 2 populations.

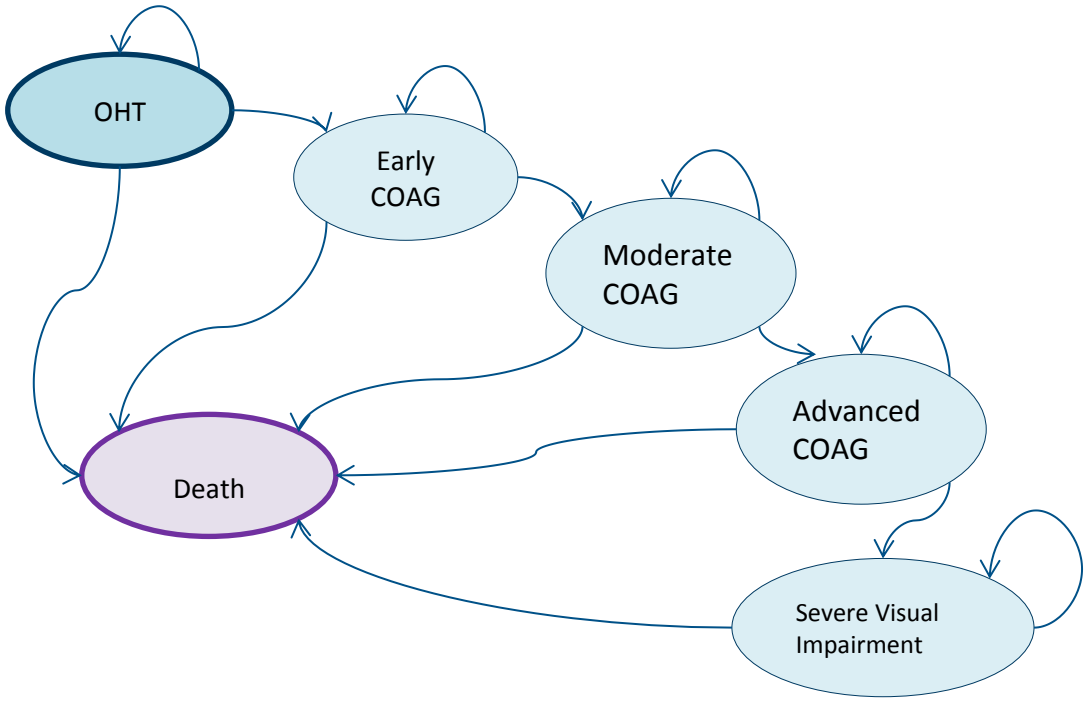
Figure 103: Model Structure – Initial Decision Tree Section



Source/Note: The square nodes represent decision nodes and they appear twice in the model: the model first evaluates the most cost-effective strategy on the right (that is, the most cost-effective treatment strategy for people with a certain IOP as defined by the subgroup and the various central corneal thickness levels – low (<555µm), intermediate (555-590 µm) and high(>590 µm). The model then evaluates the initial strategies compared on the left. It estimates the cost effectiveness of no treatment versus BB versus PGA for each CCT category and then feeds the results of the most cost-effective treatment for each CCT level into the remaining evaluation of the model. Individuals are distributed in different CCT categories as defined by probabilities p1, p2 and p3 (see section N.2.3.2).

Following the initial decision tree part of the model, each treatment strategy (no treatment, BB and PGA) was followed by the Markov part of the model. This is represented in Figure 104 below.

Figure 104: Markov section of the model



Note: Individuals in every strategy start in the OHT state; from there they have a probability of converting to early COAG, which is dependent on the treatment. Once individuals move to Early COAG, the probability of progressing to later stages is independent from the initial strategy (treatment). Throughout the model, individuals have a probability of dying which is age-dependent and independent from the OHT or COAG stage they are in.

The main effect of each strategy was considered to be the increase or decrease in risk of developing COAG. However, in the literature the most commonly reported treatment outcome is the change in IOP from baseline. In the original guideline, a systematic search was conducted to find the relative risk (RR) of developing COAG for each unit (mmHg) of IOP and another systematic search was conducted to find data on the probability of progression from one COAG stage to the next.

Each strategy was associated with upstream and downstream costs: the former are costs associated with the specific treatments while the latter are costs associated with the severity of the disease and thus dependent on the progression to later stages.

Some treatments could cause adverse events. Nevertheless, not all of them result in important increased costs or reduced quality of life. Asthma was the only complication associated with beta-blockers, for which incidence and annual cost per patient could be estimated. Other minor adverse events not requiring medical treatment were accounted for in the case of a change of COAG therapy.

N.2.2.2 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 10,000 times for each base-case analysis and 1,000 times for each sensitivity analysis; the results were summarised.

The way in which distributions were defined reflects the nature of the data; for example, probabilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a probability cannot be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 31 and the relevant inputs are detailed in Table 32. Probability distributions in the analysis were parameterised using error estimates from data sources where available.

Table 31: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Progression probabilities and effectiveness of treatments	Beta	Bounded between 0 and 1. Derived from mean of a domain and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ $\text{Beta} = \text{Alpha} \times [(1-\text{mean})/\text{mean}]$
CCT thickness probabilities	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Utility decrements (excluding SVI)	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its estimated standard error (assuming SE is 20% of mean or using confidence interval), using the method of moments. Alpha and Beta values were calculated as follows: $\text{Alpha} = \text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ $\text{Beta} = \text{Alpha} \times [(1-\text{mean})/\text{mean}]$

Parameter	Type of distribution	Properties of distribution
Utility of SVI and EQ-5D utilities used in SA4	Uniform	A uniform distribution fitted between the minimum and maximum range allows an equal chance of any value within this range being selected in any simulated run of the probabilistic analysis.
Costs	Gamma	Bounded at 0, positively skewed. Derived from mean and estimated standard error (assuming CI width is half the mean or using interquartile range). Alpha and Lambda values were calculated as follows: Alpha = $(mean/SE)^2$ Lamda = $Mean/SE^2$
Risk Ratios of conversion to COAG	Lognormal	Mean of logs = ln(RR) Standard deviation of logs = SE[ln(RR)]
Hazard Ratio	Lognormal	Mean of the logs= ln(HR) Standard error of logs =(ln[95hi)-ln[95lo])/1.962

An NMA was undertaken to estimate the treatment effect of beta-blockers and prostaglandin analogues informing the model; please see Appendix O for details. To account for uncertainty in the NMA output, in each probabilistic simulation of the model, a different NMA simulation output was randomly selected to inform the 2 treatment effects in the model.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold (which was deemed to be fixed by NICE)
- the cost of BB and PGA medication as this was assumed to be fixed. The difference in costs by different manufacturers was taken into account when estimating the cost of drugs
- the cost of performing a CCT test. This was assumed to be 5 minutes of a medical consultant's time of which the cost of staff was assumed to be fixed with national variation in staff costs already accounted for in the estimates
- the costs derived from NHS reference costs (cost of hospital or community visits), as these were assumed to be fixed with national variation in costs already accounted for in the estimates.

In addition, various probabilistic and deterministic sensitivity analyses were undertaken to test the robustness of model assumptions (see section A.2.5 for details of each additional sensitivity analysis). In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

N.2.3 Model inputs

N.2.3.1 Summary table of model inputs

Model inputs were based on clinical evidence identified through systematic reviews of evidence and a network meta-analysis (NMA) undertaken for the guideline update, supplemented by additional data sources as required. Model inputs were validated with clinical members of the committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 32 below. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 32: Overview of parameters and parameter distributions used in the model

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Baseline risk				
Annual probability of developing COAG untreated	Depends on age, IOP and CCT (e.g. If age 63, IOP < 24 CCT L then = 0.017)	None		Gordon (2002) [240] See section N.2.3.3
Effectiveness of treatments				
Change in IOP BB versus no treatment	3.3	See section N.2.3.5		Network meta-analysis (see Appendix O)
Change in IOP BB versus PGA	0.3	See section N.2.3.5		Network meta-analysis (see Appendix O)
Change in IOP PGA versus no treatment	3.6	See section N.2.3.5		Network meta-analysis (see Appendix O)
Annual probability of progression to COAG - treated	See section A.2.3.7			
Costs (£)				
The cost of 1 year in EG stage	£559	Gamma	α=60.86 λ=0.829	Traverso (2005) [662] See section N.2.3.11.2
The cost of 1 year in MG stage	£629	Gamma	α=61.31 λ =0.0974	Traverso (2005) [662] See section N.2.3.11.2
The cost of 1 year in AG stage	£500	Gamma	α=61.31 λ=0.122	Traverso (2005) [662] See section N.2.3.11.2
The cost of 1 year with SVI	£7,046.85	Gamma	α=61.27 λ=0.078	Traverso (2005) [662] See section N.2.3.11.2N.2.3.11.2
The cost of 1 year of low ICS inhaler medication for asthma	£58	Gamma	α=61.07 λ=1.056	Asthma guideline (out for consultation) See section N.2.3.11.4
The cost of exacerbation (including 2 GP visits + steroid medication)	£73 See section A.2.3.11.4	Gamma	α=60.86 λ=0.829	Asthma guideline (out for consultation)
The cost of an outpatient ophthalmology visit (hospital)	£89	Gamma	α=17.96 λ=0.201	NHS Reference Costs 2014-15
The cost of 1 month of BB medication	£2.39	None		Drug Tariff September 2016 See section N.2.3.11.1

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
The cost of 1 month of PGA medication	£5.52 See section A.2.3.11.1	None		Drug Tariff September 2016
The cost of 1 community visit	£51.2	None		See section N.2.3.11.3
The cost of switching medication from BB		None		Expert Opinion See section N.2.3.11.4
The cost of switching medication from PGA		None		Expert Opinion See section N.2.3.11.4
Probabilities				
The probability of having low corneal thickness (<555µm)	0.62	Dirichlet	α_1=609.46 α_2=275.24 α_3=98.3	The Bridlington Eye Assessment Project [261] See section N.2.3.4
The probability of having an intermediate corneal thickness (555-590µm)	0.28	Dirichlet	α_1=609.46 α_2=275.24 α_3=98.3	The Bridlington Eye Assessment Project [261] See section N.2.3.2
The probability of having a high corneal thickness (>590µm)	0.10	Dirichlet	α_1=609.46 α_2=275.24 α_3=98.3	The Bridlington Eye Assessment Project [261]
The annual probability of progressing from EG to MG	0.086	Beta	α=22.764 β=241.933	Burr (2007)[93] See section N.2.3.4
The annual probability of progressing from EG to MG when initial dB is 4 (SA2)	0.165	Beta	α=20.71 β=104.805	Burr (2007)[93] See section N.2.3.4
The annual probability of progressing from MG to AG (SA2)	0.064	Beta	α=23.336 β=341.289	Burr (2007)[93] See section N.2.3.4
The annual probability of progressing from AG to SVI	0.055	Beta	α=23.57 β=404.975	Burr (2007)[93] See section N.2.3.4
The annual probability of switching from BB including switching from asthma	0.025	Beta	α=158 β=474	Zhou (2004)[719] See section N.2.3.8
The annual probability of switching from BB excluding switching from asthma	probability of switching treatment with BB – probability of switching from asthma	None		Assumption See section N.2.3.8

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
The annual probability of switching from PGA	0.13	Beta	α=19 β=130	Zhou (2004)[719] See section N.2.3.8
Proportion of people treated with BB who develop asthma	0.019	Beta	α=50.26 β=2594.74	Kirwan (2002)[335] See section N.2.3.8
Proportion of people treated with PGA who develop asthma	0	None		See section N.2.3.8
Proportion of people given no treatment who develop asthma	0	None		See section N.2.3.8
Utilities				
The utility of no COAG	0.87	Beta	α=10.230 β=1.528	Wolfram (2013)[693] See section N.2.3.10
The utility decrement of EG	0.02	Gamma	α=0.017778 λ = 0.888889=0.569	Wolfram (2013)[693] See section N.2.3.10
The utility decrement of MG	0.1	Beta	α=0.189036 β=1.890359	Wolfram (2013)[693] See section N.2.3.10
The utility decrement of AG	0.17	Beta	α=0.282227 β=1.660156	Wolfram (2013)[693] See section N.2.3.10
The utility decrement of SVI	0.14	Uniform	Lower limit=0.287 Upper limit=0.618	Rein (2007)[566] See section N.2.3.10
The utility decrement of ashma	0.012	Beta	α=24.688 β=2032.65	Asthma guideline (out for consultation)
Relative risks (RR)				
RR of COAG development for low IOP low CCT compared to overall population	1.26	Log-normal	Meanlog=0.23 Sdlog=0.62	Gordon (2002)[240] See section N.2.3.3
RR of COAG development for low IOP intermediate CCT compared to overall population	0.76	Log-normal	Meanlog=-0.28 Sdlog=0.79	Gordon (2002)[240] See section A.2.3.3
RR of COAG development for low IOP high CCT compared to overall population	0.30	Log-normal	Meanlog=-1.22 Sdlog=1.11	Gordon (200[240] See section A.2.3.3
RR of COAG development for high IOP low CCT compared to overall	2.54	Log-normal	Meanlog=0.93 Sdlog=0.62	Gordon (2002)[240] See section A.2.3.3

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
population				
RR of COAG development for high IOP intermediate CCT compared to overall population	0.98	Log-normal	Meanlog=-0.02 Sdlog=0.70	Gordon (2002)[240] See section A.2.3.3
RR of COAG development for high IOP high CCT compared to overall population	0.52	Log-normal	Meanlog=-0.66 Sdlog=0.89	Gordon (2002)[240] See section A.2.3.3
HR of the increase in probability of conversion for every increased unit of mmHg (IOP)	1.1	Log-normal	Meanlog=0.10 Sdlog=0.03	Gordon (2002)[240] See section N.2.3.6
Age				
Age at diagnosis of OHT	63	User defined distribution		Kymes (2006)[360]
Discount rates and cycle length				
Discount rate for costs	3.5%	None		NICE reference case (NICE Methods of Technology Appraisal)
Discount rate for QALYs	3.5%	None		NICE reference case (NICE Methods of Technology Appraisal)
Cycle length	1 year	None		

Abbreviations: AG: advanced glaucoma; BB: beta blocker; CCT: central corneal thickness; COAG: chronic open-angle glaucoma; EG: early glaucoma; GP: general practitioner; ICS: inhaled corticosteroids; IOP: intraocular pressure; MG: moderate glaucoma; PGA: prostaglandin analogues; QALYs: quality-adjusted life-years; RR: risk ratio; SA2: sensitivity analysis 2; SVI: severe visual impairment

N.2.3.2 Initial cohort settings

In the base-case analyses, people were 63 years old. However, from the review on risk of progression we know that age is a significant risk factor for development of COAG. For this reason, a one-way sensitivity analysis was conducted on the age at decision point.

In the part of the model where CCT is considered, individuals were distributed into different CCT categories according to data collected in the Bridlington Eye Assessment Project.[261] In this study, 983 eyes of 983 consecutive subjects over 65 years of age registered with the general practitioners in the town of Bridlington, England, were screened for eye disease. IOP was measured by a calibrated Goldmann tonometer and CCT was measured by ultrasound pachymetry. Central corneal thickness was normally distributed and the mean CCT was 544.1, while the Standard deviation (SD) was 36.5µm. Knowing that CCT was normally distributed, the SD from the mean was used to obtain the proportion of individuals with a CCT <555µm, the proportion of individuals with CCT> 590µm or more. This was calculated as:

$CCT<555 = \Phi_{\mu\sigma 2}(CCT)$ where CCT=555,

$CCT>590 = 1- \Phi_{\mu\sigma 2}(CCT)$ where CCT=590,

where μ=mean CCT, σ^2=CCT variance= CCT SD squared, and where $\Phi_{\mu\sigma 2}$(CCT) gives the cumulative distribution function for a normal distribution with mean μ and variance σ^2.

The remaining category of CCT 555-590 was estimated as a residual of the 2 categories above. The values obtained are reported in Table 33.

Table 33: Distributions in CCT categories

	Proportion of individuals	Source
CCT <555 μm	61.7%	Bridlington Eye Assessment Project
CCT 555 – 590 μm	27.8%	
CCT >590 μm	10.4%	

N.2.3.3 Baseline probability of developing COAG

In the original guideline, a search was conducted to identify papers looking at progression from OHT to COAG and within COAG stages. The committee experts advised that no new good quality large UK population studies have been published on this topic since the previous guideline; therefore, the model relied on data selected for the previous guideline model.

A cost-effectiveness study[360] reported the annual risk of developing COAG in untreated OHT patients based on the results of the Ocular Hypertension Treatment Study, a multicentre RCT with 1,636 participants randomised to either treatment or no treatment and followed-up for a mean of 6 years. In addition to the estimate of probability of progression in the absence of treatment, the study calculated the hazard ratio of each clinical parameter for developing COAG through a multivariate Cox proportional hazards model.

The calculation of the probability of conversion from OHT to COAG was based on different combinations of those parameters that resulted in significant risk factors for the progression from OHT to COAG. Following the exclusion of pattern standard deviation and cup-disc ratio since they are already clinical signs of COAG, the significant risk factors identified were age, IOP and CCT. First, the probability of progression for each age group was inputted in the model, as reported in Table 34.

Table 34: Annual probability of developing COAG according to age in untreated patients

Age group	Annual probability
40-49 years	1.50%
50-59 years	1.90%
60-69 years	2.27%
70-80 years	2.69%

Source: Kymes et al (2006)[360]

This was then multiplied by a risk ratio (RR) resulting from the combination of IOP and CCT as follows:

I pCOAG = pCOAG[age] x RR[CCT,IOP]

To obtain the RR for the combinations of CCT and IOP, data from the same study was used. First, the proportion of individuals who developed COAG over 6 years was obtained, reported in Table 35 below.

Table 35: Probabilities of COAG development over 6 years

	CCT			TOTAL
IOP	<555μm	590-555 μm	>590 μm	
>25.75 mmHg	0.36	0.13	0.06	

	CCT			TOTAL
>23.75-25.75 mmHg	0.12	0.10	0.07	
≤23.75 mmHg	0.17	0.09	0.02	
TOTAL				**0.12**

Source: Gordon et al (2002)[240]

The original IOP categories reported in the study[240] were IOP >21–23.75 mmHg, IOP 23.75-25.75 mmHg, and IOP 25.75–32 mmHg. The committee in CG85 (the original guideline) felt that keeping the middle group was 'clinically meaningless', as the range limits were so close; therefore, the events and cohort of this group were incorporated into the 2 remaining groups IOP >21–25 mmHg and IOP >25–32 mmHg. Results are reported in Table 36.

Table 36: Probabilities of COAG development over 6 years – revised IOP groups

	CCT			TOTAL
IOP	<555µm	590-555 µm	>590 µm	
≥25 mmHg	0.29	0.12	0.07	
<25 mmHg	0.15	0.09	0.04	
TOTAL				**0.12**

For each CCT and IOP group, the RR for developing COAG compared to the overall cohort was estimated. This was estimated by first transforming the 6 year probabilities into rates of conversion and then into annual probabilities. The RRs were then calculated by dividing the annual probability of COAG in the group by the annual probability of COAG in the overall cohort. The results are reported in Table 37. The values were used to estimate the baseline risk for specific subgroups as per equation I.

Table 37: RR of COAG development for specific subgroups compared to the overall population

	CCT		
IOP	<555µm	590-555 µm	>590 µm
≥25 mmHg	2.54	0.98	0.52
<25 mmHg	1.26	0.76	0.30

N.2.3.4 Baseline probability of progression within COAG stages

In the original guideline, the source for the baseline probability of progression within COAG stages was a Health Technology Assessment (HTA)[93] where stages of mild, moderate and severe COAG corresponded to the definitions of early, moderate and advanced COAG agreed for this guideline. The approach adopted in the HTA was to use estimated progression rates by visual field mean defects as reported in available RCTs for the treated people.

Based on the data from the OHT treatment study,[240] people who developed COAG were diagnosed when their mean defect (MD) was between -1.5 and -2.0 dB. In the model base-case, 2.00dB as the starting point for people who develop COAG from OHT was used, as it was assumed they would be monitored and conversion detected soon enough. A sensitivity analysis using -4.00dB as the starting point for people who develop COAG from OHT was also conducted.

In the HTA, the EMGT study[267] was used to inform the annual probability of moving to the next stage of COAG; this study reported the initial and the final observed MD, and therefore the mean dB change per year could be estimated for the treated patients. Similarly, the mean change in dB in the

Moderate COAG group was obtained from the treated cohort of the CNTGS study[138]. Since no RCT was found for the severe stage, its progression was projected from the previous stages.

The mean dB change per year and the resulting annual probability of progressing to the next stage are reported in Table 38.

Table 38: Data on progression from one COAG stage to the next

	Initial MD [(a)] (dB) A	Final MD [(a)] (dB) B	dB change per year C	Years required to progress D = (B-A)/C	Rate (event per 100 patient year) E = 1/D	Annual probability 1 – exp(-E)
Early to Moderate COAG	-2 (a)	-6	-0.36	11.1	0.09	8.6%
Moderate to Advanced COAG	-6	-12	-0.40	15	0.07	6.4%
Advanced COAG to SVI	-12	-20	-0.45	17.8	0.06	5.5%

(a) Based on the stage definition, except for the initial MD for Early COAG which corresponds to the MD at diagnosis for people who developed COAG from OHT in the OHT Treatment Study.

N.2.3.5 Relative treatment effects

The main outcome of effectiveness reported in RCTs was change in IOP from baseline. This was used as a surrogate outcome of effectiveness.

A network meta-analysis (NMA) was conducted to estimate the average IOP change from baseline with each strategy evaluated in the model. In the initial NMA conducted, the absolute change in IOP from baseline was used. As some of the studies included in the NMA were on people with normal tension glaucoma, the absolute change in IOP was reduced compared to a population with OHT or higher-pressure glaucoma, a second NMA analysis was conducted. In the second analysis, the percentage change in IOP from study baseline was calculated. This was then converted into an absolute value by assuming the baseline IOP was the average IOP in all the studies included in the base-case and sensitivity analysis 2 of the NMA (24 mmHg). Details of this are reported in Appendix O.

The data used in the model are reported in the table below:

Table 39: Mean IOP change from baseline

	Mean difference versus no treatment (mmHg)	Mean difference versus BB (mmHg)
No treatment		
BB	-3.3	
PGA	-3.6 (a)	-0.3

(a) Estimated as the sum of the difference between PGA and BB and the difference between BB and no treatment.

Data informing the base-case analysis were obtained from studies meeting the pre specified inclusion criteria. In a sensitivity analysis (see Appendix O), the inclusion criteria was relaxed and more studies were included in the NMA. A sensitivity analysis of the model was conducted using the results of the sensitivity analysis of the NMA as the treatment. Details of this sensitivity analysis can be found in section N.2.5 and results in section N.3.2.

N.2.3.6 Link between IOP reduction and COAG conversion

In the original guideline, a search was conducted in order to find a measure of the link between IOP and protection against COAG conversion. Studies were only included if they reported the RR or HR of each mmHg in IOP for conversion, defined by deterioration in visual field or optic nerve appearance or both.

A study was identified that reported the influence that baseline IOP has on progression to COAG[240] expressed as a hazard ratio of 1.1 per unit increase in IOP. A new search was not conducted, as the committee was not aware of any more recent evidence on the link between IOP and COAG conversion. Due to a lack of data on the link between treatment modified IOP and probability of conversion to COAG, for the original model conducted for CG85 and for this model, the assumption had to be made that the relationship between baseline IOP and the outcome is identical to the extent to which treatment-related reduction in IOP modifies outcome.

N.2.3.7 Probability of developing COAG with treatment

The overall effectiveness of the interventions considered was calculated as follows:

II $pCOAG_{treat}$ = ratetoprob((probtorate(prob)/HR^treatmenteffect

II

where

$pCOAG_{treat}$ is the annual probability of developing COAG with 1 of the treatments, probis the baseline annual probability of developing COAG in the untreated population (different for each subgroup depending on IOP and CCT), HR is the hazard ratio of developing COAG per unit of IOP reduction (1.1 in this case), and treatment effect is the expected reduction in IOP achieved from the treatment.

