National Guideline Centre

Final

Glaucoma

Glaucoma: diagnosis and management

NICE guideline 81

Methods, evidence and recommendations

October 2017

Final

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Partial update 2017

This is a partial update of the 2009 clinical guideline on Glaucoma: diagnosis and management of chronic open-angle glaucoma and ocular hypertension.

The sections new or updated in 2017 are:

- Guideline committee and scope
- Methodology
- Case finding, diagnosis and monitoring
- Service models
- Prognostic risk tools
- Treatment of ocular hypertension, suspected chronic open-angle glaucoma and chronic open-angle glaucoma

All other sections and recommendations for the 2009 guideline remain unchanged.

The content of other sections has not been amended, and we have integrated these new sections into the relevant chapters of the old publication. This has inevitably led to inconsistencies in style of write up for reviews.

Unamended sections of the guideline are highlighted in a pale orange box and have a '2009' bar in the right hand margin.

To view the 2009 guideline in its entirety, please see appendix U.

The National Guideline Centre, formally the National Clinical Guideline Centre, was formed in April 2009 following the merger of the National Collaborating Centres for Acute Care, Chronic Conditions, Nursing and Supportive Care and Primary Care.

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2009

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1 Guideline summary

1.1 Algorithms

Figure 1: Referral algorithm