The overall probability depends on the baseline probability of conversion and the mean IOP change from baseline.

N.2.3.8 Probability of discontinuation and adverse effect

1 UK study was found reporting the proportion of patients discontinuing treatment for reasons other than treatment failure (that is, adverse events, intolerance). In this study, 19 out of 149 patients (13%) treated with prostaglandin analogues and 158 out of 632 patients (25%) treated with beta-blockers discontinued within 1 year. From the latter figure 1.9% was subtracted, the proportion of people developing asthma that would have been included in the discontinuation of beta-blockers; the remaining annual probability discontinuing treatment for this group is 23.1%. Data for later years were not available; thus, these probabilities were used only during the first year of treatment.

Probability of developing asthma after use of beta-blockers was estimated from a prospective cohort study comparing the difference in respiratory disease in 2,645 people treated with beta-blockers to 9,094 unexposed people.[719] The difference between the proportions of people given a new prescription of drug for reversible airways obstruction in 12 months after treatment was 1.9%. The same study reported that the risk of respiratory problems ceased to be significant after the first year of exposure; therefore, the probability of developing asthma was kept in the model only within the first year.

N.2.3.9 Life expectancy

Life expectancy was assumed the same as the general population in England.[508] In the model, a 50/50 split between men and women was assumed and life expectancy reflects this assumption.

N.2.3.10 Utilities

A systematic search was conducted to identify utility values in order to calculate utility decrements for people with OHT and people in different stages of COAG. Only studies reporting utilities separately for different stages were of interest; therefore, studies reporting the average utility value for people with COAG were not considered.

Two studies were considered: one[693] which assessed quality of life data by the Health Utility Index (HUI3) for 154 people in Germany, and one[566] used in the previous model, which applied utilities for visual acuity to each category of visual field loss. In the base-case model, the utility values for OHT, EG, MG and AG were taken from Wolfram (2013),[693] as HUI3 is more sensitive to changes in visual function and it was the recommended quality of life instrument for sight conditions.[189] The utility value for the SVI health state was not reported in the Wolfram study; therefore, this value was calculated by extrapolating data from Rein (2007) and adjusting it to reflect the baseline value of 0.87 for people with OHT (also equivalent to the age-related average utility of the general population. The other study[566] was used in a sensitivity analysis (see N.2.5).

N.2.3.11 Resource use and costs

N.2.3.11.1 Drugs

Firstly, the cost per month of each preparation available in the UK within the BB and PGA classes was estimated. From data on prescription in England (2015) (http://content.digital.nhs.uk/catalogue/PUB20664), the proportion of prescriptions for each drug within their class was estimated and an average cost for the class as was obtained, illustrated in Table 40.

Table 40: Weighted cost of drugs

CLASS		A Number of items dispensed	B % within their class (A/total A)	C Average cost per month[(a)]	Weighted cost per month (B * C)
BB	Betaxolol	41.815	6%	2.28	0.14
	Carteolol	37.653	5%	8.00	0.43
	Levobunolol	57.742	8%	1.85	0.15
	Timolol	556.768	80%	2.08	1.67
	Weighted cost of BB				**2.39**
PGA	Bimatoprost	1,159.943	27%	11.71	3.14
	Latanoprost	2,464.371	57%	1.54	0.88
	Tafluprost	109.847	3%	Not available	-
	Travoprost	592.284	14%	1.50	1.50
	Weighted cost of PGA				**5.52**

(a) Source: Drug Tariff September 2016

N.2.3.11.2 Health states

The annual cost of the no COAG health state was assumed only to include the cost of monitoring visits; therefore, the cost of no COAG was given by:

The cost of a monitoring visit *annual monitoring frequency

See section N.2.3.11.3 for details on how the cost of a monitoring visit was calculated. The monitoring frequency was assumed to be once every 2 years in the base-case and a sensitivity analysis was conducted varying monitoring frequency to once per year.

The downstream annual costs of the COAG stages were taken from a cost of illness study reporting the direct healthcare cost per patient associated with each COAG stage).[661] This study was used in the previous model and was selected because the staging system was the same system that we adopted (Hodapp, Parrish and Anderson classification), and it contained UK data. The 2004 Euro costs reported in the study were converted into sterling using OECD purchasing power parities and then inflated to current price levels using the healthcare specific inflation indices taken from the most recent PSSRU publication[153] on the unit costs for health and social care.

In the Traverso (2006) paper, the costs of severe COAG and blindness did not account for social costs, thus leading to an underestimation of the true costs. Therefore, for the last stage (Severe Visual Impairment), the cost analysis was based on the services provided to patients with blindness as described in Meads and Hyde (2003).[433]

Table 41 illustrates the services considered in the analysis, the calculation of their costs, and the proportion of patients receiving each service as reported in Meads and Hyde (2003).[433]

Table 41: Cost of severe visual impairment

Service	Cost (£)	Source	Proportion of patients receiving the service
Blind registration	£154.92	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008) – figures uplifted to year 2015	95%
Low vision aids	£189.26	Meads and Hyde (2003)[433] – figures uplifted to year 2015	33%
Low vision rehabilitation	£261.18	Curtis (2007)[152] - NHS community occupational therapist cost of episode of care including qualification – figures uplifted to year 2015	11%
Community care	£1,0366.38	Curtis (2007)[152] - Annual cost for a local authority home care worker – figures uplifted to year 2015	6%
Residential care	£2,0621.72	Curtis (2007)[152] - Annual cost of private residential care assuming that 30% of residents pay themselves – figures uplifted to year 2015	30%

N.2.3.11.3 Cost of referral and reassessment

Referral

For the strategies based only on IOP (no CCT), the cost of referral for the no treatment arm was assumed to be zero, as no one would be referred; therefore, no costs would be incurred. For BB and PGA arms in the same group, the cost of a referral visit was assumed to be made of the cost of a hospital outpatient ophthalmology clinic visit for 90% of people and the cost of a community optometrist visit for 10% of people (expert opinion). The cost of a community visit was assumed to be 80% of the 2016/17 tariff for an ophthalmology follow-up visit by single professional.

The costs of hospital and community visits are reported in the summary Table 32.

People would usually need to be referred to a secondary care clinic to have their CCT measured; therefore, for the strategies that are part of the CCT test arm, the cost of a referral visit for all 3 strategies for every CCT subgroup was assumed to be the cost of a hospital outpatient ophthalmology clinic visit.

Reassessment

For the strategies based only on IOP (no CCT measurement required), the cost of reassessment was assumed to be made up of the cost of a hospital outpatient ophthalmology clinic visit for 90% of people and the cost of a community optometrist visit for 10% of people (expert opinion). The costs of hospital and community visits are reported in the summary Table 32.

For the strategies that are part of the CCT test arm the cost of reassessment was assumed to be the cost of a hospital outpatient ophthalmology visit as it was assumed patients would continue to be monitored in secondary care, where they had initially been referred.

N.2.3.11.4 Cost of adverse events and discontinuation

The only adverse event that was included in the model was the risk of developing asthma from taking beta-blockers. The cost of asthma in the model included the cost of 1 year of medication for a low dose-ICS inhaler as well as the cost of having a non-hospitalised exacerbation (which includes 2 GP visits and 1 course of steroid medication). These costs were taken from the NICE asthma guideline (due to publish October 2017).

The cost of discontinuation of treatment and switching to an alternative treatment was assumed to be the cost of 1 extra monitoring visit.

N.2.4 Computations

The model was constructed in TreeAge Pro 2016 and was evaluated by cohort simulation. Time dependency was built in by cross referencing the cohorts age as a respective risk factor for mortality and as a risk factor for the development of COAG.

People started in cycle 0 in the OHT health state. People moved to the dead health state and to COAG stages at the end of each cycle, as defined by the mortality and progression transition probabilities.

Life-years for the cohort were computed each cycle. To calculate QALYs for each cycle, Q(t), the time spent in the alive state of the model was weighted by a utility value that was dependent on the time spent in the model and the treatment effect. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%) but QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle. Costs per cycle, C(t), were calculated in the same way as QALYs. Initial cost of referral visits and CCT test were applied to cycle 0 only and the half cycle correction was not applied to these costs. Costs were

discounted to reflect time preference (discount rate 3.5%) in the same way as QALYs using the following formula:

Discount formula:

$\text{Discounted total} = \frac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

N.2.4.1 Calculating QALYs gained

For the IOP only strategies, the expected QALYs per cohort of people in each cycle were calculated as follows:

Expected QALYs = $U_{OHT} * P_{OHT} + U_{EG} * P_{EG} + U_{MG} * P_{MG} + U_{AG} * P_{AG} + U_{SVI} * P_{SVI} + P_{ASTHMA} * U_{ASTHMA}$

where

U_{OHT} , U_{EG} , U_{MG} , U_{AG} , U_{SVI} = the utility score for each stage

U_{ASTHMA} = the utility detriment due to asthma (negative number)

P_{OHT} , P_{EG} , P_{MG} , P_{AG} , P_{SVI} = the proportion of people in each of the COAG stage at the end of each cycle

P_{ASTHMA} = the proportion of people developing asthma in each cycle

The proportion of people in each COAG stage depends on the baseline risk of progression, progression reduction from treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected QALYs are given by the sum of QALYs calculated for each cycle. For the strategy of measuring CCT as well as IOP, the expected QALYs and costs of the individual strategies of BB, PGA or no treatment for each CCT subgroup were calculated in the same way as the IOP only strategies. However, the expected QALYs and costs of the entire strategy we calculated as follows:

Expected QALYs: strategy measuring CCT = $P_{CCT\,L} * QALYS_{CCT\,L} + P_{CCT\,I} * QALYS_{CCT\,I} + P_{CCT\,H} * QALYS_{CCT\,H}$

where

$QALYS_{CCT\,L}$, $QALYS_{CCT\,I}$, $QALYS_{CCT\,H}$ = the Expected QALYs for each subgroup of CCT if they are treated with the most cost-effective treatment for the subgroup

$P_{CCT\,L}$, $P_{CCT\,I}$, $P_{CCT\,H}$ = the probability of being in each CCT subgroup

The incremental QALYs gained associated with a treatment strategy were calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

N.2.4.2 Calculating costs

For the IOP only strategies, the expected cost per cohort of people in each cycle was calculated as follows:

Expected cost = UCa x Pa + Σ DCi x Pi

where

UCa = upstream cost of the initial treatment strategy

Pa = proportion of people in the initial treatment strategy

DCi = downstream cost of stage i

Pi = proportion of people in the stage i

and where stage i could be any later stage

The overall lifetime expected costs are given by the sum of costs calculated for each cycle.

For the strategy of measuring CCT, costs were calculated in the same way as QALYs (see section N.2.4.1) and expected costs for the whole strategy measuring CCT were calculated as follows:

Expected COST of strategy measuring CCT = $P_{CCT\,L}$ * $COST_{CCT\,L}$ + $P_{CCT\,I}$ * $COST_{CCT\,I}$ + $P_{CCT\,H}$ * $COST_{CCT\,H}$

The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

N.2.5 Sensitivity analyses

SA1: NMA studies

A sensitivity analysis was conducted using the results of a sensitivity analysis of the NMA (SA1 in appendix O), as the treatment effect in the model. The sensitivity analysis of the NMA relaxed the criteria for the inclusion of studies in the NMA (that was conducted to estimate the reduction in IOP from the different treatment options [BB ad PGA]). In the base-case NMA, studies were only included if the washout period was specified to have been at least 4 weeks for all drugs. In SA1 of the NMA, this was relaxed to at least 4 weeks for at least 1 drug but not for all drugs in the study. See Appendix O for details and for the list of studies included in both the base-case and SA1. The data used in this sensitivity analysis are reported in the table below:

Table 42: Mean IOP change from baseline – SA1

	Mean difference vs no treatment (mmHg)	Mean difference vs BB (mmHg)
No treatment		
BB	-2.8	
PGA	-3.7 (a)	-0.9

(a) Estimated as the sum of the difference between PGA and BB and the difference between BB and no treatment.

SA2: initial mean defect for the early COAG stage

In the base-case, the mean defect at diagnosis of early COAG was assumed to be -2.00dB; in a sensitivity analysis, this was varied to -4.00dB with the corresponding annual probability of progression as described in the table below.

Table 43: SA on progression from one COAG stage to the next

	Initial MD (dB) A	Final MD (dB) B	dB change per year C	Years required to progress D = (B-A)/C	Rate (event per 100 patient year) E = 1/D	Annual probability 1 – exp(-E)
Early to Moderate COAG	-4.00	-6.00	-0.36	5.6	0.18	16.5%

SA3: Reassessment intervals

In the base-case, it was assumed that people with OHT would be reassessed once every 2 years but SA3 was performed varying it to reassessments once per year.

SA4: Utilities

In a sensitivity analysis, we used EQ-5D utility values from Rein (2007).[566] These were estimated from the formula:

III Health utility = $0.98991+0.0022*dBs - 0.00080518*dBs^2$

where dBs are expressed as an absolute numbers and is therefore a positive number.

Since the stages in the model were defined as ranges of visual field defect, it was possible to calculate the upper and lower limits and the central utility score for each stage by substituting the range limits and the central value of the stage definition (Table 44). The central value of the severe visual impairment stage was assumed to be -26dB following the World Health Organization definition of blindness as reported in Rein et al (2007),[566] while the upper limit was assumed to be 30dB. The quality of life in OHT patients was assumed to be equal to perfect health, as there was no visual field defect. However, all these utilities were adjusted by the average utility in the general population (0.87) as reported in Ara (2011).[28] To make these utility values, probabilistic uniform distributions were assumed between the upper and lower limits.

Table 44: SA4 – health utilities by COAG stage

	Lower limit	Upper limit	Central value
OHT	-	-	0.87
Early COAG	0.845432	0.85932	0.858452
Moderate COAG	0.7812	0.845432	0.819392
Advanced COAG	0.618016	0.7812	0.710892
Severe Visual Impairment	0.287308	0.618016	0.436604

SA5: Discount rate

The NICE reference case in the NICE Methods of Technology Appraisal recommends using a discount rate of 3.5% for costs and effects. However, as the treatments for OHT are preventative, the costs are borne in the short term but effects are rewarded over a long period of time. SA5 was undertaken reducing the discount rates for both costs and effects to 1.5%.

SA6: Published NMA

SA6 was performed using the results found in a published NMA[397] for the change in IOP from baseline for both PGA and BB treatments. This NMA was not used in our base-case as inclusion and exclusion criteria were different to the ones set for this guideline (for example, no exclusion based on minimum treatment duration, washout period and so on).

The effectiveness data from this NMA that were used in SA6 are reported in Table 45 below.

Table 45: Mean IOP change from baseline from Li 2016 – SA6

	Mean difference vs no treatment (mmHg)	Mean difference vs BB (mmHg)
No treatment		
BB	-3.63	

	Mean difference vs no treatment (mmHg)	Mean difference vs BB (mmHg)
PGA	-5.03	-1.4

SA7: Generic drugs only

The committee noted that 1 of the PGA drugs is now available as a generic preparation and its price is considerably lower than other PGA preparations. Therefore, we wanted to explore the impact that using only the generic PGA would have on the results of the model. The cost of a monthly treatment with PGA in SA7 was £1.54, as opposed to £5.52 in the base-case analysis.

SA8: Increasing the number of IOP categories to three to match the original baseline risk data

The RRs of baseline risk of conversion to COAG were calculated from data from Gordon (2002). The original study split the population into 3 categories of IOP (≤23.75,>23.75 to ≤25.75 and >25.75). In the baseline model, this data was merged into 2 categories to fit the IOP low and IOP high populations. A sensitivity analysis was conducted using RRs that were calculated keeping the original 3 categories.

Revised RRs used in SA8

IOP	CCT <=555	CCT >555 to <= 588	CCT >588
≤23.75	1.54	0.79	0.17
>23.75 to <= 25.75	1.07	0.88	0.61
>25.75	3.62	1.16	0.52

Additional sensitivity analysis

Additional threshold analyses were performed on: the age at decision point (to identify the age at which it no longer becomes cost effective to offer treatment), treatment effect (to identify how low the treatment effect needs to be for no treatment to become cost effective), as well as baseline risks of conversion and the hazard ratio.

N.2.6 Model validation

The model was developed in consultation with the committee; model structure, inputs and results were presented to and discussed with the committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations.

N.2.7 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher, the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$	Cost-effective if: • ICER < Threshold

Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$Net\ Monetary\ Benefit\ (X) = (QALYs(X) \times \lambda) - Costs(X)$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost-effective if: • Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation, NMB is used in this analysis to identify the optimal strategy.

N.2.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[487] sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

N.3 Results

All results presented below show how treatment strategies were ranked according to cost effectiveness for a willingness to pay threshold of £20,000 per QALY.

N.3.1 Base-case

Table 46 shows that in the base-case analysis of the IOP low population, beta-blockers were the most cost-effective treatment strategy for all CCT subgroups. Table 47 shows that in the base-case analysis of the IOP high population, beta-blockers were the most cost effective for the CCT high and CCT intermediate groups but PGA were the most cost effective for the CCT low subgroup. Table 48 shows that when assessing whether it was cost effective to measure CCT and treat the CCT high and intermediate groups with beta-blockers and the CCT low group with PGA or give everyone one of the treatments, giving everyone beta-blockers was the most cost effective strategy; measuring CCT and treating accordingly was not cost effective.

Table 46: Base-case probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.45	£4,117.68		£244,950.26	Dominated	0.10
Low	BB	12.54	£3,746.91	BB versus no Tx: no Tx dominated	£247,118.75	1	0.71
Low	PGA	12.55	£4,099.96	PGA versus BB: £38,396.59/QALY gained	£246,949.60	2	0.19
Intermediate	No Tx	12.57	£3,172.97		£248,257.30	Dominated	0.23
Intermediate	BB	12.64	£3,006.03	BB versus no Tx: no Tx dominated	£249,771.29	1	0.65
Intermediate	PGA	12.65	£3,411.45	PGA versus BB: £59,781.56/QALY gained	£249,501.50	2	0.12
High	No Tx	12.70	£2,096.31		£251,949.53	2	0.52
High	BB	12.74	£2,190.54	BB versus no Tx: £2,430.79/QALY gained	£252,630.58	1	0.42
High	PGA	12.74	£2,656.42	PGA versus BB: £118,620.08/QALY gained	£252,243.25	3	0.06

Table 47: Base-case probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.21	£6,076.82		£238,082.61	Dominated	0.02
Low	BB	12.33	£5,374.40	BB versus no Tx: no Tx dominated	£241,302.59	2	0.67
Low	PGA	12.35	£5,623.09	PGA versus BB: £18,899.01/QALY gained	£241,317.07	1	0.31
Intermediate	No Tx	12.51	£3,592.18		£246,681.43	Dominated	0.16
Intermediate	BB	12.59	£3,331.00	BB versus no Tx: no Tx dominated	£248,517.39	1	0.69
Intermediate	PGA	12.60	£3,712.05	PGA versus BB: £46,531.63/QALY gained	£248,300.12	2	0.15
High	No Tx	12.64	£2,590.30		£250,228.26	Dominated	0.35
High	BB	12.69	£2,557.11	BB versus no Tx: no Tx dominated	£251,323.47	1	0.56

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
High	PGA	12.70	£2,994.84	PGA versus BB: £80,924.14/QALY gained	£250,993.93	2	0.09

Table 48: Base-case probabilistic results for all strategies for IOP H subgroup

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	12.34	£4,916.34		£241,821.07	Dominated	0.06
BB	12.44	£4,487.82	BB versus no Tx: no Tx dominated	£244,357.83	1	0.66
CCT	12.45	£4,674.56	CCT versus BB: £22,904.99/QALY gained	£244,334.14	2	0.13
PGA	12.45	£4,792.30	PGA versus CCT: £41,557.86/QALY gained	£244,273.07	3	0.15

N.3.2 Sensitivity analyses

SA1: NMA studies

Table 49 and Table 50 show that when the inclusion criteria for the NMA (conducted to estimate the treatment effect of the interventions) was relaxed and the number of studies included in the NMA increased, PGA became the most cost-effective treatment strategy for all CCT subgroups for both the IOP low and IOP high populations. As PGA was the most cost effective for all subgroups, measuring CCT was not cost effective.

Table 49: SA1 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.63	£4,117.81		£248,523.84	Dominated	0.13
Low	BB	12.71	£3,840.82	BB versus no Tx: no Tx dominated	£250,272.42	2	0.11
Low	PGA	12.77	£3,774.86	PGA versus BB: BB dominated	£251,570.39	1	0.76
Intermediate	No Tx	12.78	£3,069.64		£252,501.85	Dominated	0.28
Intermedi	BB	12.83	£2,987.31	BB versus no Tx:	£253,584.57	2	0.14

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
ate				no Tx dominated			
Intermediate	PGA	12.87	£3,099.24	PGA versus BB: £2,765.40/QALY gained	£254,282.11	1	0.59
High	No Tx	12.86	£2,134.95		£255,021.45	3	0.54
High	BB	12.89	£2,264.78	BB versus no Tx: £3,951.11/QALY gained	£255,548.80	2	0.13
High	PGA	12.92	£2,551.77	PGA versus BB: £10,794.08/QALY gained	£255,793.57	1	0.34

Table 50: SA1 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.36	£6,090.77		£241,183.97	Dominated	0.02
Low	BB	12.47	£5,522.16	BB versus no Tx: no Tx dominated	£243,848.08	Dominated	0.04
Low	PGA	12.56	£5,154.65	PGA versus BB: BB dominated	£246,106.25	1	0.94
Intermediate	No Tx	12.69	£3,630.45		£250,145.16	Dominated	0.19
Intermediate	BB	12.75	£3,440.05	BB versus no Tx: no Tx dominated	£251,640.13	2	0.14
Intermediate	PGA	12.81	£3,453.91	PGA versus BB: £256.62/QALY gained	£252,706.32	1	0.67
High	No Tx	12.76	£2,694.12		£252,407.41	3	0.41
High	BB	12.81	£2,699.18	BB versus no Tx: £101.30/QALY gained	£253,401.55	2	0.14
High	PGA	12.85	£2,882.60	PGA versus BB: £4,400.93/QALY gained	£254,051.69	1	0.45

SA2: Mean defect

Table 51 shows that changing the mean defect from -2.00dB to -4.00dB made beta-blockers the most cost-effective treatment strategy for all CCT subgroups for the IOP population. Table 52 shows that for the IOP high subgroup, beta-blockers were the most cost-effective strategy for the CCT intermediate and high groups. For the low CCT group, PGA was the most cost-effective treatment

strategy. Table 48 Table 56: SA3 probabilistic results for all strategies for IOP H subgroup shows that when assessing whether it was cost effective to measure CCT and treat the CCT high and intermediate groups with beta-blocker and the CCT low group with PGA or give everyone one of the treatments, measuring CCT and treatment accordingly was the most cost-effective strategy.

Table 51: SA2 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.51	£4,630.52		£245,576.02	Dominated	0.08
Low	BB	12.62	£4,148.71	BB versus no Tx: no Tx dominated	£248,277.19	1	0.69
Low	PGA	12.63	£4,491.83	PGA versus BB: £26,806.74/QALY gained	£248,190.07	2	0.24
Intermediate	No Tx	12.70	£3,431.17		£250,530.93	Dominated	0.18
Intermediate	BB	12.77	£3,199.62	BB versus no Tx: no Tx dominated	£252,288.48	1	0.68
Intermediate	PGA	12.78	£3,609.85	PGA versus BB: £52,083.63/QALY gained	£252,035.78	2	0.14
High	No Tx	12.81	£2,346.59		£253,761.90	3	0.44
High	BB	12.86	£2,387.81	BB versus no Tx: £817.79/QALY gained	£254,728.75	1	0.48
High	PGA	12.86	£2,850.73	PGA versus BB: £87,931.45/QALY gained	£254,371.12	2	0.08

Table 52: SA2 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.16	£6,940.85		£236,240.39		0.01
Low	BB	12.32	£6,077.44	BB versus no Tx: no Tx dominated	£240,268.69	2	0.63
Low	PGA	12.34	£6,317.25	PGA versus BB: £13,412.71/QALY gained	£240,386.47	1	0.37
Intermediate	No Tx	12.59	£4,079.29		£247,656.29	Dominated	0.12

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Intermediate	BB	12.69	£3,706.42	BB versus no Tx: no Tx dominated	£249,996.94	1	0.69
Intermediate	PGA	12.70	£4,084.88	PGA versus BB: £37,718.30/QALY gained	£249,819.16	2	0.19
High	No Tx	12.68	£2,985.18		£250,590.88	Dominated	0.30
High	BB	12.75	£2,868.14	BB versus no Tx: no Tx dominated	£252,186.42	1	0.56
High	PGA	12.76	£3,299.21	PGA versus BB: £49,297.01/QALY gained	£251,930.24	2	0.14

Table 53: SA2 probabilistic results for all strategies for IOP H subgroup

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	12.33	£5,629.73		£240,998.49	4	0.04
BB	12.46	£5,061.84	BB versus no Tx: no Tx dominated	£244,226.08	2	0.63
CCT	12.48	£5,243.10	CCT versus BB: £16,318.49/QALY gained	£244,266.98	1	0.13
PGA	12.48	£5,359.25	PGA versus CCT: £31,694.48/QALY gained	£244,224.12	3	0.21

SA3: Monitoring intervals

Table 54 and Table 55 show that changing the monitoring interval from once every 2 years to once every year did not change the cost-effectiveness results. Beta-blockers continued to be the most cost-effective treatment strategy for every CCT subgroup in the IOP low population. In the IOP high population, BB were the most cost effective for the CCT high and CCT intermediate groups, but PGA was the most cost effective for the CCT low subgroup. However, Table 48 shows that when assessing whether it was cost effective to measure CCT and treat the CCT high and intermediate groups with beta-blocker and the CCT low group with PGA or give everyone 1 of the treatments, giving everyone beta-blockers was the most cost-effective strategy; measuring CCT and treatment accordingly was not cost effective.

Table 54: SA3 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.63	£4,597.22		£248,044.42	Dominated	0.10
Low	BB	12.72	£4,268.21	BB versus no Tx: no Tx dominated	£250,066.29	1	0.71
Low	PGA	12.73	£4,627.28	PGA versus BB: £37,313.07/QALY gained	£249,899.68	2	0.19
Intermediate	No Tx	12.78	£3,605.80		£251,965.70	Dominated	0.25
Intermediate	BB	12.84	£3,487.15	BB versus no Tx: no Tx dominated	£253,234.33	1	0.64
Intermediate	PGA	12.84	£3,908.06	PGA versus BB: £72,781.19/QALY gained	£252,929.09	2	0.11
High	No Tx	12.86	£2,721.71		£254,434.68	2	0.50
High	BB	12.90	£2,829.60	BB versus no Tx: £2,845.17/QALY gained	£255,085.16	1	0.44
High	PGA	12.90	£3,299.06	PGA versus BB: £120,744.82/QALY gained	£254,693.46	3	0.06

Table 55: SA3 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.36	£6,470.93		£240,803.80	Dominated	0.01
Low	BB	12.49	£5,822.99	BB versus no Tx: no Tx dominated	£243,884.90	2	0.69
Low	PGA	12.50	£6,085.22	PGA versus BB: £19,572.18/QALY gained	£243,890.63	1	0.30
Intermediate	No Tx	12.69	£4,138.84		£249,636.77	Dominated	0.17
Intermediate	BB	12.76	£3,901.29	BB versus no Tx: no Tx dominated	£251,381.99	1	0.68

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Intermediate	PGA	12.77	£4,292.65	PGA versus BB: £51,606.20/QALY gained	£251,142.30	2	0.15
High	No Tx	12.76	£3,249.58		£251,851.95	Dominated	0.38
High	BB	12.81	£3,224.64	BB versus no Tx: no Tx dominated	£253,016.30	1	0.51
High	PGA	12.82	£3,664.68	PGA versus BB: £65,554.26/QALY gained	£252,710.51	2	0.11

Table 56: SA3 probabilistic results for all strategies for IOP H subgroup

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	12.49	£5,362.84		£244,524.58	Dominated	0.07
BB	12.60	£4,973.80	BB versus no Tx: no Tx dominated	£246,957.12	1	0.67
CCT	12.60	£5,189.26	CCT versus BB: £25,887.77/QALY gained	£246,908.12	2	0.09
PGA	12.61	£5,289.44	PGA versus CCT: £35,981.26/QALY gained	£246,863.62	3	0.17

SA4: Utilities

Table 57 shows that using different utilities values made beta-blockers the most cost-effective treatment strategy for every CCT subgroup in the IOP low population and IOP high populations.

Table 57: SA4 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.71	£4,117.81		£250,134.09	Dominated	0.22
Low	BB	12.78	£3,750.85	BB versus no Tx: no Tx dominated	£251,800.72	1	0.57
Low	PGA	12.79	£4,105.97	PGA versus BB: £44,802.22/QALY	£251,604.13	2	0.22

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
				gained			
Intermediate	No Tx	12.80	£3,069.64		£252,904.70	Dominated	0.29
Intermediate	BB	12.85	£2,922.73	BB versus no Tx: no Tx dominated	£254,029.95	1	0.57
Intermediate	PGA	12.85	£3,340.92	PGA versus BB: £72,222.81/QALY gained	£253,727.56	2	0.14
High	No Tx	12.90	£2,134.95		£255,871.96	3	0.49
High	BB	12.93	£2,225.71	BB versus no Tx: £3,484.21/QALY gained	£256,302.19	1	0.44
High	PGA	12.93	£2,693.50	PGA versus BB: £115,999.74/QALY gained	£255,915.05	2	0.07

Table 58: SA4 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.55	£6,090.77		£244,892.49	Dominated	0.18
Low	BB	12.64	£5,392.69	BB versus no Tx: no Tx dominated	£247,335.01	1	0.46
Low	PGA	12.65	£5,649.76	PGA versus BB: £23,238.83/QALY gained	£247,299.18	2	0.36
Intermediate	No Tx	12.76	£3,630.45		£251,619.54	Dominated	0.25
Intermediate	BB	12.82	£3,359.49	BB versus no Tx: no Tx dominated	£253,004.83	1	0.57
Intermediate	PGA	12.82	£3,747.61	PGA versus BB: £58,259.45/QALY gained	£252,749.95	2	0.17
High	No Tx	12.85	£2,694.12		£254,254.81	Dominated	0.35
High	BB	12.89	£2,645.35	BB versus no Tx: no Tx dominated	£255,074.76	1	0.54
High	PGA	12.89	£3,083.09	PGA versus BB: £87,866.15/QALY gained	£254,736.66	3	0.11

SA5: Discount rate

Table 59 and Table 60 show that changing the discount rate to 1.5% (3.5% in base-case analyses) did not change the cost-effectiveness results. Beta -blockers continued to be the most cost-effective treatment strategy for every CCT subgroup in the IOP low population. In the IOP high population BB were the most cost effective for the CCT high and CCT intermediate groups but PGA was the most cost effective for the CCT low subgroup. Table 61 shows that when assessing whether it was cost effective to measure CCT and treat the CCT high and intermediate groups with beta-blocker and the CCT low group with PGA or give everyone 1 of the treatments, measuring CCT and treatment accordingly was the most cost-effective treatment strategy.

Table 59: SA5 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	16.01	£6,205.95		£314,070.58	Dominated	0.08
Low	BB	16.15	£5,523.51	BB versus no Tx: no Tx dominated	£317,397.88	1	0.70
Low	PGA	16.16	£5,938.84	PGA versus BB: £27,466.81/QALY gained	£317,284.97	2	0.23
Intermediate	No Tx	16.24	£4,600.30		£320,195.20	Dominated	0.19
Intermediate	BB	16.33	£4,241.21	BB versus no Tx: no Tx dominated	£322,391.42	1	0.67
Intermediate	PGA	16.34	£4,749.30	PGA versus BB: £55,446.22/QALY gained	£322,066.61	2	0.14
High	No Tx	16.37	£3,106.79		£324,253.56	3	0.45
High	BB	16.43	£3,118.93	BB versus no Tx: £200.14/QALY gained	£325,454.97	1	0.47
High	PGA	16.43	£3,701.98	PGA versus BB: £96,790.00/QALY gained	£324,992.40	2	0.08

Table 60: SA5 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	15.60	£9,241.16		£302,744.16	Dominated	0.01
Low	BB	15.78	£8,086.49	BB versus no Tx: no Tx dominated	£307,602.64	2	0.64
Low	PGA	15.81	£8,363.67	PGA versus BB:	£307,737.00	1	0.35

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
				£13,470.10/QALY gained			
Intermediate	No Tx	16.10	£5,474.99		£316,469.59	Dominated	0.13
Intermediate	BB	16.22	£4,931.31	BB versus no Tx: no Tx dominated	£319,398.22	1	0.68
Intermediate	PGA	16.23	£5,395.38	PGA versus BB: £38,567.15/QALY gained	£319,174.81	2	0.19
High	No Tx	16.21	£3,987.79		£320,238.53	Dominated	0.31
High	BB	16.30	£3,785.42	BB versus no Tx: no Tx dominated	£322,220.90	1	0.5
High	PGA	16.31	£4,323.70	PGA versus BB: £52,386.30/QALY gained	£321,888.12	2	0.13

Table 61: SA5 probabilistic results for all strategies for IOP H subgroup

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	15.80	£7,543.82		£308,468.89	Dominated	0.04
BB	15.96	£6,738.38	BB versus no Tx: no Tx dominated	£312,415.16	2	0.64
CCT	15.97	£6,947.10	CCT versus BB: £16,330.85/QALY gained	£312,462.06	1	0.13
PGA	15.97	£7,093.54	PGA versus CCT: £33,431.33/QALY gained	£312,403.22	3	0.20

SA6: Published NMA

Table 62 and Table 64 show that using the results of the published NMA (which had less strict inclusion criteria than our NMA) for the treatment effect changed the cost-effectiveness results. PGA became the most cost-effective treatment strategy for the CCT low and intermediate subgroups of the IOP low population, while BB remained the most cost-effective for the CCT high subgroup. When assessing whether it would be cost effective to measure CCT and give PGA to the CCT low and intermediate groups and BB to the CCT high group or give everyone the same treatment, Table 63 shows that treating everyone with PGA was the most cost-effective strategy, measuring CCT and treating accordingly was not cost effective. For the IOP high population, PGA became the most cost-effective treatment strategy for all CCT subgroups.

Table 62: SA6 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.63	£4,117.81		£248,523.84	Dominated	0.09
Low	BB	12.72	£3,685.45	BB versus no Tx: no Tx dominated	£250,812.74	2	0.41
Low	PGA	12.76	£3,872.49	PGA versus BB: £6,096.15/QALY gained	£251,239.33	1	0.50
Intermediate	No Tx	12.78	£3,069.64		£252,501.85	Dominated	0.20
Intermediate	BB	12.84	£2,876.40	BB versus no Tx: no Tx dominated	£253,945.12	2	0.47
Intermediate	PGA	12.86	£3,170.62	PGA versus BB: £14,642.05/QALY gained	£254,052.79	1	0.33
High	No Tx	12.86	£2,134.95		£255,021.45	3	0.48
High	BB	12.90	£2,198.78	BB versus no Tx: £1,553.66/QALY gained	£255,779.33	1	0.35
High	PGA	12.91	£2,594.37	PGA versus BB: £29,883.62/QALY gained	£255,648.50	2	0.18

Table 63: SA6 probabilistic results for all strategies for IOP L subgroup

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	12.70	£3,507.60		£250,409.47	Dominated	0.14
BB	12.77	£3,275.53	BB versus no Tx: no Tx dominated	£252,224.06	3	0.42
CCT	12.80	£3,509.36	CCT versus BB: £9,496.35/QALY gained	£252,482.69	2	0.13
PGA	12.80	£3,512.86	PGA versus CCT: £2,611.22/QALY gained	£252,505.96	1	0.31

Table 64: SA6 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.36	£6,090.77		£241,183.97	Dominated	0.01
Low	BB	12.50	£5,300.76	BB versus no Tx: no Tx dominated	£244,636.00	2	0.24
Low	PGA	12.54	£5,303.49	PGA versus BB: £58.06/QALY gained	£245,571.88	1	0.75
Intermediate	No Tx	12.69	£3,630.45		£250,145.16	Dominated	0.13
Intermediate	BB	12.77	£3,306.26	BB versus no Tx: no Tx dominated	£252,099.33	2	0.45
Intermediate	PGA	12.80	£3,542.72	PGA versus BB: £8,867.30/QALY gained	£252,396.20	1	0.42
High	No Tx	12.76	£2,694.12		£252,407.41	Dominated	0.34
High	BB	12.82	£2,604.50	BB versus no Tx: no Tx dominated	£253,760.95	2	0.38
High	PGA	12.84	£2,939.33	PGA versus BB: £16,035.77/QALY gained	£253,843.73	1	0.28

SA7: Generic PGA costs

Table 65 and Table 66 show that replacing the monthly cost of PGA with the monthly cost of generic PGA only (not using a weighted average cost) changed the cost-effectiveness results. Generic PGA became the most cost-effective treatment strategy for all CCT categories for both the IOP low and IOP high populations. As the most cost-effective treatment strategy was the same for all subgroups, measuring CCT was not cost effective.

Table 65: SA7 probabilistic results for CCT strategy IOP L subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.63	£4,117.81		£248,523.84	Dominated	0.03
Low	BB	12.72	£3,750.85	BB versus no Tx: no Tx dominated	£250,583.65	Dominated	0.09
Low	PGA	12.73	£3,546.35	PGA versus BB: BB	£250,980.61	1	0.88

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
				dominated			
Intermediate	No Tx	12.78	£3,069.64		£252,501.8	Dominated	0.11
Intermediate	BB	12.84	£2,922.73	BB versus no Tx: no Tx dominated	£253,798.76	Dominated	0.06
Intermediate	PGA	12.84	£2,732.68	PGA versus BB: BB dominated	£254,104.47	1	0.83
High	No Tx	12.86	£2,134.95		£255,021.45	Dominated	0.35
High	BB	12.90	£2,225.71	BB versus no Tx: £2,393.65/ QALY gained	£255,689.05	Dominated	0.05
High	PGA	12.90	£2,044.50	PGA versus BB: BB dominated	£255,948.02	1	0.61

Table 66: SA7 probabilistic results for CCT strategy IOP H subgroup

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.36	£6,090.77		£241,183.97		0.00
Low	BB	12.49	£5,392.69	BB versus no Tx: no Tx dominated	£244,315.20		0.15
Low	PGA	12.50	£5,182.19	PGA versus BB: BB dominated	£244,793.66		0.85
Intermediate	No Tx	12.69	£3,630.45		£250,145.16	Dominated	0.05
Intermediate	BB	12.76	£3,359.49	BB versus no Tx: no Tx dominated	£251,923.79	Dominated	0.09
Intermediate	PGA	12.77	£3,164.27	PGA versus BB: BB dominated	£252,270.68	1	0.86
High	No Tx	12.76	£2,694.12		£252,407.41	Dominated	0.20

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
High	BB	12.81	£2,645.35	BB versus no Tx: no Tx dominated	£253,595.60	Dominated	0.06
High	PGA	12.82	£2,458.53	PGA versus BB: BB dominated	£253,916.67	1	0.74

SA8: Original IOP categories from the ocular hypertension treatment study

Table 67 shows that when the baseline RRs were calculated keeping the original 3 IOP categories that were used in Gordon (2002) for the lowest IOP category (≤23.75), BB is the most cost-effective treatment strategy for all the CCT subgroups; therefore, measuring CCT is not cost effective. Table 68 shows that for the middle IOP category (>23.75 to ≤25.75) treating all CCT subgroups with BB is the most cost-effective strategy; therefore, measuring CCT is not cost effective. Table 69 shows that for the highest IOP category (>25.75) BB were the most cost-effective strategy for the CCT high and intermediate subgroups, but PGA became the most cost-effective strategy for the CCT low subgroup. Table 70 shows that measuring CCT and treating the CCT high and intermediate with BB and CCT low with PGA was the most cost-effective strategy.

Table 67: SA8 probabilistic results for CCT strategy lowest IOP category (≤23.75)

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.55	£4,701.56		£246,217.09	Dominated	0.07
Low	BB	12.64	£4,236.19	BB versus no Tx: no Tx dominated	£248,654.17	1	0.73
Low	PGA	12.65	£4,566.78	PGA versus BB: £32,749.63/QALY gained	£248,525.47	2	0.20
Intermediate	No Tx	12.70	£3,441.40		£250,581.50	Dominated	0.23
Intermediate	BB	12.77	£3,237.68	BB versus no Tx: no Tx dominated	£252,196.82	1	0.63
Intermediate	PGA	12.78	£3,633.46	PGA versus BB: £50,636.7	£251,957.36	2	0.14

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
				9/QALY gained			
High	No Tx	12.81	£2,201.01		£253,942.20	3	0.62
High	BB	12.85	£2,323.28	BB versus no Tx: £2,916.76/ QALY gained	£254,658.33	1	0.30
High	PGA	12.85	£2,788.26	PGA versus BB: £100,658. 05/QALY gained	£254,285.74	2	0.08

Table 68: SA8 probabilistic results for CCT strategy middle IOP category (>23.75 to ≤25.75)

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.64	£3,998.85		£248,875.25	Dominated	0.16
Low	BB	12.72	£3,694.94	BB versus no Tx: no Tx dominated	£250,718.34	1	0.67
Low	PGA	12.73	£4,061.53	PGA versus BB: £44,362.6 7/QALY gained	£250,517.02	2	0.17
Intermed iate	No Tx	12.64	£3,847.04		£248,885.89	Dominated	0.21
Intermed iate	BB	12.71	£3,590.96	BB versus no Tx: no Tx dominated	£250,636.23	1	0.63
Intermed iate	PGA	12.72	£3,965.37	PGA versus BB: £50,782.8 2/QALY gained	£250,409.27		0.16
High	No Tx	12.77	£2,980.60		£252,399.78	Dominated	0.32
High	BB	12.82	£2,881.78	BB versus no Tx: no Tx	£253,615.50	1	0.58

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
				dominated			
High	PGA	12.83	£3,305.48	PGA versus BB: £72,295.10/QALY gained	£253,309.02	2	0.11

Table 69: SA8 probabilistic results for CCT strategy highest IOP category (>25.75)

CCT subgroup	Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
Low	No Tx	12.20	£7,562.66		£236,366.52	Dominated	0.01
Low	BB	12.33	£6,727.85	BB versus no Tx: no Tx dominated	£239,873.92	2	0.60
Low	PGA	12.35	£6,916.59	PGA versus BB: £12,464.20/QALY gained	£239,988.03	1	0.39
Intermediate	No Tx	12.57	£4,146.19		£247,328.74	Dominated	0.14
Intermediate	BB	12.66	£3,811.58	BB versus no Tx: no Tx dominated	£249,441.12	1	0.68
Intermediate	PGA	12.67	£4,174.61	PGA versus BB: £39,912.33/QALY gained	£249,260.00	2	0.18
High	No Tx	12.75	£2,815.57		£252,234.08	Dominated	0.37
High	BB	12.81	£2,756.03	BB versus no Tx: no Tx dominated	£253,454.54	1	0.51
High	PGA	12.82	£3,186.35	PGA versus BB: £70,756.86/QALY gained	£253,145.85	2	0.12

Table 70: SA8 probabilistic results for all strategies for the highest IOP category (>25.75)

Strategy	QALYs	Cost	ICER	NMB at £20,000 threshold	Rank at £20,000 threshold	Probability of being CE at £20,000 threshold
No Tx	12.36	£6,019.06		£241,145.85	Dominated	0.03
BB	12.47	£5,485.01	BB versus no Tx: no Tx dominated	£243,948.99	2	0.50
CCT	12.49	£5,509.92	CCT versus BB: £1,783.75/QALY gained	£244,203.42	1	0.33
PGA	12.48	£5,746.25	PGA versus CCT: £168,421.36/QALY gained	£243,939.03	3	0.14

N.4 Discussion

N.4.1 Summary of results

The base-case results show that for people with an average age of 63 at diagnosis of OHT, no treatment is not cost effective for any CCT category within either IOP subgroup. The estimated reduction in probability of progression to COAG that treatment brings, through reducing intraocular pressure, outweighs the relatively low cost of lifetime treatment.

The base-case results show that for both IOP populations offering everyone beta-blockers as the first-line treatment for OHT was the most cost-effective treatment compared to offering everyone PGA or measuring CCT and then offering people the most cost-effective treatment according to their CCT level, or not treating anyone. A CCT measurement does not need to be taken when deciding what treatment to offer.[a] Although the model conducted for the original guideline found that no treatment was the most cost-effective strategy if CCT was >555µm and IOP was within the 21–32 mmHg range, new evidence on effectiveness, updated costs, and updated model methodology has led to new estimates that no treatment is now not cost-effective for any subgroups within the model population. The previous model found that PGA was the most cost-effective treatment for people with thin corneas (CCT≤555µm) for any IOP. The new base-case results show that PGA are the most cost-effective treatment for this subgroup in the IOP high group only, but that BB are still more cost effective overall when the cost of measuring CCT is taken into account. This is likely to be because the NMA found that the incremental treatment effect of PGA versus BB was not as large as previously estimated.

Results of SA1 show that when the treatment effect estimates came from a larger number of studies (with less strict criteria for inclusion) PGA became cost effective for all CCT categories for both the IOP low and IOP high populations.

The results of SA7 show that when the monthly cost of PGA was replaced with the monthly cost of the generic drug, the cost effectiveness results changed. Generic PGA became the most cost-effective treatment for all CCT levels in both IOP subgroups; therefore, treatment with generic PGA (without measuring CCT) overall became the most cost-effective strategy for both IOP populations.

[a] This does not mean that CCT should not ever be measured as it can provide clinicians with useful information on prognosis.

This is because the monthly cost of the generic PGA (Latanoprost; £1.54) is significantly lower than the cost of other PGA drugs that are currently being prescribed.

N.4.2 Limitations and interpretation

The model has a number of limitations that need to be taken into account when interpreting the findings.

The Ocular Hypertension Treatment Study (OHTS)[316] was used to determine the baseline risk of progression according to IOP and CCT levels that fed into the model. Theoretically, the model population was people with OHT, which in practice is considered to be anyone with an IOP>21 mmHg. Based on this clinical classification followed in practice, the IOP low subgroup in the model was classified as people with an IOP level of between >21 and <25, and the IOP high subgroup being people with IOP between 25 and 32 mmHg. Although this was the theoretical classification, the baseline risk probabilities for the subgroups were calculated from data on people in the ocular hypertension treatment study, where the initial inclusion criteria for the study were that people had an IOP of 24 mmHg or more but because of repeat measurements later in the study the average IOP levels for the subgroups were 23 mmHg and 27 mmHg. The issue with this data is that the relative risks of the people in the IOP low population have been calculated from a population of people who had all previously had an IOP of greater than 24 mmHg recorded. Due to a lack of available data, the model does not include accurate baseline risk data for people who have an IOP<24 mmHg who have *never* had an IOP of 24 mmHg or more on assessment. A threshold analysis was performed on the baseline risk of conversion to COAG to see what level the baseline risk would have to be for no treatment to become cost effective. The results found that the baseline risk of conversion to COAG (which is made up of the factors of age, IOP and CCT) would have to be below 0.43% for no treatment to be cost effective.

Another limitation is that the 4 studies included in the NMA, conducted to estimate the treatment effects, did not come strictly from OHT populations. Two of the studies[20,657] were on normal tension glaucoma patients with mean IOPs in each study arm of between 12.5 mmHg and 16.0 mmHg and 1 of the studies[228] (the largest study) had a mean baseline IOP of 30 mmHg or higher – a very high risk population. To account for this the percentage, change in IOP from baseline (from treatment) was calculated for each study. The percentage changes were then converted into absolute differences by anchoring the percentage change to 24 mmHg, the mean baseline IOP of the studies included in the NMA and a sensitivity analysis of the NMA that had relaxed inclusion criteria. Despite this approach, it does not fully account for the fact that the treatment effect feeding into the model was not estimated from data coming strictly from people considered to have OHT.

A third limitation is that the model assumes a linear relationship between increased units of mmHg (IOP) and an increase in a person's relative probability of conversion to COAG, derived from the Gordon (2002)[240] study. However, the study reported the effect that baseline IOP had on conversion to COAG, not the effect that treatment moderated IOP has on probability of conversion. Due to a lack of evidence on the relationship between treatment moderated IOP and conversion to COAG, an assumption had to be made that the effect that treatment modified IOP has on probability of conversion to COAG is identical to the effect of baseline IOP. No strong evidence was identified on the shape of the relationship for different baseline levels of IOP. The committee believed that it is more likely that this relationship is non-linear. For lower baseline IOP levels (for example, IOP < 24 mmHg), the committee believed that a reduction in IOP is likely to be associated with less than a 10% reduction in the probability of conversion to COAG (if any) as there is no established evidence that such people are actually at an increased risk of COAG in the first place. Equally, for people with extremely high IOP, (for example, IOP > 30 mmHg) who are at an extremely high risk already, reducing their IOP by 1 unit is not likely to correspond to a 10% reduction in their probability of conversion. As the committee felt the effect that lowering IOP would have on probability of conversion in the IOP low group was likely to be lower than 10%, threshold analyses were conducted

on the hazard ratio to see at what levels no treatment would become the most cost-effective treatment strategy. The results are presented in Table 71 below. The table shows that the thinner a person's cornea is, and therefore the higher their risk, the lower their relative decreased probability of conversion to COAG (from IOP lowering treatment) needs to be to make treatment cost effective.

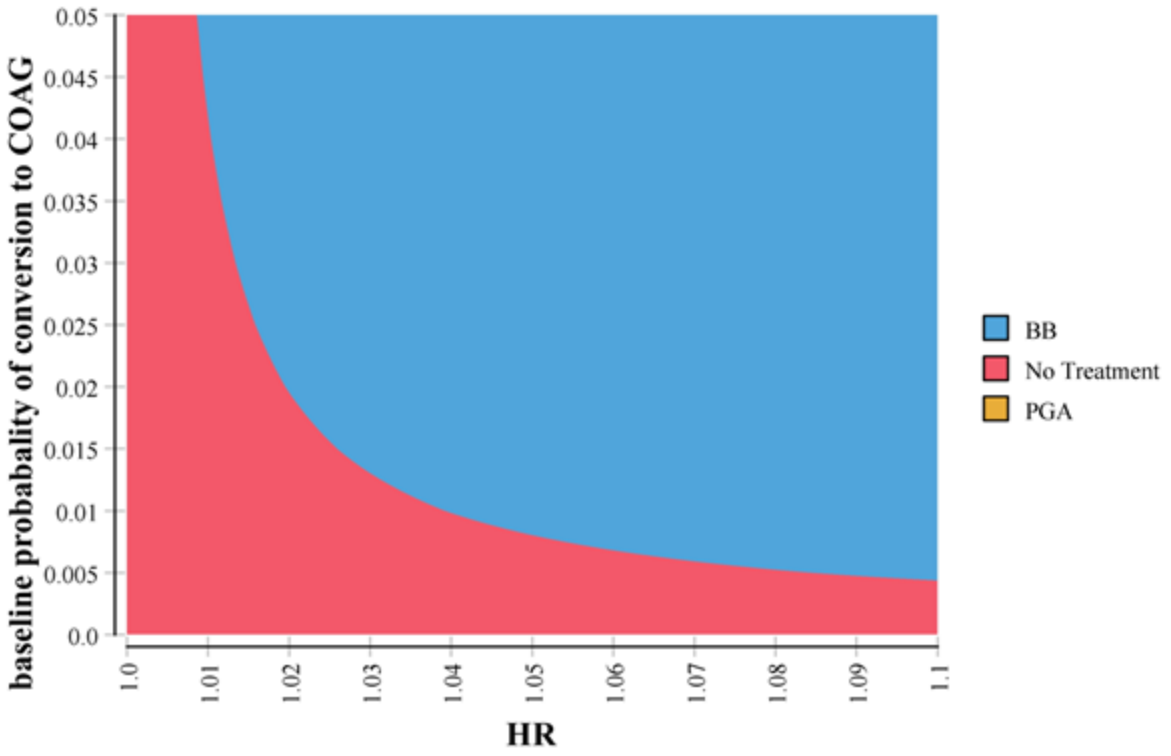
Table 71: Threshold analyses on the HR of unit increase in (mmHg) IOP and progression - IOP L

CCT level	Threshold value of the HR(a)
CCTL – < 555 micrometres	1.014
CCTI – 555-590 micrometres	1.022
CCTH – > 590 micrometres	1.055

(a) No treatment is cost effective if HR is below the threshold; BB is cost effective if HR is above the threshold.

A two-way sensitivity analysis was performed varying the hazard ratio of the increase in probability of conversion to COAG for every increased unit of mmHg IOP level and the baseline risk of conversion, as both of these factors contribute to a person's overall probability of conversion to COAG. The results of this sensitivity analysis are presented in the figure below. This figure shows that the lower the hazard ratio, the higher the baseline risk (made up of age, IOP and CCT) needs to be to make treatment cost effective.

Figure 105: Two-way sensitivity analysis on baseline probability of conversion and HR



Another limitation of the model is that it assumes that Goldmann Applanation Tonometry (used to measure IOP) has 100% sensitivity and 100% specificity; however, although GAT is the best instrument available to measure IOP, it is not 100% accurate. For simplicity, the model assumes that once a person has had their IOP measured, a clinician will be able to determine whether they require treatment (in accordance with which treatment is the most cost effective for their IOP subgroup). In

reality, however, IOP is associated with a high level of variation throughout the day, which can lead to spurious results if measured on a single occasion. This means that before a treatment decision is made, a clinician may want to monitor and reassess to see if their IOP is consistently over the treatment threshold, especially if they are close to the threshold. As this is a limitation that affects all treatment comparators in the model, assuming 100% diagnostic accuracy is not likely to bias the comparative results; although overall, it may reduce precision near boundary values.

The treatments compared in the model can be associated with adverse events and complications, which often require further interventions. In our model, we have incorporated the costs and effects of the most common and serious complication: asthma from beta-blockers. However, we were unable to incorporate any others since there is no good up-to-date literature on this topic; therefore, we were unable to estimate their cost or effects.

N.4.3 Generalisability to other populations or settings

The results of the OHT treatment model can be extrapolated to a COAG population. If generic PGA treatment is cost effective in an OHT population, it can be inferred that they are also cost effective in a COAG population, as people with COAG are at increased risk of progression to sight loss. This means that although the costs of medication will be the same, the benefits of treatment would be greater. Costs that would differ for the COAG population are that 100% of people would be monitored in a Hospital Eye Service (HES) setting and people would be monitored more frequently; however, as these costs would be applied to every treatment arm in the COAG model, they would not change the cost-effectiveness results – that it is cost effective to treat people with COAG with generic Prostaglandin Analogues.

The OHT treatment model was structured assuming that the majority of people being treated (90%) are monitored in a Hospital Eye Service setting. If a greater number of community optometrists were to upskill and become qualified to diagnose and monitor OHT then the proportion of treated people monitored in a HES setting would decrease. This would decrease the cost of monitoring, as the cost of a community visit is assumed to be 80% of the 2016-17 Tariff for an Ophthalmology follow-up visit by a single professional. Reducing the cost of monitoring would make treatment even more cost effective as well as free up capacity in HES for people diagnosed with COAG.

N.4.4 Conclusions

The results of the base-case analysis found that treating everyone with beta-blockers (BB) is cost effective compared to treating everyone with prostaglandin analogues (PGA), measuring CCT and giving people the most cost-effective treatment (BB, PGA or no treatment) according to their CCT category or and not treating anyone.

- In people with an IOP between >21 and <25 mmHg and central corneal thickness low: <555µm, BB dominated no treatment. PGA was not cost effective compared to BB producing an ICER of £38,396.59 per QALY gained.
- In people with an IOP between >21 and <25 mmHg and central corneal thickness intermediate: 555–590µm, BB dominated no treatment. PGA was not cost effective compared to BB producing an ICER of £59,781.56 per QALY gained.
- In people with an IOP between >21 and <25 mmHg and central corneal thickness high: > 590µm, BB was cost effective compared to no treatment producing an ICER of £2,430.79 per QALY gained. PGA was not cost effective compared to BB producing an ICER of £118,620.08 per QALY gained.
- In people with an IOP≥25 mmHg and central corneal thickness low: <555µm, BB dominated no treatment. PGA were cost effective compared to beta-blockers producing an ICER of £18,899.01 per QALY gained.

- In people with an IOP≥25 mmHg and central corneal thickness intermediate: 555-590 µm, BB dominated no treatment. PGA were not cost effective compared to BB producing an ICER of £46,531.63 per QALY gained.
- In people with an IOP≥25 mmHg and central corneal thickness high: > 590µm, beta-blockers dominated no treatment. PGA were not cost effective compared to BB producing an ICER of £80,924.14 per QALY gained.
- In people with an IOP≥25 mmHg, treating everyone with beta-blockers dominated not treating anyone. Measuring CCT and then treating with the most cost-effective treatment for each CCT subgroup was not cost effective compared to treating everyone with BB producing an ICER of £22,904.99 per QALY gained.

The results of a sensitivity analysis on the cost of PGA (SA7) found that the *generic* prostaglandin analogues (Latanoprost) dominated beta-blockers and no treatment for all categories of CCT for both the IOP low and IOP high population subgroups.

N.4.5 Implications for future research

This analysis has identified that there is a lack of evidence on the baseline risk of conversion to COAG for people with OHT who have an IOP below 24 mmHg and who have never had an IOP of above 24 mmHg on assessment. Although these people are clinically considered to have OHT, the historical threshold followed in practice is not sufficiently backed up by any strong evidence of risk. Therefore, evidence on the baseline risk of people with IOP between >21 and 24 mmHg would improve understanding in this area.

Having a better understanding of the relationship between treatment-related IOP reduction and reduction in probability of conversion to COAG (and subsequent progression of COAG) would also benefit future health economic research in this field.

Despite the limitations, the model still provides useful information on determining what treatment should be offered to people being treated for Ocular Hypertension. Unfortunately, the model could not determine a threshold of IOP at which treatment should be initiated. To answer this question, a different modelling approach would be needed requiring clinical data that compares the same treatments being initiated at different levels of IOP (for different groups) and that measures the health outcomes (rates of conversion) of the groups overtime. This type of analysis would provide evidence on the optimum treatment threshold.

Appendix O: Network meta-analysis: the effectiveness of beta-blockers and prostaglandin analogues in lowering intraocular pressure

O.1 Introduction

This network meta-analysis (NMA) was undertaken to estimate the effectiveness of prostaglandin analogues (PGAs) and beta-blockers (BBs) in lowering intraocular pressure (IOP) to prevent the conversion to chronic open-angle glaucoma (COAG) for people with ocular hypertension (OHT). The treatment effect data was needed to feed into the cost-effectiveness analysis undertaken to estimate the cost effectiveness of BB and PGA pharmacological treatments for people with OHT (please see Appendix N for details on the cost-effectiveness analysis). Initially, the NMA was conducted using the mean absolute change in IOP from baseline that each study reported. The committee noted that some of the studies in the base-case NMA were on populations of people with normal tension glaucoma and therefore the absolute change in IOP was reduced compared to a population with OHT or high-pressure glaucoma. A secondary analysis was then conducted reanalysing the data. For the secondary analysis, the percentage change in IOP from the study baselines were calculated. The percentage changes were then converted into absolute values assuming the baseline IOP was the average IOP in all the studies (24mmHg), including studies that did not meet the criteria for the base-case NMA.

For both the initial analysis and the secondary analysis, 2 sensitivity analyses SA1 and SA2 were undertaken relaxing the inclusion criteria for studies to be included in the NMAs.

O.2 Methods

O.2.1 Inclusion of studies in the NMA

From the systematic review on the pharmacological treatment question, we selected those studies that could inform the estimate of the direct and indirect effectiveness of treatments at reducing intraocular pressure (IOP) from baseline. The NMA focuses on treatment options for first-choice treatment (no treatment, BB and PGA) and therefore studies where pharmacological treatment was not used as first choice were only included in the NMA if they were indirectly informing the effectiveness of the 3 included strategies.

The criteria for inclusion in the NMA were:

- the study reported a change in IOP from baseline to follow-up (or this was estimable)
- the availability of 95% confidence interval or standard deviation (SD) or standard error for either IOP change or baseline and final IOP
- the people in the studies were either newly diagnosed or had a washout period of any previous treatment of at least 4 weeks.

The exclusion criteria were:

- the aim of the study was to assess the effectiveness of adjunctive therapy to the existing one
- the aim of the study was to assess the effectiveness of switching treatment or adding a new treatment if current treatment was suboptimal.

Studies where the washout period was at least 4 weeks for some drugs were included in a sensitivity analysis (SA1) together with the studies included in the base-case; studies where the washout period was a maximum of 3 weeks or had not been reported were included in another sensitivity analysis (SA2) together with all the studies included in SA1.

The list of all the studies included in the review and their inclusion or exclusion status are reported in Table 72 below.

Table 72: Clinical studies included in pharmacological treatment review

Study	Inclusion or exclusion status	Reasons for exclusion
ALM 1995	Only in sensitivity analysis 1 and 2	Less than 4 week washout period for some treatments
ANG 2008	Included	
AUNG 2014	Only in sensitivity analysis 1 and 2	Less than 4 week washout period for some treatments
BUCCI 1999	Excluded	People with uncontrolled IOP with current medication
CAMRAS 1996A	Only in sensitivity analysis 2	Washout period maximum 3 weeks
CAMRAS 2005	Only in sensitivity analysis 2	No study treatment one month before; other treatments washout not reported
EPSTEIN 1989	Excluded	IOP only reported in a graph
FELLMAN 2002	Excluded	No parameters available for NMA
FREZZOTTI 2014	Excluded	Intra-class comparison
FUCHSJAGER-MAYRL 2010	Excluded	Patients not responding to BB or CAI were excluded from the study
GARWAY-HEATH (UKGTS) 2015	Included	
GOLDBERG 2001	Excluded	No parameters available for NMA
HEIJL 2000	Excluded	No IOP outcome
HIGGINBOTHAM 2002A	Excluded	People with uncontrolled IOP with current medication
HOLLO 2014	Excluded	Intra-class comparison
KAMAL 2003	Only in sensitivity analysis 2	Washout period not reported
KAMPIK 2002	Excluded	People with uncontrolled IOP with current medication
KITAZAWA 1990	Excluded	No IOP outcome
KRUPIN 2011	Excluded	IOP was measured only in people reaching study end with no visual field progression
LEBLANC 1998	Only in sensitivity analysis 1 and 2	Less than 4 week washout period for some treatments
MANNI 2004	Excluded	People currently treated with BB
MARCH 2000	Excluded	No parameters available for NMA
MARTIN 2007	Only in sensitivity analysis 1 and 2	Less than 4 week washout period for some treatments
MASTROPASQUA 1999	Only in sensitivity analysis 2	Washout period maximum 3 weeks
MIGLIOR (EGPS) 2005	Only in sensitivity analysis 2	Washout period maximum 3 weeks
MILLS 1983	Excluded	Intra-class comparison

Study	Inclusion or exclusion status	Reasons for exclusion
NETLAND 2001	Excluded	No parameters available for NMA
ORENGO-NANIA 2001	Excluded	People with uncontrolled IOP with current medication
OZTURK 2007	Excluded	Would be included in sensitivity analyses 1 and 2 but treatments are not part of the NMA
PFEIFFER 2002	Excluded	People with uncontrolled IOP with current medication
POLO 2005	Excluded	People currently treated with BB
RISMANCHIAN 2008	Excluded	Would be included but the treatments are not part of the NMA
SCHULZER 1991	Only in sensitivity analysis 2	Exclude – washout period not reported
SCHUMAN 1997	Excluded	No parameters available for NMA
SCHWARTZ 1995	Included	
SHERWOOD 2006	Excluded	No IOP outcome
SIESKY 2010	Excluded	Patients in the study had an initial trial with BB
STRAHLMAN 1995	Only in sensitivity analysis 2	Washout period maximum 3 weeks
TOMITA 2004	Included	
TSAI 2005	Included	
VARMA 2010	Excluded	Outcome is change in IOP fluctuation
VETRUGNO 2004	Excluded	Study aim is to assess effect of PGA after initial reduction with BB
WATSON 2006	Only in sensitivity analysis 1 and 2	Less than 4 week washout period for some treatments
WHITSON 2013	Excluded	No IOP outcome

O.2.1.1 Data for the base-case analysis

In the base-case analysis, only studies strictly meeting the inclusion criteria were included; these are reported in the table below together with their estimates used for the NMA.

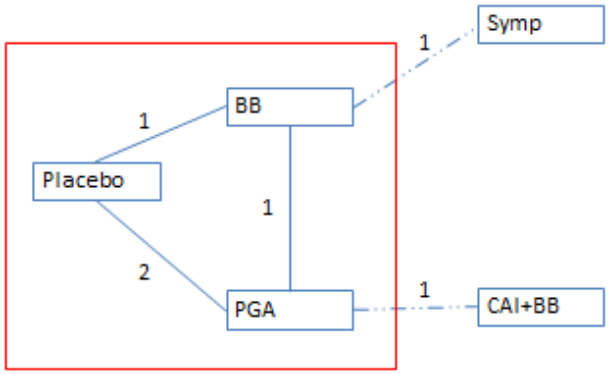
Table 73: Base-case analysis – studies included

Heading	Comparison	Follow up (a)	Population	Washout
Ang 2008	PGA versus placebo	6 months	Normal tension glaucoma, untreated	Not applicable (untreated patients)
Garway-Heath 2015	PGA versus placebo	24 months	Primary open-angle glaucoma, untreated	Not applicable (untreated patients)
Schwartz 1995	BB versus placebo	9 to 15 months	OHT, untreated	Not applicable (untreated patients)
Tomita 2004	BB versus PGA	36 months	Normal tension glaucoma	At least 4 weeks

(a) This is the follow up at which effectiveness data were extracted for the NMA; it does not represent the longest follow-up time of the study.

Two studies (Tsai 2005 and Rismanchian 2008) met the inclusion criteria but the treatments evaluated, BB versus Sympathomimetics and PGA versus CAI+BB, would not inform the effectiveness of the interventions of interest (that is, they were outside the loop), as shown in the picture below.

Figure 106: NMA diagram – base-case



The line connecting 2 interventions represents the availability of effectiveness data for that comparison and the number on the line represents the number of studies available. The dotted lines represent those comparisons that would not influence the effectiveness estimates of the main first choice treatment evaluated. Only the part inside the red box is included in the base-case analysis.

The estimates of effectiveness used for the NMA are reported in the table below. The data are reported as mean changes in IOP from baseline, together with the standard errors.

Table 74: Base-case – NMA data

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Tomita 2004	BB	PGA	1.9 (0.4)	2.1 (0.4)
Schwartz 1995	BB	Placebo	4.4 (1.0)	0.05 (1.2)
Ang 2008	PGA	Placebo	2.5 (0.5)	0.1 (0.5)
Garway-Heath 2015	PGA	Placebo	3.8 (0.2)	0.9 (0.2)

If studies reported more than 1 effectiveness estimate, for example, if treatments were assessed at different times of the day or more than 1 drug within the same class were included in the analysis, an average of the available effectiveness values was used.

O.2.1.2 Data for sensitivity analysis 1

In this sensitivity analysis, studies were included if the washout period was at least of 4 weeks for some drugs. The list of studies included in this analysis is reported in the table below. Outcomes were extracted at 6 months in all the studies; if data were not available at 6 months, the closest follow-up time available was used if this was after 6 months.

Table 75: Sensitivity analysis 1 – studies included

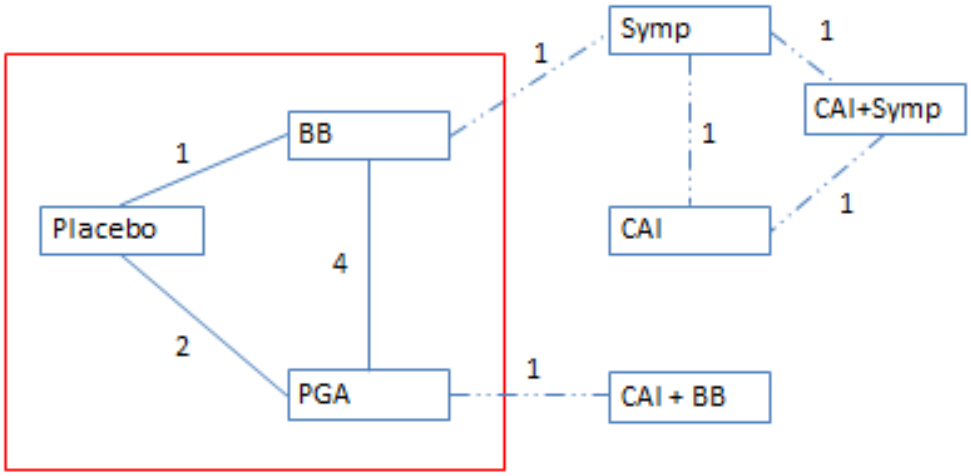
Heading	Comparison	Follow up (a)	Population	Washout
Alm 1995	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	2 weeks for adrenergic

Heading	Comparison	Follow up (a)	Population	Washout
				agonists, 5 days pilocarpine or CAI; 6 months for BB
Ang 2008	PGA versus placebo	6 months	Normal tension glaucoma, untreated	Not applicable (untreated patients)
Garway-Heath 2015	PGA versus placebo	24 months	Primary open-angle glaucoma, untreated	Not applicable (untreated patients)
Leblanc 1998	BB versus sympathomimetics	12 months	Primary open-angle glaucoma or OHT	4 days for pilocarpine or CAI,2 weeks alpha agonists, 4 weeks BB
Martin 2007	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	1 week for CAI, 3 weeks alpha agonists. 4 weeks BB, 6 weeks PGA
Schwartz 1995	BB versus placebo	9 to 15 months	OHT, untreated	Not applicable (untreated patients)
Tomita 2004	BB versus PGA	36 months	Normal tension glaucoma	At least 4 weeks
Watson 2006	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors; 6 months for BB

(a) This is the follow up at which effectiveness data were extracted for the NMA; it does not represent the longest follow-up time of the study.

Four studies (Aung 2014, Ozturk 2007, Tsai 2005 and Rismanchian 2008) met the inclusion criteria but the treatments evaluated (CAI versus sympathomimetics versus CAI+ sympathomimetics; PGA versus CAI+BB; BB versus sympathomimetics), would not inform the effectiveness of the interventions of interest (that is, they are outside the loop), as shown in the picture below.

Figure 107: NMA diagram – SA1



The estimates of effectiveness used for the NMA-SA1 are reported in the table below. The data are reported as mean change in IOP from baseline together with the standard error.

Table 76: SA1 – NMA data

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Alm 1995	BB	PGA	6.7 (0.4)	8.20 (0.5)
Martin 2007	BB	PGA	7.5 (0.5)	10.6 (0.6)
Tomita 2004	BB	PGA	1.9 (0.4)	2.1 (0.4)
Watson 2006	BB	PGA	8.30 (0.4)	8.50 (0.2)
Schwartz 1995	BB	Placebo	4.4 (1.0)	0.05 (1.2)
Ang 2008	PGA	Placebo	2.5 (0.5)	0.1 (0.5)
Garway-Heath 2015	PGA	Placebo	3.8 (0.2)	0.9 (0.2)

O.2.1.3 Data for sensitivity analysis 2

In this sensitivity analysis, studies were included if the washout period was at least 3 weeks for some drugs or not reported. The list of studies included in this analysis is reported in the table below.

Table 77: Sensitivity analysis 2 – studies included

Heading	Comparison	Follow up (a)	Population	Washout
Alm 1995	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	2 weeks for adrenergic agonists, 5 days pilocarpine or CAI; 6 months for BB
Ang 2008	PGA versus placebo	6 months	Normal tension glaucoma,	Not applicable (untreated people)

Heading	Comparison	Follow up (a)	Population	Washout
			untreated	
Aung 2014	Symp versus CAI	6 months	Primary open-angle glaucoma or OHT	5 days miotics and CAI, 14 days for alpha or beta agonists, 4 weeks beta antagonists, PGA and combinations
Camras 1996	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	3 weeks for beta-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or CAI
Camras 2005	PGA versus symp	6 months	Primary open-angle glaucoma or OHT	Not reported
Garway-Heath 2015	PGA versus placebo	24 months	Primary open-angle glaucoma, untreated	Not applicable (untreated people)
Kamal 2003	BB versus placebo	5 years	OHT	Not reported
Leblanc 1998	BB versus sympathomimetics	12 months	Primary open-angle glaucoma or OHT	4 days for pilocarpine or CAI,2 weeks alpha agonists, 4 weeks BB
Martin 2007	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	1 week for CAI, 3 weeks alpha agonists. 4 weeks BB, 6 weeks PGA
Mastropasqua 1999	BB versus PGA	6 months	Pigmentary glaucoma	3 weeks for beta-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or CAI
Miglior 2005	Placebo versus CAI	6 months	OHT	3 weeks
Schulzer 1991	BB versus placebo	unclear	OHT	Not reported
Schwartz 1995	BB versus placebo	9 to 15 months	OHT, untreated	Not applicable (untreated people)
Strahlman 1995	BB versus CAI	6 months	Primary open-angle glaucoma or OHT	3 days for muscarinic agonists, 1 week adrenergic agonists, 3 weeks beta-adrenoceptor antagonists, CAI

Heading	Comparison	Follow up (a)	Population	Washout
				and alpha-adrenoceptor agonists
Tomita 2004	BB versus PGA	36 months	Normal tension glaucoma	At least 4 weeks
Tsai 2005	BB versus symp	6 months	Primary open-angle glaucoma, newly diagnosed	At least 4 weeks
Watson 2006	BB versus PGA	6 months	Primary open-angle glaucoma or OHT	2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors; 6 months for BB

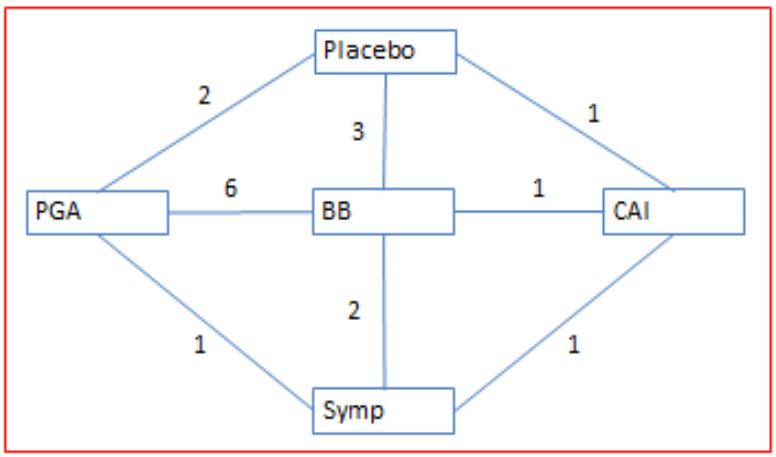
(a) This is the follow up at which effectiveness data were extracted for the NMA; it does not represent he longest follow-up time of the study.

Some of the studies that would have had been included in the base-case, but their comparators were outside the main loop, are now included in this analysis as their data would contribute to estimating the effectiveness of the interventions under evaluation (BB, PGA and placebo).

However, the studies by Ozturk 2007 and Rismanchian 2008 (comparing PGA versus CAI+BB) are still outside the loop; similarly 1 of the interventions compared in the included study Aung 2014 (CAI+Symp) does not influence the other part of the NMA and it is excluded from the analysis, while the other 2 arms of the study are included.

The NMA diagram for this analysis is reported in the figure below.

Figure 108: NMA diagram – SA2



The estimates of effectiveness used for the NMA-SA2 are reported in the table below. The data are reported as mean change in IOP from baseline together with the standard error.

Table 78: SA2 – NMA data

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Alm 1995	BB	PGA	6.7 (0.4)	8.2 (0.5)
Camras 1996	BB	PGA	4.9 (0.2)	6.7 (0.3)
Martin 2007	BB	PGA	7.5 (0.5)	10.6 (0.6)
Mastropasqua 1999	BB	PGA	4.8 (0.7)	6.0 (1.1)
Tomita 2004	BB	PGA	1.9 (0.4)	2.1 (0.4)
Watson 2006	BB	PGA	8.3 (0.4)	8.5 (0.2)
Kamal 2003	BB	Placebo	4.7 (0.2)	1.9 (0.2)
Schulzer 1991	BB	Placebo	4.5 (0.5)	-0.2 (0.4)
Schwartz 1995	BB	Placebo	4.4 (1.0)	0.05 (1.2)
Leblanc 1998	BB	Symp	5.9 (0.4)	5.4 (0.4)
Tsai 2005	BB	Symp	5.5 (0.2)	5.8 (0.1)
Strahlman 1995	BB	CAI	5.8 (0.3)	5.2 (0.2)
Ang 2008	PGA	Placebo	2.5 (0.5)	0.1 (0.5)
Garway-Heath 2015	PGA	Placebo	3.8 (0.2)	0.9 (0.2)
Camras 2005	PGA	Symp	5.8 (0.4)	3.3 (0.4)
Miglior 2005	Placebo	CAI	2.2 (0.2)	3.4 (0.1)
Aung 2014	Symp	CAI	6.9 (0.3)	7.0 (0.4)

O.2.1.4 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS. We adapted fixed-effects and random-effects code from the NICE Decision Support Unit (http://www.nicedsu.org.uk/evidence-synthesis-tsd-series(2391675).htm). This model accounts for the correlation between study-level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome subgroup, a diagram of the evidence network was presented above.

Both random-effects and fixed-effects logistic regression models were used, with parameters estimated by Markov chain Monte Carlo simulation. For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

For each analysis, the deviance information criterion (DIC) was used to estimate the relative fit of the random-effects and fixed-effects models. If the difference in DIC between the fixed-effects and random-effects models indicated that there was no important difference between the 2 (the difference was < 3), then the fixed-effects model was used. If the difference between the DIC was greater than 5, then only the random-effects model was considered, and if the difference was between 3 and 5, then both models were considered. A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another.

Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. This heterogeneity is a problem for network meta-analysis but may

be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the treatment effects from the direct evidence (from pair-wise meta-analysis) to the treatment effects from the combined direct and indirect evidence (from NMA). We concluded that the evidence was inconsistent if the mean treatment effect from the NMA did not fit within the 95% confidence interval of the treatment effect from the direct comparison.

O.2.2 Results – base-case

Table 79: Results – base-case

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random-effect model			
PGA versus BB	-0.2 (1.48)		
BB versus placebo	-3.2 (1.57)		
PGA versus placebo	-2.9 (1.15)		
			17.4
Fixed-effect model			
PGA versus BB	0 (0.54)		
BB versus placebo	-2.9 (0.60)		
PGA versus placebo	-2.9 (0.29)		
			16.1

The difference in the deviance information criterion (DIC) between the random-effect and the fixed-effect model indicates no important difference between the 2, and therefore the fixed-effect model should be used.

O.2.3 Results – SA1

Table 80: Results – SA1

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random-effect model			
PGA versus BB	-0.9 (0.81)		
BB versus placebo	-2.3 (1.22)		
PGA versus placebo	-3.2 (1.07)		
			31.0
Fixed-effect model			
PGA versus BB	-0.8 (0.28)		
BB versus placebo	-2.1 (0.38)		
PGA versus placebo	-2.9 (0.26)		
			35.9

The difference in the deviance information criterion (DIC) between the random-effect and the fixed-effect model is between 3 and 5; for this reason, both models should be considered for the analysis.

We ran an inconsistency model and compared it with the random-effect model; the DIC difference was still >5 which suggested there is inconsistency.

O.2.4 Results – SA2

Table 81: Results – SA2

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random-effect model			
PGA versus BB	-1.1 (0.45)		
BB versus placebo	-2.6 (0.56)		
PGA versus placebo	-3.7 (0.59)		
			56.2
Fixed-effect model			
PGA versus BB	-1.1 (0.18)		
BB versus placebo	-2.3 (0.18)		
PGA versus placebo	-3.4 (0.20)		
			88.1

The difference in the DIC between the random effect and the fixed effect is more than 5; therefore, only the random effect could be considered. However, due to the inconsistency in the model its results should not be used in any analysis.

O.2.5 Second analysis – using a percentage change from baseline and anchoring it to a baseline average IOP

The committee noted that some of the studies in the base-case were on people with normal tension glaucoma and therefore the absolute change in IOP was reduced compared to a population with OHT or high-pressure glaucoma.

We reanalysed the data in the following way:

1. We calculated the percentage change in IOP from the study baseline.
2. We converted the percentage change into an absolute value assuming the baseline IOP was the average IOP in all the studies, including those added only in SA2; this was 24 mmHg.
3. We used the SD from the original values also for the recalculated changes.

O.2.5.1 Data for base-case analysis (% change)

The estimates of effectiveness used for the base-case NMA are reported in the table below.

Table 82: Base-case – NMA data (% change)

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Tomita 2004	BB	PGA	2.9 (0.4)	3.4 (0.4)
Schwartz 1995	BB	Placebo	4.6 (1.0)	0.1 (1.2)
Ang 2008	PGA	Placebo	4.0 (0.5)	0.2 (0.5)
Garway-Heath 2015	PGA	Placebo	4.7 (0.2)	1.1 (0.2)

O.2.5.2 Data for SA1 (% change)

The estimates of effectiveness used for SA1 are reported in the table below.

Table 83: SA1 – NMA data (% change)

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Alm 1995	BB	PGA	6.5 (0.4)	7.8 (0.5)
Martin 2007	BB	PGA	7.5 (0.5)	10.6 (0.6)
Tomita 2004	BB	PGA	2.9 (0.4)	3.4 (0.4)
Watson 2006	BB	PGA	7.8 (0.4)	8.1 (0.2)
Schwartz 1995	BB	Placebo	4.6 (1.0)	0.1 (1.2)
Ang 2008	PGA	Placebo	4.0 (0.5)	0.2 (0.5)
Garway-Heath 2015	PGA	Placebo	4.7 (0.2)	1.1 (0.2)

O.2.5.3 Data for SA2 (% change)

The estimates of effectiveness used for SA2 are reported in the table below.

Table 84: SA2 – NMA data (% change)

Study	Intervention1	Intervention 2	Mean (SE) Intervention 1	Mean (SE) Intervention 2
Alm 1995	BB	PGA	6.5 (0.4)	7.8 (0.5)
Camras 1996	BB	PGA	4.8 (0.2)	6.5 (0.3)
Martin 2007	BB	PGA	7.5 (0.5)	10.6 (0.6)
Mastropasqua 1999	BB	PGA	4.8 (0.7)	5.9 (1.1)
Tomita 2004	BB	PGA	2.9 (0.4)	3.4 (0.4)
Watson 2006	BB	PGA	7.8 (0.4)	8.1 (0.2)
Kamal 2003	BB	Placebo	4.3 (0.2)	1.8 (0.2)
Schulzer 1991	BB	Placebo	4.1 (0.5)	-0.2 (0.4)
Schwartz 1995	BB	Placebo	4.6 (1.0)	0.1 (1.2)
Leblanc 1998	BB	Symp	5.7 (0.4)	5.1 (0.4)
Tsai 2005	BB	Symp	5.5 (0.2)	5.8 (0.1)
Strahlman 1995	BB	CAI	5.4 (0.3)	4.9 (0.2)
Ang 2008	PGA	Placebo	4.0 (0.5)	0.2 (0.5)
Garway-Heath 2015	PGA	Placebo	4.7 (0.2)	1.1 (0.2)
Camras 2005	PGA	Symp	5.7 (0.4)	3.2 (0.4)
Miglior 2005	Placebo	CAI	2.2 (0.2)	3.5 (0.1)
Aung 2014	Symp	CAI	6.4 (0.3)	6.5 (0.4)

O.2.6 Results – base-case (% change)

Table 85: Results – base-case (% change)

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random-effect model			
PGA versus BB	-0.2 (1.37)		
BB versus placebo	-3.6 (1.45)		
PGA versus placebo	-3.8 (1.06)		
			16.8

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Fixed-effect model			
PGA versus BB	-0.3 (0.54)		
BB versus placebo	-3.3 (0.59)		
PGA versus placebo	-3.6 (0.29)		
			15.2

The difference in the deviance information criterion (DIC) between the random-effect and the fixed-effect model indicates no important difference between the 2, and therefore the fixed-effect model should be used for the analysis.

O.2.7 Results – SA1 (% change)

Table 86: Results – SA1 (% change)

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random-effect model			
PGA versus BB	-1.0 (0.70)		
BB versus placebo	-3.0 (1.06)		
PGA versus placebo	-4.0 (0.92)		
			30.4
Fixed-effect model			
PGA versus BB	-0.9 (0.28)		
BB versus placebo	-2.8 (0.38)		
PGA versus placebo	-3.7 (0.26		
			32.5

The difference in the deviance information criterion (DIC) between the random-effect and the fixed-effect model is less than 3; for this reason, the fixed-effect model should be considered for the analysis.

We ran an inconsistency model and compared it with the random-effect model; the DIC difference was less than 5, which suggested there is not significant inconsistency.

O.2.8 Results – SA2

Table 87: Results – SA2

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
Random effect model			
PGA versus BB	-1.3 (0.36)		
BB versus placebo	-2.7 (0.45)		
PGA versus placebo	-4.0 (0.47)		
			54.9
Fixed effect model			
PGA versus BB	-1.3 (0.18)		
BB versus placebo	-2.4 (0.18)		

Comparison	Mean effect (SD) – reduction in IOP from baseline		DIC
PGA versus placebo	-3.7 (0.20)		
			69.9

The difference in the DIC between the random-effect and the fixed-effect is more than 5; therefore, only the random effect could be considered. However, due to inconsistency in the model, its results should not be used in any analysis.

O.3 Discussion

This Network Meta-Analysis was undertaken to estimate the treatment effect of beta-blockers and prostaglandin analogues at reducing intraocular pressure to in turn reduce the probability of conversion from ocular hypertension (OHT) to chronic open-angle glaucoma (COAG) or reduce the rate of progression through the COAG stages to severe visual impairment.

Initially the analysis was undertaken using the absolute unit reduction in IOP from baseline that the studies reported. However, as some of the studies included in the NMA came from normal-tension glaucoma populations, the secondary analysis was undertaken using the percentage reduction in IOP from baseline and then anchoring this to the average IOP of the studies (even if only included in the sensitivity analysis), and IOP of 24mmHg.

The fact that some of the studies are in a normal-tension glaucoma population is a limitation of the results of the NMA. Reduction in IOP is only a surrogate outcome for the reduction in probability of conversion or progression. It is estimated that a unit reduction in IOP is equivalent to a ten per cent decrease in probability of conversion to COAG in an OHT population. However, with normal-tension glaucoma, it is likely that the glaucoma is caused by something other than raised IOP; therefore, reducing IOP is not likely to have the same effect in reducing progression as it does in people with glaucoma caused by raised pressure. It could also be argued that as the studies are only measuring the surrogate outcome (the abilities of the pharmacological treatments in reducing IOP), studies on normal-tension glaucoma populations still provide valuable information on the effectiveness of the treatments. Despite this limitation, the committee felt confident in the base-case results of the secondary analysis of the NMA.

The committee decided to use the results of the base-case of the secondary analysis as the treatment effects for beta-blockers and prostaglandin analogues feeding in to the cost-effectiveness analysis undertaken for this guideline update. The results of SA1 were used in a sensitivity analysis of the model; however, the committee agreed that relaxing the inclusion criteria also reduced the confidence they had in the results of SA1, compared to the base-case analysis.

O.4 Conclusions

- The base-case result of the secondary analysis estimate that prostaglandin analogues have a mean treatment effect of reducing IOP by 3.6 mmHg units from baseline.
- The base-case results of the secondary analysis estimate that beta-blockers have a mean treatment effect of reducing IOP by 3.3mmHg units from baseline.
- Prostaglandin analogues are more effective than beta-blockers at reducing IOP.

O.5 NMA Codes

Base-case – fixed effects

```
# Normal likelihood, identity link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
           rk[k]<-nt+1-rank(d[],k)
best[k]<-equals(nt+1-rank(d[],k),1)}

d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise treatment effects
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  D[c,k] <- d[k] - d[c]
             }
         }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                               # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=4, nt=3, meanA=3, precA=4)
```

t[,1]	t[,2]	y[,1]	y[,2]	se[,1]	se[,2]	na[]
2	3	2.5	0.1	0.478819094	0.451041279	2
2	3	3.8	0.9	0.223703576	0.23737697	2
1	3	4.4	0.05	0.970978888	1.222957481	2

```
1        2        1.9      2.1      0.389743505   0.42207246    2
END

 Initial Values
#chain 1
list(d=c( NA, 0,0), mu=c(0, 0, 0, 0))
#chain 2
list(d=c( NA, -1,-3), mu=c(-3, -3, -3, -3))
#chain 3
list(d=c( NA, 2,2), mu=c(-3, 5, -1, -3))
```

SA1 fixed effects

```
# Normal likelihood, identity link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
            rk[k]<-nt+1-rank(d[],k)
best[k]<-equals(nt+1-rank(d[],k),1)}

d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise treatment effects
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  D[c,k] <- d[k] - d[c]
             }
         }
# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
```

```
for (k in 1:nt) { T[k] <- A + d[k]  }
}                              # *** PROGRAM ENDS
```

Data

```
# ns= number of studies; nt=number of treatments
list(ns=4, nt=3, meanA=3, precA=4)
```

t[,1]	t[,2]	y[,1]	y[,2]	se[,1]	se[,2]	na[]
2	3	2.5	0.1	0.478819094	0.451041279	2
2	3	3.8	0.9	0.223703576	0.23737697	2
1	3	4.4	0.05	0.970978888	1.222957481	2
1	2	1.9	2.1	0.389743505	0.42207246	2

END

Initial Values

```
#chain 1
list(d=c( NA, 0,0), mu=c(0, 0, 0, 0))
#chain 2
list(d=c( NA, -1,-3), mu=c(-3, -3, -3, -3))
#chain 3
list(d=c( NA, 2,2), mu=c(-3, 5, -1, -3))
```

SA1 random effects

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
      theta[i,k] <- mu[i] + delta[i,k]  # model for linear predictor
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
```

```
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
            rk[k]<-nt+1-rank(d[],k)
best[k]<-equals(nt+1-rank(d[],k),1)}

d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)

# pairwise treatment effects
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  D[c,k] <- d[k] - d[c]
             }
         }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                              # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=7, nt=3, meanA=4, precA=4)
t[,1]     t[,2]     y[,1]     y[,2]     se[,1]    se[,2]    na[]
1         2         6.70      8.20      0.4       0.5       2
2         3         2.50      0.10      0.5       0.5       2
2         3         3.80      0.90      0.2       0.2       2
1         2         7.50      10.60     0.5       0.6       2
1         3         4.40      0.05      1.0       1.2       2
1         2         1.90      2.10      0.4       0.4       2
1         2         8.30      8.50      0.4       0.2       2
END

 Initial Values
#chain 1
list(d=c( NA, 0,0), sd=1, mu=c(0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c( NA, -1,-3), sd=4, mu=c(-3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c( NA, 2,2), sd=2, mu=c(-3, 5, -1, -3, -3, 5, -1))
```

Secondary analysis base-case – fixed effects

```
# Normal likelihood, identity link
```

```
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
           rk[k]<-nt+1-rank(d[],k)
best[k]<-equals(nt+1-rank(d[],k),1)}

d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise treatment effects
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  D[c,k] <- d[k] - d[c]
             }
         }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                               # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=4, nt=3, meanA=3, precA=4)
t[,1]     t[,2]     y[,1]     y[,2]     se[,1]    se[,2]    na[]
2         3         4.0       0.2       0.48      0.45      2
2         3         4.7       1.1       0.22      0.24      2
1         3         4.6       0.1       0.97      1.22      2
1         2         2.9       3.4       0.39      0.42      2
END

Initial Values
#chain 1
```

```
list(d=c( NA, 0,0), mu=c(0, 0, 0, 0))
#chain 2
list(d=c( NA, -1,-3), mu=c(-3, -3, -3, -3))
#chain 3
list(d=c( NA, 2,2), mu=c(-3, 5, -1, -3))
```

Secondary analysis SA1 – fixed effects

```
# Normal likelihood, identity link
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                  #   LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            #  LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)   # calculate variances
      prec[i,k] <- 1/var[i,k]      # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k]) # binomial likelihood
# model for linear predictor
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]]
#Deviance contribution
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]
    }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
totresdev <- sum(resdev[])          #Total Residual Deviance

# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
            rk[k]<-nt+1-rank(d[],k)
best[k]<-equals(nt+1-rank(d[],k),1)}

d[1]<-0      # treatment effect is zero for control arm
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }

# pairwise treatment effects
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  D[c,k] <- d[k] - d[c]
             }
         }

# Provide estimates of treatment effects T[k] on the natural scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { T[k] <- A + d[k]  }
}                               # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=7, nt=3, meanA=4, precA=4)
```

t[,1]	t[,2]	y[,1]	y[,2]	se[,1]	se[,2]	na[]
1	2	6.5	7.8	0.4	0.5	2
2	3	4.0	0.2	0.5	0.5	2
2	3	4.7	1.1	0.2	0.2	2
1	2	7.5	10.6	0.5	0.6	2
1	3	4.6	0.1	1.0	1.2	2
1	2	2.9	3.4	0.4	0.4	2
1	2	7.8	8.1	0.4	0.2	2

END

Initial Values

```
#chain 1
list(d=c( NA, 0,0), mu=c(0, 0, 0, 0, 0, 0, 0))
#chain 2
list(d=c( NA, -1,-3), mu=c(-3, -3, -3, -3, -3, -3, -3))
#chain 3
list(d=c( NA, 2,2), mu=c(-3, 5, -1, -3, -3, 5, -1))
```

Appendix P: CG85 Cost-effective analysis

P.1 NCC-AC model: Cost-effectiveness of treatment

Please refer only to the COAG model in this Appendix. For information on the OHT model, please see Appendix N.

Our aim in constructing the model was to determine the most cost-effective strategy in managing OHT and COAG patients from the point of diagnosis.

We found a number of economic evaluations in the published literature (Chapters 7 and 8 in Appendix U) but still it was necessary to develop our own analysis to determine the most cost-effective treatment strategy for different subgroups of patients. We took this approach because we found limited applicability in the published economic evaluations, mainly because the important long-term consequences (i.e. development of blindness) were ignored[6], drugs were lumped together in a single medical treatment group[6],[360],[636], or important alternatives such as surgery were not considered[370]. Furthermore most of the published studies did not evaluate cost-effectiveness using the NICE reference case[6],[370].

The medical interventions we compared in the model are those which are licensed to be used as first-line treatments (beta-blockers and prostaglandin analogues). For COAG patients, trabeculectomy was compared to beta-blockers and prostaglandin analogues.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- We followed the methods of the NICE reference case[486]. Therefore costs were calculated from a health services perspective. Health gain was measured in terms of quality-adjusted life-years (QALYs) gained. Both future costs and QALYs were discounted at 3.5%.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained.

P.1.1 General method

Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover. The model is thus represented by a Markov model where patients cannot go back to previous stages. The cycle length was set at 2 months as this was thought to be the minimum time after which a change in treatment could occur. All the probabilities, costs and health utilities were converted in order to reflect the two-month values.

When defining the COAG stages we have used an adapted version of the Hodapp, Parrish and Anderson classification (Table 88). We have opted for this staging system as it allows us to use costs and utility values associated with different severity levels of COAG already present in the literature (see P.1.1.10 and P.1.1.13). It was also used in previous glaucoma economic models[89, 360] and in the selected sources of probability of progression[89].

Compared to the original staging system, we have collapsed the last two stages (severe COAG and blindness) as there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe COAG to blindness.

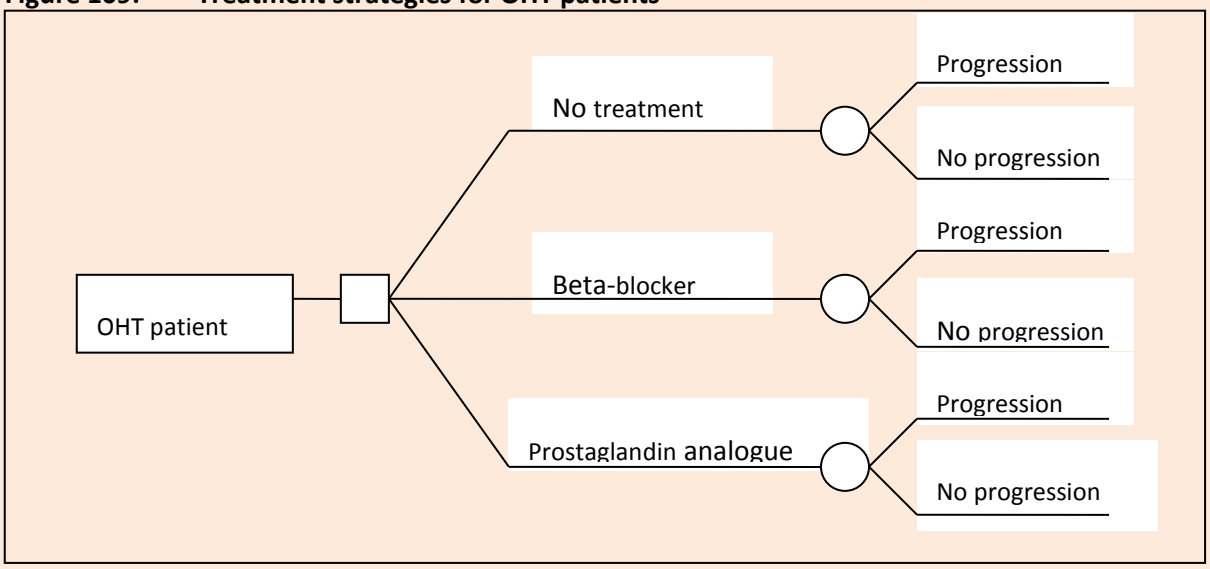
Table 88: Staging classification in the model

COAG STAGE	MEAN DEFECT SCORE
No COAG (a)	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00
Severe Visual Impairment	-20.01 or worse

(a) Includes OHT patients

Patients diagnosed with OHT could be initially treated with a beta-blocker or a prostaglandin analogue or could be offered no treatment until they develop COAG (Figure 109).

Figure 109: Treatment strategies for OHT patients



Patients diagnosed with COAG could be treated with a beta-blocker, a prostaglandin analogue, or trabeculectomy or could be offered no treatment until they progress to the following COAG stage (Figure 110). In the base case scenario patients were diagnosed with early COAG but in the sensitivity analysis we varied this assumption.

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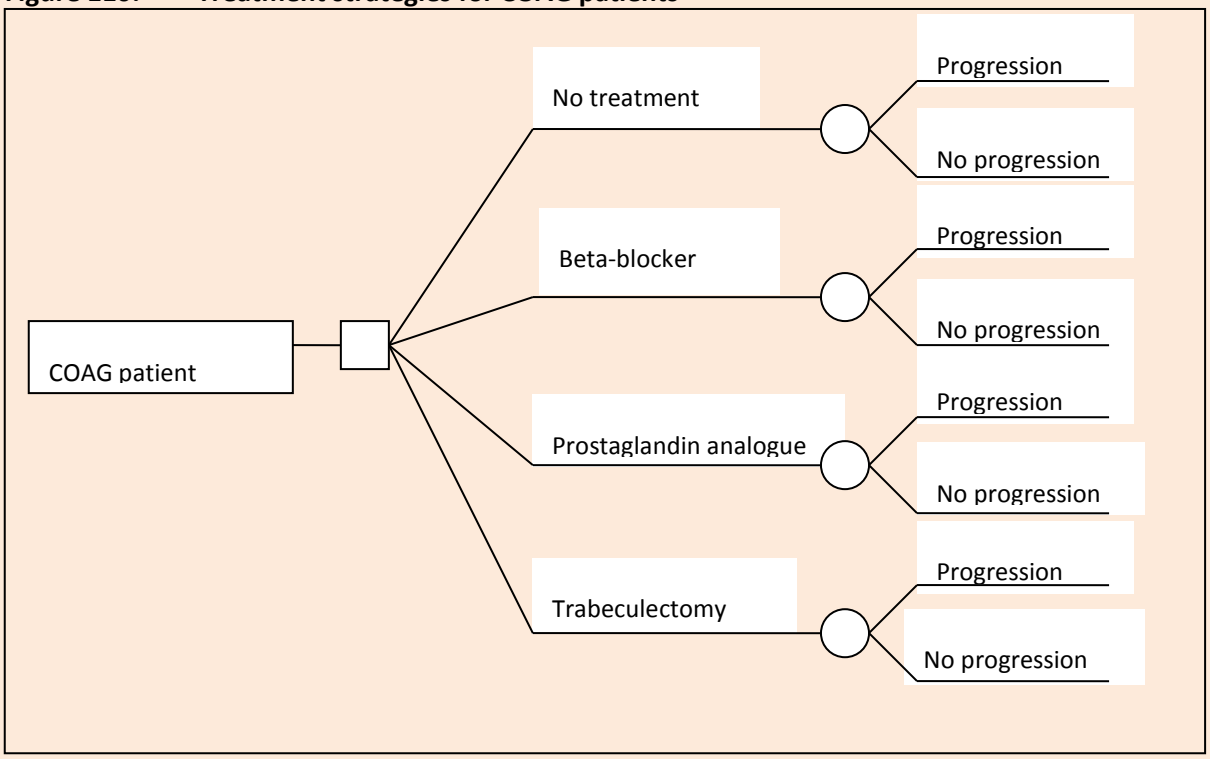
Figure 110: Treatment strategies for COAG patients



The main effect of each strategy was considered to be the increase/decrease in risk of progression to the following COAG stages. However, in the literature the most commonly reported treatment outcome is the change in intraocular pressure (IOP). Two further systematic searches were conducted: one to find the Relative Risk (RR) of progression in OHT and in patients with COAG for each unit of IOP reduction (P.1.1.6), and the other one to find data on probability of progression from one stage to the next in both untreated and treated patients (P.1.1.4).

Each strategy is associated with upstream and downstream costs: the former are costs associated with the specific treatment while the latter are costs associated with the severity of the disease and thus dependent on the progression to later stages.

Some treatments could cause adverse events (see Chapters 7 and 8 in Appendix U). Nevertheless not all of them result in important increased costs or reduced quality of life. We selected those more likely to occur and with a considerable impact on costs and quality of life using national sources[178] and expert opinion. Cataract and flat anterior chamber were the complications associated with trabeculectomy, while asthma was the only complication associated with beta-blockers for which incidence and annual cost per patient could be estimated. Other minor adverse events not requiring medical treatment are accounted for in the case of a change of COAG therapy.

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each COAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken.

We performed a probabilistic sensitivity analysis (PSA) to test the robustness of the results against the imprecision of these estimates and the other model parameters, and to obtain more accurate estimates of expected costs and QALYs.

In the base case of the OHT model, patients are 60 years old. However, from the review on risk of progression (see P.1.1.4) we know that age is a significant risk factor for development of COAG. For this reason, we conducted a one-way sensitivity analysis on the age at decision point.

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P.1.1.1 Time horizon

We considered the cost of treatment and health effects during a lifetime.

P.1.1.2 Key assumptions

In both COAG and OHT models the following assumptions were made:

4. In the absence of treatment, the change in IOP is equal to 0.
5. The change in IOP due to a treatment does not depend on whether the patient has COAG or OHT.
6. A patient starting with a prostaglandin analogue who demonstrates intolerance to this drug is switched to a beta-blocker.
7. A patient starting with a beta-blocker who demonstrates intolerance to this drug (including development of asthma) is switched to a prostaglandin analogue.
8. After a first switch in treatment, a second one can occur only after progression and thus its cost is included in the downstream cost of the stage.
9. When used after a treatment switch, beta-blockers and prostaglandin analogues have the same IOP lowering effect as when they are used as a first-choice treatment.
10. The severity of the condition is similar in both eyes of a patient.

In the COAG model the following assumptions were made:

1. In the base case the average age of patients at the beginning of the model is 72 years, as this was the mean age of COAG patients in the UK[666].
2. Patients are reviewed every three months.
3. The surgical procedure is trabeculectomy with or without enhancement.
4. Trabeculectomy is performed first in one eye then in the other after 2 months.
5. If post-surgery complications occur, the patient is treated appropriately and trabeculectomy is performed on the second eye if this has not already been done.

In the OHT model the following assumptions were made:

1. In the base case the average age of patients at the beginning of the model is 60 years, being the mid-point of the range 40-80 for which data on progression is available.
2. Untreated patients are reviewed on average every six months.
3. Treated patients are reviewed on average every three months.

P.1.1.3 Software

The cost-effectiveness analysis was conducted using TreeAge Pro 2007.

P.1.1.4 Baseline probability of progression

A search was conducted to identify papers looking at progression in OHT and COAG. We selected papers which reported the probability for one or more of the following progressions:

- from OHT to COAG in untreated patients
- from Early to Moderate COAG in treated and untreated patients
- from Moderate to Advanced COAG in treated and untreated patients
- from Advanced COAG to Severe Visual Impairment in treated and untreated patients

Only studies using a definite staging system and published after 1998 were included since it was GDG opinion that before that time the detection of COAG was not accurate. We found three studies in total matching our inclusion criteria:

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Lee et al (2006)[380] is a retrospective cohort study where patients in OHT and COAG stages were followed up for 5 years to detect progression. It was excluded due to its small sample size (on average 25 patients in each stage) and short follow-up.

A cost-effectiveness study[360] reported the annual risk of developing COAG in untreated OHT patients based on the results of the Ocular Hypertension Treatment Study[240], a multicentre RCT with 1636 participants randomised to either treatment or no treatment and followed-up for a mean of 6 years. In addition to the estimate of probability of progression in the absence of treatment, the study[240] calculated the hazard ratio of each clinical parameter for developing COAG through a multivariate Cox proportional hazards model.

A Health Technology Assessment (HTA)[89] estimated the progression rates by COAG stage defined as mild, moderate and severe COAG, corresponding to our definitions of early, moderate and advanced COAG. The approach adopted was to use RCTs of treatment compared to control to calculate the progression rate by visual field mean defect. Since no RCT was found for the severe stage, its progression was projected from the previous stages.

Table 89 summarises the studies selected and their results.

Table 89: Baseline probability of progressions

	Annual Probability Of Progression In Treated Patients	Annual Probability Of Progression In Untreated Patients	Source
OHT to COAG	-	2.2% (a)	Ocular Hypertension Treatment Study[240],[360]
Early to Moderate COAG	20%	25%	HTA – Burr (2007)[89]
Moderate to Advanced COAG	7%	11%	HTA – Burr (2007)[89]
Advanced COAG to Severe Visual Impairment	6%	10%	HTA – Burr (2007)[89]

(a) Average value. See Table 90and Table 91 for all the combinations of risk factors.

The calculation of the probability of conversion from OHT to COAG was based on different combinations of those parameters that resulted in significant risk factors for the progression from OHT to COAG. Following the exclusion of pattern standard deviation and cup-disc ratio since they are already clinical signs of COAG, the significant risk factors identified were age, IOP and central corneal thickness (CCT). First, we inputted the probability of progression for each age group in the model (Table 90), and then we multiplied this by the RR resulting from the combination of IOP and CCT (Table 91) as follows:

$$\mathbf{IV} \quad pCOAG = pCOAG[age] \times RR$$

Table 90: Probability of developing COAG in OHT patients (a)

Age group	Annual probability of progression in untreated patients
40-49 years	1.50%
50-59 years	1.90%
60-69 years	2.27%

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70-80 years	2.69%

(a) *Source: Kymes et al (2006)*[360]

Table 91: Relative risk for progression to COAG in OHT patients (a)

IOP	CCT	RR
>21 – 25 mmHg	>590 µm	0.16
>25 – 32 mmHg	>590 µm	0.49
>21 – 25 mmHg	555-590 µm	0.73
>25 – 32 mmHg	555-590 µm	1.06
>21 – 25 mmHg	≤555 µm	1.39
>25 – 32 mmHg	≤555 µm	2.93

(a) *Source: Gordon et al (2002)*[240]

The original IOP categories reported in the study[240] were IOP >21- 23.75 mmHg, IOP 23.75-25.75 mmHg, and IOP 25.75 - 32 mmHg. The GDG felt that keeping the middle group was clinically meaningless as the range limits are so close; therefore we incorporated this group into the two remaining groups IOP >21 – 25 mmHg and IOP >25 – 32 mmHg. The CCT categories in the study were CCT>588µm, CCT 555-588 µm, and CCT≤555 µm, which for clinical simplicity were rounded to CCT>590 µm, CCT 555-590 µm, and CCT ≤555 µm.

P.1.1.5 IOP reduction

Data on change in IOP from baseline due to each treatment was derived from the systematic review of clinical effectiveness of treatments in OHT and COAG patients (Appendix U Chapters 7 and 8). No studies comparing prostaglandin analogues to no treatment and trabeculectomy to no treatment met the inclusion criteria. The data used in the model is summarised in Table 92 and correspond to the results of the forest plots in Figures 5 and 10 in Appendix U and Figure 81 in Appendix K. Among the comparisons of trabeculectomy with any medical treatment, the Collaborative Initial Glaucoma Treatment Study (2001)[399] was the only study comparing beta-blockers to trabeculectomy and thus the only trial included for this specific comparison (Figure 81 – subgroup 2).

Table 92: Mean difference in change in IOP from baseline

	Mean difference
Beta-blockers vs No treatment	- 2.88 mmHg
Prostaglandin analogues vs Beta-blockers	- 1.32 mmHg
Trabeculectomy vs Beta-blockers	- 3.6 mmHg

P.1.1.6 IOP reduction and progression

We conducted a search in order to find a measure of the link between IOP reduction and protection against progression. Two scenarios were considered:

- a link between IOP reduction and reduced conversion from OHT to COAG,
- a link between IOP reduction and reduced progression of established COAG.

We included only studies reporting the RR of each mmHg reduction in IOP for progression or conversion, defined by deterioration in visual field or optic nerve appearance or both.

2009

We found a study reporting the RR of developing COAG from OHT per unit of IOP reduction[240] and two studies reporting the RR of progression in COAG patients per unit of IOP reduction[385,386]. Leske et al (2007)[386] an update of Leske et al (2003)[385], is more up to date, and more conservative and so we used this in the base-case model.

In OHT patients, the percentage reduction in the probability of developing COAG was 10% per mmHg of IOP reduction. In COAG patients, the percentage reduction in the probability of progressing was 8% per mmHg of IOP reduction.

The overall effectiveness of each intervention was calculated by multiplying the mean difference in IOP reduction with the percentage reduction in progression per mmHg of IOP reduction.

Table 93: Overall Effectiveness of interventions

INTERVENTION	MEAN CHANGE IN IOP (mmHg)	PROGRESSION REDUCTION per mmHg change in IOP		PROGRESSION REDUCTION (overall effectiveness) Mean change in IOP * Progression Reduction/mmHg for each treatment option	
		OHT	COAG	OHT	COAG
No treatment	0	10%	8%	0	0
Beta-blockers	2.88	10%	8%	29%	23%
Prostaglandin analogues	4.2	10%	8%	42%	34%
Trabeculectomy	6.48	NA	8%	NA	52%

2009

P.1.1.7 Probability of progression after treatment

In each branch of the model where patients received a treatment, the baseline probability of progression in the absence of treatment was adjusted by the overall effectiveness of the respective treatment:

V Baseline probability * (1-overall effectiveness)

For example, a patient with Early COAG would have an annual probability of progression to Moderate COAG of 25% if untreated, and 25%*(100%-34%) = 16.5% if treated with a prostaglandin analogue.

The probability thus calculated was used for the time during which the patients received that treatment in the model. Once a switch in treatment occurred without progression this probability was recalculated according to the new drug used. Once a patient has progressed to the following stage, the new probability is the baseline probability in treated patients for that stage (Table 89). The rationale is that after progression any new treatment could be introduced, for which we cannot estimate the effectiveness. As a consequence, we used progression estimates for nonspecific treatments.

P.1.1.8 Other probabilities

Other probabilities used in the model were:

- Probability of developing asthma after use of beta-blockers: it was estimated from a prospective cohort study[334] comparing the difference in respiratory disease in 2,645 patients treated with beta-blockers to 9,094 unexposed patients. The difference between the proportions of patients

given a new prescription of drug for reversible airways obstruction in 12 months after treatment was 3.3%. The same study[334] reports that the risk of respiratory problems ceases to be significant after the first year of exposure; therefore the probability of developing asthma is kept in the model only within the first year.

- Probability of discontinuation due to reasons other than treatment failure: we found one UK study[719] reporting the proportion of patients discontinuing treatment for reasons other than treatment failure (i.e. adverse events, intolerance). In this study, 19 out of 149 patients (13%) treated with prostaglandin analogues and 158 out of 632 patients (25%) treated with beta-blockers discontinued within 1 year. From the latter figure we subtracted 3.3% which was the proportion of patients developing asthma that would have been included in the discontinuation of beta-blockers; the remaining annual probability for this group is 21.7%. Data for later years were not available; thus these probabilities were used only during the first year of treatment.
- Probability of post-surgery complications: the GDG identified those complications that require further treatment and are therefore associated with extra costs. Rare (with an incidence of1% or less) and promptly resolving complications were excluded. Cataract and flat anterior chamber were the two complications identified. There was overall agreement between experts' estimates and national sources on the incidence of cataract. The probability was obtained from the National Survey of Trabeculectomy[178] considering only the cases that required cataract extraction (2.5%). The incidence of flat anterior chamber requiring treatment was estimated by experts as 0.75%, reported in the National Survey[178] as 0.2%, and in the Moorfields Glaucoma service annual audits 2001-2007 as 4%. We decided to use an average of these figures (1.65%) to estimate the probability of reformation of anterior chamber. Cataract extraction and reformation of anterior chamber were assumed to occur in the model only in the two months (1cycle) following surgery for both the first eye and the second eye operation.
- Probability of needing medication after surgery: the probability of adding a medication because of poor IOP control after trabeculectomy was obtained from the National Survey of Trabeculectomy[177]. Patients requiring post-operative anti-glaucoma medications were 147/1105 (13.3%) after 1 year. This probability was also used in the following years.

2009

P.1.1.9 Life expectancy

Life expectancy in patients with COAG or OHT was assumed to be the same as the general population in England and Wales. Life expectancy was estimated for each age by calculating the mean of the figures for men and women reported in the Life Tables for the general population of England and Wales in the year 2004-2006 in the Government Actuary Department (http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp)

P.1.1.10 Quality of life

The utility scores in Table 94: Health Utilities by COAG stage

are a measure of the quality of life associated with each of the COAG stage on a scale from 0 (death) to 1 (perfect health). A systematic search for quality of life in OHT and COAG patients was performed. Studies were included if health state utility values were reported or obtainable for stages separately and they were based on visual field defect.

One study[566], using data obtained from Brown et al (2003)[83], was selected that applied utilities for visual acuity to each category of visual field loss. Two functions to calculate health utilities for each continuous dB increment of visual field defect were developed. In order not to favour the most effective treatment, we adopted the formula that resulted in the most conservative estimate of quality of life detriment resulting from visual field defects:

VI Health utility = $0.98991+0.0022*dBs - 0.00080518*dBs^2$

where dBs are expressed as an absolute numbers and is therefore a positive number.

Since the stages in the model were defined as ranges of visual field defect (Table 88), it was possible to calculate the upper and lower limits and the central utility score for each stage by substituting the range limits and the central value of the stage definition. The central value of the severe visual impairment stage was assumed to be -26dB following the World Health Organization definition of blindness as reported in Rein et al (2007)[566], while the upper limit was assumed to be -30dB. The quality of life in OHT patients was assumed to be equal to perfect health as there was no visual field defect.

Table 94: Health Utilities by COAG stage

STAGE	LOWER LIMIT	UPPER LIMIT	CENTRAL VALUE
OHT	-	-	1
Early COAG	0.974	0.990	0.989
Moderate COAG	0.900	0.974	0.944
Advanced COAG	0.712	0.900	0.819
Severe Visual Impairment	0.331	0.712	0.503

When we compared our estimates with other published studies[92,251,341,373] we found that overall we had been more conservative.

Adverse events were assumed to be negligible in terms of quality of life because they could be promptly treated, with the exception of asthma. A search for quality of life measures in the CEA Registry (https://research.tufts-nemc.org/cear/default.aspx) retrieved a study[592] where the health utility in treated asthma patients was 0.84. Hence, it was assumed that treated asthma symptoms produce a decrease in quality of life of 0.16 over one year. This is probably an overestimation because the treatment with beta-blockers should be immediately discontinued with the consequent reduction of symptoms. On the other hand, beta-blockers are known to have other important adverse events for which incidence, costs and quality of life detriment could not be estimated.

2009

P.1.1.11 Calculating QALYs gained

For each strategy, the expected QALYs per cohort of patients in each cycle are calculated as follows:

VII Expected QALYs = $U_{OHT} \times P_{OHT} + U_e \times P_e + U_m \times P_m + U_a \times P_a + U_b \times P_b + P_{ast} \times U_{ast}$
where

U_{OHT} , U_e , U_m , U_a , U_b = the utility score for each stage

U_{ast} = the utility detriment due to asthma (negative number)

P_{OHT} , P_e , P_m , P_a , P_b = the proportion of patients in each of the COAG stage at the end of each cycle

P_{ast} = the proportion of patients developing asthma in each cycle

The proportion of patients in each COAG stage depends on the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected QALYs are given by the sum of QALYs calculated for each cycle. The incremental QALYs gained associated with a treatment strategy are calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

P.1.1.12 Upstream treatment costs

Upstream treatment costs are those directly associated with the treatment strategy considered and so those arising before a progression. The resources used in each cycle for the different strategies are summarised in Table 95. These resources are used only until the patient remains in the treatment strategy assigned at the beginning of the model. Patients in the beta-blocker and prostaglandin analogue arms can interchange treatment in which case the cost of an additional visit is added and the cycle cost is calculated according to the new treatment.

Table 95: Resources used

	No Treatment	Beta-blockers	Prostaglandin analogues	Surgery	Source
Drugs	-	2 bottles of Timolol	2 bottles of either Latanprost, Travoprost, Bimatoprost	Used post-operatively: 1 bottle Chloramphenicol + 4 bottles Predforte + 1bottle Cyclopentolate 1bottle of either a prostaglandin or a beta-blocker in the two months between surgery in first eye and second eye	Expert opinion
Trabeculectomy inpatient	-	-	-	34% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Trabeculectomy daycase	-	-	-	66% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Monitoring visits - OHT	0.33 (a)	0.33 (a) + 1 if treatment switch	0.33 (a) + 1 if treatment switch	0.33 (a)	Expert opinion and recommendation in the Guideline
Monitoring visits - COAG	0.67 (b)	0.67 b + 1 if treatment switch	0.67 b + 1 if treatment switch	0.67 (b)	Expert opinion and recommendation in the Guideline

(a) One visit every 6 months
(b) One visit every 3 months

The costs of the resources used are reported in Table 96. All the cost figures are expressed in 2006 Pound Sterling.

Table 96: Cost per unit of resource used

	COST	SOURCE

2009

Bottle of beta-blocker	£3.12	BNF 56
Bottle of prostaglandin analogue	£11.70 (a)	BNF 56
Post-operative drug treatment	£9.7 (b)	BNF 56
Trabeculectomy – inpatient	£1,316	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)
Trabeculectomy – daycase	£789	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)
Trabeculectomy – weighted average cost	£968 (c)	NCC-AC calculation
Cost of monitoring visit	£62	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – Consultant led follow up attendance outpatient face to face - specialty code 130 Ophthalmology

(a) Mean cost of Travoprost, Latanoprost and Bimatoprost
(b) Cost of 1 Chloramphenicol + 4 Predforte + 1Cyclopentolate (£2.72 + 4 x £1.50 + £0.97)
(c) Proportion of inpatient x cost inpatient + proportion daycase x cost daycase

P.1.1.13 Downstream treatment costs

While a calculation of the resources used was made for the upstream costs, it would have been inaccurate if not impossible to do that for the costs arising after a disease progression. We conducted a systematic search on the cost of glaucoma stages and we selected a cost-of-illness study[151] reporting the direct healthcare cost per patient associated with each COAG stage. We chose this study because the staging system was the same that we adopted (Hodapp, Parrish and Anderson classification, Appendix U section 1.2), and it contained UK data. The figures in Table 97 were obtained by converting the 2004 Euros into GBP by a conversion factor of 0.67, which was the reciprocal of the one used by the author to convert GBP into Euros.

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Table 97: Annual cost of COAG stage per patient

Stage	Cost year per patient (£)	Source
Early COAG	399	Traverso et al (2006)[661]
Moderate COAG	449	Traverso et al (2006) [661]
Advanced COAG	357	Traverso et al (2006) [661]

In the paper, the costs of severe COAG and blindness did not account for social costs, thus leading to an underestimation of the true costs. Therefore for the last stage (Severe Visual Impairment) we based our cost analysis on the services provided to patients with blindness as described in Meads and Hyde (2003)[433]. Table 98 illustrates the services considered in our analysis, the calculation of their costs, and the proportion of patients receiving each service as reported in Meads and Hyde (2003)[433]. The same study includes the cost of depression and hip replacement in individuals with visual impairment. We did not use these data, as they were not controlled for incidence in the general population.

Table 98: Cost of severe visual impairment

Service	Cost (£)	Source	Proportion of patients receiving the

			service
Blind registration	122.78 (one-off)	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008)	95%
Low vision aids	150 (one-off)	Meads and Hyde (2003)[433] – figures uplifted to year 2008	33%
Low vision rehabilitation	207 (one-off)	Curtis (2007)[152] - NHS community occupational therapist cost of episode of care including qualification	11%
Community care	8,216	Curtis (2007) [152] - Annual cost for a local authority home care worker	6%
Residential care	16,344	Curtis (2007) [152] - Annual cost of private residential care assuming that 30% of residents pay themselves	30%

The cost of OHT was not used in the model because it is always dependent on the treatment strategy adopted (upstream cost).

For each strategy, the expected cost per cohort of patients in each cycle is calculated as follows:

VIII $$\text{Expected cost} = UC_a \times P_a + \Sigma\, DC_i \times P_i$$

where

UC_a = upstream cost of the initial treatment strategy

P_a = proportion of patients in the initial treatment strategy

DC_i = downstream cost of stage i

P_i = proportion of patients in the stage i

and where stage i could be any later stage

The proportion of patients in each COAG stage depends on the magnitude of the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected costs are given by the sum of costs calculated for each cycle. The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

P.1.1.14 Adverse events and complications costs

Three main adverse events and complications were identified (P.1.1.8) and their costs estimated as shown in Table 99.

We searched for UK cost of illness studies on asthma. We found one study[686] but being too old, we opted for a bottom-up approach. We estimated the cost of an annual treatment with beta-agonist and corticosteroids from a NICE Technology Appraisal[82].

The cost of treating the two post-operative complications, cataract and anterior flat chamber, corresponds to the cost of cataract extraction and anterior chamber reformation.

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Table 99: Cost of adverse events and complications

	COST	SOURCE
Annual cost of asthma treatment	£147 (a)	Brocklebank et al (2001) [82]
Cataract extraction	£977 (b)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ03Z
Reformation of anterior chamber of eye	£974 (c)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ19Z

(a) annual cost of beta-agonist + corticosteroids = 105+42 = £147
(b) all daycase
(c) weighted cost - £556 x 46%(daycase) + £1,330 x 54%(inpatient)

In addition, a treatment change following asthma is always associated with the one-off cost of an extra visit (£62).

P.1.1.15 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the OHT and COAG models results to plausible variations in the model parameters.

Probability distributions were assigned to each model parameter, where there was some measure of parameter variability (Table 100). We then re-calculated the main results 10000 times, and each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random. When some distributions were used either in the OHT model or in the COAG model only, this is specified in Table 100.

Table 100 - Parameters used in the probabilistic sensitivity analysis (a)

Description of variable	Mean value	Probability distribution	Parameters	Source	Model
Mean difference in change in IOP from baseline – BB vs No Treatment	- 2.88 mmHg	Normal	SD = 0.643	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – PGA vs BB	-1.32 mmHg	Normal	SD = 0.24	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – trabeculectomy vs BB	-3.6 mmHg	Normal	SD = 0.418	Systematic review of clinical effectiveness	COAG model
Age at diagnosis of OHT	60 years	none		assumption	OHT model

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Age at diagnosis of COAG	72 years	Custom distribution	age range/probability: 40-44 1.6% 45-49 2.3% 50-54 3.5% 55-59 5.4% 60-64 8.8% 65-69 13.4% 70-74 16.3% 75-79 18.5% 80-84 16.3% 85-89 13.9%	Tuck et al (1998)154	COAG model
Cost of Early COAG	£399	Gamma	α = 61.46 λ = 0.154 based on +/-25% for upper and lower bounds	Traverso et al (2006)151	OHT model
Cost of Moderate COAG	£449	Gamma	α = 61.46 λ = 0.137 based on +/-25% for upper and lower bounds	Traverso et al (2006)151	COAG and OHT models
Cost of Advanced COAG	£357	Gamma	α = 61.46 λ = 0.172 based on +/-25% for upper and lower bounds	Traverso et al (2006)151	COAG and OHT models
Cost of Severe Visual Impairment	see P.1.1.13	none		NCC-AC calculation of cost of Severe Visual Impairment	COAG and OHT models
Cost of Blindness Registration	£122.78	Gamma	α = 61.46 λ = 0.500 based on +/-25% for upper and lower bounds	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008)	COAG and OHT models
Cost of low-vision aids	£150	Gamma	α = 61.46 λ = 0.410 based on +/-25% for upper and lower bounds	Meads and Hyde (2003)96	COAG and OHT models
Cost of low-vision rehabilitation	£207	Gamma	α = 61.46 λ = 0.297 based on +/-25% for upper and lower bounds	Curtis (2007)28	COAG and OHT models

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Cost of community care for blindness	8,216	Gamma	α = 61.46 λ = 0.007 based on +/-25% for upper and lower bounds	Curtis (2007)28	COAG and OHT models
Cost of residential care for blindness	16,344	Gamma	α = 61.46 λ = 0.004 based on +/-25% for upper and lower bounds	Curtis (2007)28	COAG and OHT models
Cost of beta-blockers	see Table 96	none		BNF 56	COAG and OHT models
Cost of prostaglandin analogues	see Table 96	none		BNF 56	COAG and OHT models
Cost of trabeculectomy	see P.1.1.12	none		National Schedule of Reference Costs 2006-07 – Glaucoma category 2 (HRG BZ18Z)	COAG model
Cost of trabeculectomy – inpatient	£1,316	Gamma	α = 7.55 λ = 0.0057 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost of trabeculectomy – daycase	£789	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost of follow-up visit	£62	Gamma	α = 14.45 λ = 0.233 based on IQR	National Schedule of Reference Costs 2006-07	COAG and OHT models
Cost of asthma	£147	Gamma	α = 61.46 λ = 0.42 based on +/-25% for upper and lower bounds	Broklebank et al (2001)[82]	COAG and OHT models
Cost cataract extraction	£977	Gamma	α = 11.77 λ = 0.014 based on IQR	National Schedule of Reference Costs 2006-07 non-phacoemulsification cataract surgery (HRG code BZ03Z)	COAG model
Cost anterior chamber reformation	See P.1.1.14	none		National Schedule of Reference Costs 2006-07 – Glaucoma – category 1 (HRG code BZ19Z)	COAG model

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Cost anterior chamber reformation – daycase	£556	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost anterior chamber reformation – inpatient	£1,776	Gamma	α = 4.41 λ = 0.0025 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Proportion of trabeculectomy daycase: inpatient	66%: 34%	none		Hospital Episode Statistics 2006/07	COAG model
Proportion of anterior chamber reformation – daycase: inpatient	46%: 54%	none		Hospital Episode Statistics 2006/07	COAG model
Discount rate (cost and QALYs)	3.5%	none		NICE reference case[485]	COAG and OHT models
Number of follow-up visits per year – COAG and treated OHT patients	4	Triangular	Min = 2 Likeliest = 4 Max = 6	Experts opinion	COAG and OHT models
Number of follow-up visits per year – OHT untreated patients	2	Triangular	Min = 1 Likeliest = 2 Max = 3	Experts opinion	OHT model
Annual probability of developing COAG – untreated	see P.1.1.4	none		Gordon et al (2002)[240]	OHT model
Relative Risk for progression to COAG – IOP >21-25 mmHg; CCT >590µm	0.16	Beta	α = 2 β = 88	Gordon et al (2002) [240]	OHT model
Relative Risk for progression to COAG – IOP >25 – 32 mmHg; CCT >590µm	0.49	Beta	α = 5 β = 75	Gordon et al (2002) [240]	OHT model
Relative Risk for progression to COAG – IOP >21-25mmHg; CCT 555-590µm	0.73	Beta	α = 7 β = 70	Gordon et al (2002) [240]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT 555-590µm	1.06	Beta	α = 10 β = 69	Gordon et al (2002) [240]	OHT model
Relative Risk for progression to COAG – IOP >21-25mmHg; CCT ≤555µm	1.39	Beta	α = 13 β = 65	Gordon et al (2002) [240]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT ≤555µm	2.93	Beta	α = 28 β = 50	Gordon et al (2002) [240]	OHT model

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Annual probability of progression Early to Moderate – untreated	25%	Triangular	Min = 12.5% Likeliest = 25% Max = 37.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[89]	COAG model
Annual probability of progression Early to Moderate – treated	20%	Triangular	Min = 10% Likeliest = 20% Max = 30% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007) [89]	OHT model
Annual probability of progression Moderate to Advanced – treated	7%	Triangular	Min = 3.5% Likeliest = 7% Max = 10.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007) [89]	COAG and OHT models
Annual probability of progression Advanced to Severe Visual Impairment – treated	6%	Triangular	Min = 3% Likeliest = 6% Max = 9% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007) [89]	COAG and OHT models
Annual probability of developing asthma in patients treated with BB	3.3%	Beta	α = 21 β = 611	Kirwan et al (2002) [334]	COAG and OHT models
Annual probability of adding a medication after surgery	13.3%	Beta	α = 147 β = 958	Edmunds et al (2001)[177]	COAG model
Probability of cataract extraction after trabeculectomy	2.3%	Beta	α = 29 β = 1211	Edmunds et al (2002)[178]	COAG model
Probability of anterior chamber reformation after trabeculectomy	1.65%	none		Edmunds et al (2002) [178] and experts opinion	COAG model
Probability of natural death	function of age	none		Life Tables England and Wales	OHT and COAG models
Probability of switching treatment with BB including asthma	25%	Beta	α = 158 β = 474	Zhou et al (2004)166	COAG and OHT models

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Probability of switching treatment with BB excluding asthma	see P.1.1.8	none		Assumption	COAG and OHT models
Probability of switching treatment with PGA	13%	Beta	α = 19 β = 130	Zhou et al (2004)[719]	COAG and OHT models
Health utility OHT	1	none		Assumption	OHT model
Health utility Early	0.989	Triangular	Min = 0.974 Likeliest = 0.989 Max = 0.990 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[566]	COAG and OHT models
Health utility Moderate	0.944	Triangular	Min = 0.900 Likeliest = 0.944 Max = 0.974 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[566]	COAG and OHT models
Health utility Advanced	0.819	Triangular	Min = 0.712 Likeliest = 0.819 Max = 0.900 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[566]	COAG and OHT models

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Health utility Severe Visual Impairment	0.503	Triangular	Min = 0.331 Likeliest = 0.503 Max = 0.712 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the WHO definition of blindness	Rein et al (2007) [566]	COAG and OHT models
Health decrement with Asthma	-0.16	none		Schermet et al (2002)[592]	COAG and OHT models
RR of progression per unit of IOP reduction – OHT	0.10	1 – Log-Normal	SE = 0.037	Gordon et al (2002)[240]	OHT model
RR of progression per unit of IOP reduction – COAG	0.08	1 – Log-Normal	SE = 0.02	Leske et al (2007)[386]	COAG model

(a) When the variable is a function, its definition is reported in the referenced paragraph.

P.1.1.16 Results of the cost-effectiveness analysis

P.1.1.16.1 OHT

We found that the results of the OHT model were particularly sensitive to the age of patients at the decision point. Age is a risk factor for the development of COAG but it is also important for estimating the likelihood of visual impairment. Table 101 shows the results of the base case analysis and the one-way sensitivity analysis conducted by varying the patient's age between 40 and 80. Beyond these limits, we do not have data on the probability of developing COAG.

For patients at an average age of 60, no treatment is the most cost-effective strategy if the CCT >555µm and IOP is within the 21 – 32 mmHg range. If the CCT ≤555 µm, treatment with prostaglandin analogues is the most cost-effective strategy for any IOP.

Table 101 - Results of OHT model – base case

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained vs No Treatment	Incremental cost (£) per QALY gained vs BB	One-way sensitivity analysis on age
IOP>21 – 25 mmHg, CCT>590 µm					
No Treatment	2,165	14.574	-	-	-
BB	4,748	14.586	213,504	-	Not sensitive to age
PGA	5,665	14.586	296,593	Dominated	Not sensitive to age
IOP >25 – 32 mmHg, CCT>590 µm					
No Treatment	2,872	14.471	-	-	-
BB	5,105	14.513	52,670	-	Not sensitive to age
PGA	5,934	14.522	59,805	94,182	Not sensitive to age

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IOP>21 – 25 mmHg, CCT 555-590 µm					
No Treatment	3,344	14.403	-	-	-
BB	5,351	14.464	32,749	-	Not sensitive to age
PGA	6,121	14.478	36,598	52,760	Not sensitive to age
IOP >25 – 32 mmHg, CCT 555-590 µm					
No Treatment	3,940	14.316	-	-	-
BB	5,672	14.399	20,864	-	If age<60 BB is more cost-effective than no treatment.
PGA	6,368	14.421	23,124	31,650	If age<58 PGA is more cost-effective than no treatment. PGA vs BB not sensitive to age.
IOP >21 – 25 mmHg, CCT ≤555 µm					
No Treatment	4,484	14.237	-	-	-
BB	5,974	14.339	14,617	-	If age>67 no treatment is more effective than BB.
PGA	6,603	14.367	16,307	22,464	If age>65, no treatment is more cost-effective than PGA. If age<58 PGA is more cost-effective than BB.
IOP >25 – 32 mmHg, CCT ≤555 µm					
No Treatment	6,475	13.949	-	-	
BB	7,179	14.102	4,605	-	If age>80 no treatment is more effective than BB.
PGA	7,566	14.150	5,429	8,056	If age>77 BB are more cost-effective than PGA. If age >80 no treatment is more cost-effective than PGA.

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The cost-effectiveness of treating OHT is strongly interconnected with the patient's risk factors for the development of COAG (age, IOP and CCT) and with the likelihood of becoming visually impaired which depends on the age at diagnosis.

In the absence of risk factors, the probability of developing COAG is so low that the little improvement in the quality of life treatment would bring does not warrant the high costs of a lifetime treatment. Not treating patients with IOP>21-25mmHg and CCT>590µm is significantly cost-effective compared to PGA as reported in Table 102, where the 95% confidence interval (CI) is above the £20,000/QALY threshold. When compared to BB, the cost-effectiveness is not significant as the lower limit crosses the £20,000/QALY threshold.

Medical treatment is cost-effective in patients with CCT≤555 µm with any IOP up to 32 mmHg and in patients with CCT 555-590 µm and IOP >25-32 mmHg. However, the 95% CI limits crossed our cost-effectiveness threshold (Table 102).

Considering only those patients for whom treatment is cost-effective, if both beta-blockers and prostaglandin analogues are available (e.g. they are not contraindicated), beta-blockers are more cost-effective if CCT 555-590 µm and IOP >25-32mmHg or if CCT<555 µm and IOP >21 – 25 mmHg while prostaglandin analogues are more cost-effective if CCT<555 µm and IOP >25 – 32mmHg. The results of the comparison between prostaglandin analogues and beta-blockers are not significant with 95% confidence (Table 102: Results of PSA – OHT model). For these groups of patients, there is an age beyond which treatment does not substantially improve the quality of life, and thus it is not cost-effective (see One-way sensitivity analysis in Table 101). For clinical simplicity, the results can be rearranged in order to round the age threshold and to limit the maximum number of age groups to two for each IOP and CCT combination. In this case after we exclude beta-blockers from the comparison, prostaglandin analogues are cost-effective up to the age of 65 in the IOP >21 – 25 mmHg and CCT<555 µm group and up to the age of 80 in the IOP >25 – 32 mmHg and CCT<555 µm group.

Table 102: Results of PSA – OHT model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
IOP>21 – 25 mmHg, CCT>590 µm				
BB vs no treat	149,606	17,713	dominated	No Treat 97%
PGA vs No treat	649,300	64,402	dominated	BB 3%
PGA vs BB	193,576	32,110	dominated	PGA 0%
IOP >25 – 32 mmHg, CCT>590 µm				
BB vs no treat	42,773	2,801	423,141	No Treat 81%
PGA vs No treat	82,141	23,334	dominated	BB 18%
PGA vs BB	50,144	10,141	665,186	PGA 1%
IOP>21 – 25 mmHg, CCT 555-590 µm				
BB vs No Treat	28,280	942	224,519	No Treat 67%
PGA vs No Treat	50,626	15,892	11,180,850	BB 28%
PGA vs BB	32,791	6,154	271,632	PGA 5%
IOP >25 – 32 mmHg, CCT 555-590 µm				
BB vs No Treat	18,647	cost saving	138,698	No Treat 48%
PGA vs No Treat	33,040	11,036	346,902	BB 37%
PGA vs BB	21,638	3,378	152,848	PGA 15%
IOP >21 – 25 mmHg, CCT ≤555 µm				
BB vs No Treat	12,844	cost saving	89,068	No Treat 33%
PGA vs No Treat	23,184	7,466	162,175	BB 35%
PGA vs BB	15,099	1,417	93,199	PGA 32%
IOP >25 – 32 mmHg, CCT ≤555 µm				
BB vs No Treat	3,720	cost saving	38,637	No Treat 8%
PGA vs No Treat	8,277	1,460	52,186	BB 9%
PGA vs BB	4,818	cost saving	39,453	PGA 83%

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P.1.1.16.2 COAG

Table 103 shows the results of the base case COAG model. Trabeculectomy is the most effective and most cost-effective option.

Table 103: Results of COAG model – base case

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained vs No Treat	Incremental cost (£) per QALY gained vs BB	Incremental cost (£) per QALY gained vs PGA	Sensitivity analysis
No Treat	6,246	8.635	-	-	-	If annual probability of progression < 6% or surgical intervention costs >£1,455, trabeculectomy is not cost-effective anymore. Results not sensitive to COAG stage.
BB	6,017	8.714	cost saving	-	-	
PGA	6,113	8.745	cost saving	3,100	-	
Trab	7,247	8.849	14,679	9,113	10,906	

When the severity of the disease (COAG stage) was varied, the overall results did not change and trabeculectomy was still the most cost-effective strategy. Sensitive parameters in the model were the annual probability of progression to the following stage and the cost of trabeculectomy. When the probability of progression was lowered from 25% in the base case to 6%, trabeculectomy was not cost-effective anymore. By using the following formula, we could calculate the rate in visual field deterioration corresponding to a 7% annual probability of progression:

IX $\text{rate} = (VF_{mod} - VF_{Early})/\text{years}$

where

VF_{mod} = absolute value of lower bound of Moderate COAG definition (6.01dB)

VF_{Early} = absolute central value of Early COAG definition (3.00)

years = years necessary to reach Moderate COAG, calculated as

X $\text{years} = 1/(\text{probability of progression})$

The rate thus calculated was

XI $\text{rate} = (6.01 - 3.00)/(1/0.06) = 0.18\text{dB/year}$

If the visual field deteriorates at a rate lower than this value, trabeculectomy is not cost-effective.

The uncertainty over the cost-effectiveness of trabeculectomy was revealed by the results of the PSA as well (Table 104). While beta-blockers and prostaglandin analogues are significantly more cost-effective than no treatment (i.e. the upper limit is below the £20,000/QALY threshold used in our economic evaluation), the upper limit of the ICER of trabeculectomy vs any other intervention always exceeds the £20,000/QALY threshold (Table 104).

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Table 104: Results of PSA - COAG model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
BB vs no treatment	cost saving	cost saving	9,461	No treatment 1% BB 4% PGA 38% Trab 57%
PGA vs no treatment	cost saving	cost saving	13,836	
Trab vs no treatment	3,488	cost saving	57,676	
PGA vs BB	3,079	cost saving	23,258	
Trab vs BB	7,483	cost saving	85,631	
Trab vs PGA	11,495	cost saving	122,050	

When the severity of COAG at the point of decision was increased to moderate or advanced, trabeculectomy became more cost-effective and this result less sensitive to the probability of progression. By applying a formula similar to IX, we estimated the minimum rate of visual field deterioration in order for trabeculectomy to be cost-effective in moderate COAG (0.09dB/year) and advanced COAG (0.08dB/year).

P.1.1.17 Discussion

The cost-effectiveness of treating OHT patients depends on their risk for development of COAG. We found that age, IOP and CCT are the clinical indicators correlated with this risk (P.1.1.4). According to the possible combinations of these parameters, different strategies can be cost-effective.

Beta-blockers are cost-effective for patients with IOP >25 – 32 mmHg and CCT 555 – 590 μm up to the age of 60. Prostaglandin analogues are cost-effective for patients with IOP> 21 – 25 mmHg and CCT<555 μm up to the age of 65 and for patients with IOP>25 – 32 mmHg and CCT≤555μm up to the age of 80. All other OHT patients should not receive treatment according to our analysis.

On the other hand, treating all COAG patients from an early stage is cost-effective. Results show that trabeculectomy is the most cost-effective treatment. Nevertheless being an invasive procedure it has drawbacks that we could have failed to capture in our analysis. More generally, some treatments are associated with common adverse events and complications that often require further interventions. In our model we have tried to incorporate the costs and effects of the most common and serious ones but we might have underestimated them since there is no good up to date literature on this topic.

In addition, the cost-effectiveness of trabeculectomy is conditional upon a considerable rate of progression in visual field defect. It could be worthwhile initiating medical treatment while monitoring for progression; only when a progression is detected could the patient be listed for surgery.

For patients in the later stages of COAG trabeculectomy is cost-effective even in the presence of a very low rate of progression (see P.1.1.16.2) because the threat to their vision is more imminent.

We have kept some parameters conservative:

- Quality of life estimates from the selected study were generally higher than in other excluded studies.
- Increase in mortality risk due to blindness or visual impairment was not included in the model.
- The probability of developing COAG in OHT patients 70-80 years old was used also for older patients, although it was likely to be higher.

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- Normal Tension Glaucoma patients were included in the IOP reduction results as well. However, including data for this population could decrease the effectiveness of treatment in reducing IOP. In fact, the effectiveness corresponds to the difference between IOP at baseline and after treatment and since their IOP at baseline is already low and drugs could be less effective in decreasing this value further.

Had we modified these assumptions, we would have favoured the most effective interventions.

However, our analysis is limited for a number of reasons:

- The OHT model is based on the findings of an RCT[240] where patients were included only if their age was between 40 and 80 years and IOP between >21and 32 mmHg. Therefore we cannot generalise our results beyond these limits.
- Some probabilities of progression were extrapolated beyond the follow-up periods cited in the literature and for advanced COAG to severe visual impairment there was no RCT data available.
- The methodology adopted by the study[566] used as the source of health utilities in the model has not been validated yet. Also, the original health utilities[83] were estimated for different ocular conditions causing a defect in visual acuity. These utilities might not be applicable to glaucoma patients since the pattern of visual loss differs from other conditions. Furthermore, generic instruments such as the EQ-5D might not completely capture the quality of life decrement caused by small changes in visual ability.

The results of our model are applicable to OHT or COAG patients who have not been treated before. Although we have included data on IOP reduction in NTG patients, we could not find any evidence on the relationship between IOP reduction and progression reduction in this population. The results of our model might not be directly applicable to these patients.

Another assumption in our model was that the severity of OHT or COAG is similar in both eyes. However, in clinical practice a patient could present with unilateral COAG or OHT. We believe that the treatment should be established according to the worse eye if treated with medical therapy. In fact, a single bottle of drops per month is used for treating either both eyes or one eye only as the bottle should be discarded after 28 days from the opening. In addition, since it is the patient who is being treated and not the eye, the cost of follow up visits and adverse events would be the same. Conversely, a surgical approach should be adopted only for the eye that requires it.

If the results of our economic analysis were adopted in the NHS, there would be an increase in surgical treatments with more pressure on Hospital Eye Services. However, if this was accompanied by a change in the referral scheme and monitoring provision, the resources freed up by the implementation of these policies could be used for the care of those patients requiring immediate treatment to prevent further progression. In addition, OHT patients with a low risk of progression would not be treated according to our model, which saves resources in terms of drugs and visits as well as patients not receiving treatment who would be monitored less frequently. On the other hand, OHT patients at a high risk for progression would receive prostaglandin analogues that are the most effective medical treatment. As a consequence, fewer people would develop COAG with less pressure on the Hospital Eye Service and the provision of surgery.

Another consequence of our results is that more emphasis would be given to the assessment of clinical parameters such as IOP and CCT for OHT patients and visual field defect for COAG patients.

Our findings are similar to those of previous studies: Kymes et al (2006)[360] and Stewart et al (2008)[636] found that treating all OHT patients is not cost-effective, while according to Kymes et al (2006)[360] selecting those with an elevated risk of conversion to COAG is a more cost-effective strategy (see Evidence Table – Appendix D). Le Pen et al (2005)[370] explored the cost-effectiveness of prostaglandin analogues compared to beta-blockers in COAG patients through a Markov model reaching conclusions similar to our model (see Evidence Table – Appendix D).

2009

P.1.2 Conclusions

- Treating all patients with OHT is not cost-effective.
- It is cost-effective to treat only OHT patients with IOP> 25 – 32 mmHg and CCT 555 – 590 µm with a beta-blocker until the age of 60 and OHT patients with IOP >21 and CCT ≤555µm with a prostaglandin analogue until the age of 80.

It is always cost-effective to treat COAG patients. However, trabeculectomy is cost-effective only when progression of visual field defect for Early COAG patients is >0.18 dB/per year – which is to say in the presence of any detectable progression. Trabeculectomy becomes more and more cost-effective the more advanced the stage of COAG.

2009

Appendix Q: Research recommendations

Q.1 Treatment for people with an IOP of 22 or 23 mmHg

Research question: What is the clinical and cost effectiveness of treating an intraocular pressure (IOP) of 22 or 23 mmHg?

Why this is important: The only proven intervention for preventing and controlling glaucoma is lowering IOP. It has been widely accepted that the upper limit of statistically normal IOP is 21 mmHg. This was also accepted as the threshold for treatment and most treatment studies aimed to achieve this target or a reduction in IOP of between 25% and 35% from baseline. However, more recently the Ocular Hypertension Treatment Study (OHTS) enrolled people with an IOP between 24 mmHg and 32 mmHg but without glaucomatous optic nerve damage to receive treatment or no treatment. The results showed a reduction in 5-year incidence of very early glaucoma (either optic-disc or visual-field changes) from 9.5% in people not receiving treatment to 4.4% in those having treatment. The absolute risk reduction of 5.1% suggests a number needed to treat (NNT) of nearly 20 people (NNT: around 50 for unequivocal early disease – optic disc and visual field changes). [316] This leaves an area of uncertainty about treatment for people with an IOP above 21 mmHg but below 24 mmHg. There are about 1.8 million people in the UK with an IOP of 22 or 23 mmHg (Chan, Foster 2017 – Unpublished). The costs associated with management in these people are sufficient to make this question of national importance.

Criteria for selecting high-priority research recommendations

PICO question	Population: People aged 40–80 years (as per OHTS) Intervention(s): Topical IOP lowering medication or Comparison: No treatment or placebo Outcome(s): Incident visual field loss or optic disc damage consistent with OHT criteria
Importance to patients or the population	The committee viewed the treatment of people with IOP 22-23mmHg of no clinically significant benefit to the UK population. However, health economic analyses point to the probable benefit (NWMA). Individual persons would probably view the priorities of treatment higher than our committee would. Therefore, the question has relevance clinically, economically and for individuals. Health-related quality of life implications are not known. The incidence of disease in this group is not well documented.
Relevance to NICE guidance	A clear benefit would then prompt reconsideration of current draft guidelines.
Relevance to the NHS	The committee have made a pragmatic decision based on available information to raise the recommended treatment threshold for ocular hypertension in the absence of other risk factors (for example, family history) to IOP >/=24mmHg.
National priorities	There are 1.8 million people in the UK with an IOP of 22 and 23mmHg (Chan, Foster 2017 – unpublished). The treatment costs of these people alone are sufficient to make this question one of national importance.
Current evidence base	The Ocular Hypertension Treatment Study (OHTS) has defined eye care policy in this area. In this trial, people without glaucomatous optic nerve damage were enrolled into a treatment or no treatment study. The enrolment criteria included raised IOP between 24 mmHg and 32mmHg. The results of the trial showed a reduction in 5-year incidence of very early glaucoma (either optic disc or visual field changes) from 9.5% untreated to 4.4% treated. The absolute risk reduction of 5.1% suggests a number needed to treat of nearly 20 people (NNT: around 50 for unequivocal early disease, optic disc and visual field changes). This leaves an area of uncertainty between the IOP of 21mmHg and the cases in which there is

	a 'proven benefit' of treatment of IOP of 24mmHg and above. The benefit in the trial was defined clinically, with no reference to patient reported outcomes or health-related quality of life.
Equality	The special groups in this analysis are the African and Caribbean-derived (ACD) populations of the UK, and the very elderly. The ACD group have a significantly higher risk of glaucoma, and suffer disproportionately from glaucoma blindness. The very elderly will experience greater glaucoma disease impact, as the disease is strongly age-related in terms of incidence and years of life affected.
Study design	Randomised controlled trial incorporating patient reported outcome measures and health economics analysis. **Secondary or primary research** Secondary research: Data from systematic reviews of risk prediction models, secondary analysis of existing data sets Primary research: A randomised controlled trial could be considered but an evaluation of value for research money would be needed Main outcome measures: Glaucoma cases, costs, public preferences, willingness to pay and quality-adjusted life-years (QALYs).
Feasibility	OHTS took 5 years, enrolled 1,636 people, and examined a higher risk group. It produced an outcome of marginal clinical significance. It is likely that the proposed study would need to enrol more participants or follow up for longer than 5 years.
Other comments	
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

Q.2 Risk tools to identify the risk of developing COAG and risk of sight loss

Research question: What is the predictive value of risk tools for identifying people in the community who are at increased risk of developing chronic open-angle glaucoma and identifying people with COAG who are at an increased risk of sight loss?

Why this is important: Most cases of COAG are first detected by case finding in community optometry after a sight test (with or without repeat measures, enhanced case finding, or referral refinement). Identifying which people are at high risk of conversion to COAG at case finding is important for guiding decisions about monitoring, treatment and referral. However, current evidence on the sensitivity and specificity of risk tools for developing COAG is of moderate-to-low quality, with all studies having a high or very high risk of bias. There was no evidence on cost effectiveness.

Similarly, a risk predicton tool that identifies people with COAG who are at risk of progression to sight loss would be useful for both patients and healthcare professionals. People at higher risk of sight loss could have more frequent testing and perhaps more intensive treatment, whereas people at lower risk could have less frequent assessments and potentially less intensive treatment.

Criteria for selecting high-priority research recommendations

PICO question	Population: Strata 1 Adult population attending for current community case finding or other potential community case finding or screening programme populations. Strata 2 Adults with open-angle glaucoma Intervention(s):

	Application of a risk tool (single or combined tests or technologies). Comparison: Usual care (for example, NHS sight testing or eye examinations in the community and enhanced schemes currently providing case finding for glaucoma and resultant referrals) or other interventions. Outcome(s): Detection of true positive cases (those at high risk of conversion to COAG or developing sight loss) necessitating initiation of formal treatment or increased monitoring, and missed cases of people (false negatives) at high risk of conversion to COAG or developing sight loss. HE/healthcare use aspects Quality of life Visual function
Importance to patients or the population	The impact on the UK based population will be high as COAG is a relatively common age-related eye disease with the potential to impact negatively upon quality of life. Most referrals arise from community case finding with a relatively high false positive rate. Ensuring that those most at risk of developing COAG are identified at the appropriate stage and referred for specialist assessment and formal diagnosis is fundamentally important within the glaucoma care pathway. Risk predictors are widely used in many health areas. An accurate risk predictor would probably be acceptable for patients. It could help reduce visual loss and impairment of quality of life.
Relevance to NICE guidance	There is uncertainty regarding the effectiveness of risk tools for identifying people in the community who are at increased risk of developing COAG and identifying those with COAG who are at an increased risk for sight loss that is reflected in the NICE guideline. A high quality diagnostic accuracy study with sufficient numbers can alter the NICE guideline and reduce uncertainty.
Relevance to the NHS	The cost of glaucoma care to the NHS is substantial and there are challenges to meet current demand. Case finding is the first part of the care pathway affecting detected and undetected disease and their associated costs. Once lost, sight cannot be restored. Thus, controlling the condition together with prevention or at least minimisation of ongoing damage, is crucial to maintaining a sighted lifetime. Implementation of a risk tool of sufficiently high sensitivity and specificity to permit a NICE recommendation will afford considerable benefit to the NHS. A risk predictor could help to reduce the number of appointments and tests as well as minimise unnecessary treatment for those with low risk of visual loss. This could provide potential savings. Identifying those at high risk of visual loss would also be cost effective due to the large cost of blindness to the NHS and the burden on people who have vision loss. The committee considered that implementation would not be difficult if research were to find good evidence for a risk tool in the future.
National priorities	There is no national screening programme for COAG, although the Royal College of Ophthalmologists and Clinical Council for Eye Health Commissioning have published NICE accredited guidance on commissioning glaucoma services. The Government has recognised that more needs to be done to prevent avoidable sight loss. The Public Health Outcomes Framework – 'Healthy lives, healthy living: Improving outcomes and supporting transparency' – includes a preventable sight loss indicator. Glaucoma is a leading cause of visual loss and visual disability in the UK, and the societal and economic burden of visual loss is substantial.
Current evidence base	Five tools were included in the NICE CG review for identifying risk of conversion to COAG and overall the evidence was of moderate to low quality, with all studies being of high to very high risk of bias, due to reasons such as not having a reasonable number of outcome events and a lack of calibration data reported.

	All 5 of the tools showed moderate discrimination according to the c-statistic, but 3 of the tools did not have sensitivity and specificity data. Some of the studies included people who had received treatment for raised IOP. There was no economic evidence. There is a risk predictor for glaucoma disease progression from the USA. However, it may not be applicable to UK populations or to the NHS.
Equality	There are no equality issues of note.
Study design	Validation and/or development of a risk predictor using data from randomised trials and/or from large UK cohorts. Prospective or retrospective Statistic measures: sensitivity, specificity, c-statistic, calibration plots and calibration statistics.
Feasibility	No feasibility issues are anticipated. It would be feasible, either prospective or retrospectively (the latter would be feasible because a relatively large number of NHS Hospital Eye Services have electronic records that could be used to determine significant disease progression).
Other comments	Representativeness of the included population to those attending for case finding means special care would need to be applied in secondary care settings (for example, treated case mix best avoided). If a prospective longitudinal cohort is proposed it would be useful to confirm longitudinally the impact of clinically significant disease progression (as determined by visual field testing) on quality of life NIHR advised. Funding should not be exclusively sourced from the industry since this step adds potential bias.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Q.3 Optical coherence tomography for glaucoma

Research question:

What is the effectiveness and cost-effectiveness of optical coherence tomography (OCT) for diagnosis and reassessment in glaucoma?

Why this is important:

Optic nerve examination and visual field testing are performed for the diagnosis and reassessment of glaucoma and related conditions. Visual field testing is subject to variability, involves considerable patient effort and is influenced by comorbidities. Automated imaging with OCT overcomes many of these limitations.

OCT has evolved over the past 2 decades and is currently used in all NHS departments for diagnosing and managing retinal diseases. The use of OCT in glaucoma is currently variable, although it may enable earlier detection of disease and progression. This could lead to improved treatment with less sight loss and blindness. However, not all structural changes detected by OCT may lead to sight loss. Unnecessary treatment is likely to be associated with side effects and increased healthcare costs. Thus, there is a need for evidence on the effectiveness and cost effectiveness of using OCT in England as a diagnostic and reassessment tool for glaucoma and related conditions.

Criteria for selecting high-priority research recommendations

PICO question	Population: people with glaucoma or those suspected of having glaucoma Intervention(s): OCT

	Comparison: use of established technologies (e.g. standard automated perimetry, stereoscopic slit-lamp biomicroscopy, gonioscopy) and clinical examination Outcome(s): Diagnostic accuracy (sensitivity and specificity), extent of glaucomatous visual field loss and optic nerve head damage, quality of life, cost-effectiveness
Importance to patients or the population	The use of OCT can potentially improve glaucoma management and patient outcomes. However there is also a risk that using OCT to make clinical decisions may lead to overtreatment
Relevance to NICE guidance	There was insufficient evidence to recommend using OCT for glaucoma diagnosis and management.
Relevance to the NHS	OCT is currently used alongside other diagnostic tools in many NHS units but it is unclear whether it is clinically and cost effective to use it for diagnosis and reassessment instead of established technologies. .
National priorities	The Government has recognised that more needs to be done to prevent avoidable sight loss. The Public Health Outcomes Framework – 'Healthy lives, healthy living: Improving outcomes and supporting transparency' – includes a preventable sight loss indicator.
Current evidence base	Current evidence suggested that OCT may add valuable information about structural damage but the evidence base was insufficient to recommend OCT for diagnosis and monitoring.
Equality	There are no equality issues of note
Study design	RCT assessing the clinical and cost effectiveness of OCT for diagnosis and detecting disease progression. Observational cohort studies assessing the diagnostic accuracy of OCT.
Feasibility	There are potential feasibility concerns for primary research regarding stability of technology and the duration of the study (as glaucoma is a slow disease)
Other comments	-
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Q.4 Instrument to measure quality of life in people with glaucoma

Research question:

What instrument should be used to measure health-related quality of life in people with glaucoma?

Why this is important:

Quality of life is the most important overall measure of treatment effect because it measures life experience and how this is affected by interventions. Patient-reported outcome measures (PROM) are used to inform patients of the value of interventions which may affect their treatment choices. They also offer a tool for auditing or evaluating glaucoma services and designing glaucoma trials.

However, there is uncertainty about which PROM instrument best measures outcomes of glaucoma interventions. Identifying a valid and responsive PROM for glaucoma would ensure meaningful comparisons between different interventions in future trials and audits.

Criteria for selecting high-priority research recommendations

PICO question	Population: people with OHT, suspected glaucoma and glaucoma Intervention(s): use of a quality of life measure to assess effectiveness of glaucoma technologies, including interventions and models of care Comparison: different instruments Outcome(s): validity (including content validity, face validity and construct validity) and responsiveness (does the instrument reflect known changes in health)
Importance to patients or the population	Quality of life is the most important overall measure of treatment effect for patients as it measures their life experience and how their life experience is affected by interventions. Patient reported outcome measures (PROM) are an important instrument for informing patients of the value of interventions which may affect their treatment choices. They also offer an effective tool in audit or service evaluations of a glaucoma services, and to design glaucoma trials.
Relevance to NICE guidance	Interventions for glaucoma have been assessed and compared according to clinical outcomes (e.g., intraocular pressure, visual field loss). However there is little evidence of the relative effectiveness of different glaucoma interventions from the point of view of patient reported outcomes and utilities
Relevance to the NHS	Having a solid instrument to measure health status would add value to the quality of evidence that is used by policy makers
National priorities	The Government has recognised that more needs to be done to prevent avoidable sight loss. The Public Health Outcomes Framework – 'Healthy lives, healthy living: Improving outcomes and supporting transparency' – includes a preventable sight loss indicator.
Current evidence base	There are a number of instruments that have been used to measure quality of life in glaucoma patients, but uncertainty exists regarding which instrument is best to inform NHS policy. It is acknowledged that EQ-5D may not be sensitive to clinically significant changes in glaucoma status as there are no domains regarding visual function.
Equality	There are no equality issues of note
Study design	Evaluation of instruments' properties, including content validity and responsiveness
Feasibility	No feasibility concerns

Other comments	-
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

Appendix R: Updates to CG85

R.1 CG85 recommendations to be deleted

CG85 recommendation	Rationale
Repeat CCT measurement as necessary (for example, following laser refractive surgery or at onset or progression of corneal pathology).	This recommendation has been deleted because the committee agreed that this is already widely accepted as common practice and does not require a recommendation.

R.2 Amended recommendations

CG85 recommendation	2017 recommendation	Rationale
Obtain an optic nerve head image at diagnosis for baseline documentation.	Obtain an optic nerve head image at diagnosis for baseline documentation (for example, a stereoscopic optic nerve head image or OCT).	Clarification added that this image may be acquired by a stereoscopic optic nerve head image (leaving it open to either biomicroscopy slit lamp examination or stereo photography) or OCT, whichever is more readily available at the time of diagnosis.
Offer standard automated perimetry (central thresholding test) to all people who have established COAG and those suspected of having visual field defects who are being investigated for possible COAG. People with diagnosed OHT and those suspected of having COAG whose visual fields have previously been documented by standard automated perimetry, as being normal may be monitored using supra-threshold perimetry (see tables 4 and 5 for recommended monitoring intervals).	When clinically indicated, repeat visual field testing using standard automated perimetry (central thresholding test) for people with COAG and those suspected of having visual field defects who are being investigated for possible COAG (see tables 2 and 3 for recommended reassessment intervals).	The original recommendation contained 2 separate instructions (1 for people with established COAG and those having initial investigation for possible COAG, and 1 for follow-up of people with an established diagnosis of suspected COAG or OHT). These 2 instructions have now been separated into 2 recommendations to improve clarity.

Offer standard automated perimetry (central thresholding test) to all people who have established COAG and those suspected of having visual field defects who are being investigated for possible COAG. People with diagnosed OHT and those suspected of having COAG whose visual fields have previously been documented by standard automated perimetry as being normal may be monitored using supra-threshold perimetry (see tables 4 and 5 for recommended monitoring intervals).	When clinically indicated, repeat visual field testing using either a central thresholding test or a supra-threshold test for people with OHT and those suspected of having COAG whose visual fields have previously been documented by standard threshold automated perimetry (central thresholding test) as being normal (see tables 1 and 2 for recommended reassessment intervals).	As above, the original recommendation contained 2 separate instructions (1 for people with established COAG and those having initial investigation for possible COAG, and 1 for follow-up of people with an established diagnosis of suspected COAG or OHT). These 2 instructions have now been separated into 2 recommendations to improve clarity. The original recommendation was suggesting that for people with OHT and COAG suspects with normal visual fields, it would be acceptable to use the supra-threshold test as opposed to the superior central thresholding test (CTT) recommended for those with established COAG. However the committee wished to clarify that the CTT is also an option for this population if it is clinically available.
Offer alternative pharmacological treatment (a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to treated people with OHT or suspected COAG whose IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss. More than one agent may be needed concurrently to achieve target IOP.	Offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with an IOP of 24 mmHg or more whose current treatment is not reducing IOP sufficiently to prevent the risk of progression to sight loss. Topical drugs from different therapeutic classes may be needed at the same time to control IOP.	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug. This clarification was considered important because committee members were aware of inappropriate switching through multiple examples of drugs from the same class (for example, multiple PGA switches).
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).	Offer preservative-free eye drops to people who have an allergy to preservatives or people with clinically significant and symptomatic ocular surface disease, but only if they are at high risk of conversion to COAG.	High risk of conversion is no longer defined in the guideline by IOP and CCT so these parameters have been removed from the recommendation. Treatment adherence may be significantly affected by both allergic and non-allergic reactions (preservative toxicity). Preservative toxicity is a particular problem for people with ocular surface diseases so this group was added to the recommendation.

Offer people with advanced COAG surgery with pharmacological augmentation (MMC or 5-FU)[4] as indicated. Offer them information on the risks and benefits associated with surgery.	Offer people with advanced COAG, surgery with pharmacological augmentation (MMC) as indicated. Offer them information on the risks and benefits associated with surgery.	5FU is no longer used as standard practice during surgical treatment and postoperative care.
Offer people who present with advanced COAG and who are listed for surgery interim treatment with a prostaglandin analogue.	Offer people who present with advanced COAG and who are listed for surgery, interim treatment with a generic PGA.	Generic PGAs are now recommended in the guideline for first-line treatment.
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[4]) 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[4]) as indicated or laser trabeculoplasty.	Ask about adherence to treatment and check the 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 1 of the following: • a drug from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); topical drugs from different therapeutic classes may be needed at the same time to control IOP • laser trabeculoplasty • surgery with pharmacological augmentation (MMC) as indicated. If the drug treatment option is chosen, after trying drugs from 2 therapeutic classes, consider offering surgery with pharmacological augmentation (MMC) as indicated or laser trabeculoplasty.	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug. 5FU is no longer used as standard practice during surgical treatment and postoperative care.
Offer surgery with pharmacological augmentation (MMC or 5-FU[4]) 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.	Offer surgery with pharmacological augmentation (MMC) 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.	5FU is no longer used as standard practice during surgical treatment and postoperative care.

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[4]) as indicated or laser trabeculoplasty.	Consider offering people with COAG who cannot tolerate a treatment: • a drug from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) or • preservative-free eye drops if there is evidence that the person is allergic to the preservative or has clinically significant and symptomatic ocular surface disease After trying drugs from 2 therapeutic classes, consider offering surgery with pharmacological augmentation (MMC) as indicated or laser trabeculoplasty.	Clarification that the drug should be from another therapeutic class when switching to another monotherapy. Treatment adherence may be significantly affected by both allergic and non-allergic reactions (preservative toxicity). Preservative toxicity is a particular problem for people with ocular surface diseases so this group was added to the recommendation. 5FU is no longer used as standard practice during surgical treatment and postoperative care.
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 analogue, 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.	After surgery offer people with COAG whose IOP has not been reduced sufficiently to prevent the risk of progression to sight loss 1 of the following: • pharmacological treatment; topical drugs from different therapeutic classes may be needed at the same time to control IOP • further surgery • laser trabeculoplasty or cyclodiode laser treatment.	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug.
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.	Offer people with COAG who prefer not to have surgery or for whom surgery is not suitable: • pharmacological treatment; topical drugs from different therapeutic classes may be needed at the same time to control IOP • laser trabeculoplasty or cyclodiode laser treatment.	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug.

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	Offer people the opportunity to discuss their diagnosis, referral, prognosis, treatment and discharge, 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 having treatment for COAG will have good quality of life and 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 condition • 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 take an active part in decision-making • 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)	Amended to indicate that people should have the opportunity to discuss referral, and discharge, and that patient information should also include: • reassurance that most people having treatment for COAG will have a good quality of life • reference to the eye clinic liaison officer (ECLO) as these now available in many clinics •reference to support organisations.

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.	• the eye clinic liaison officer (ECLO) • support organisations and 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.	

Appendix S: NICE technical team

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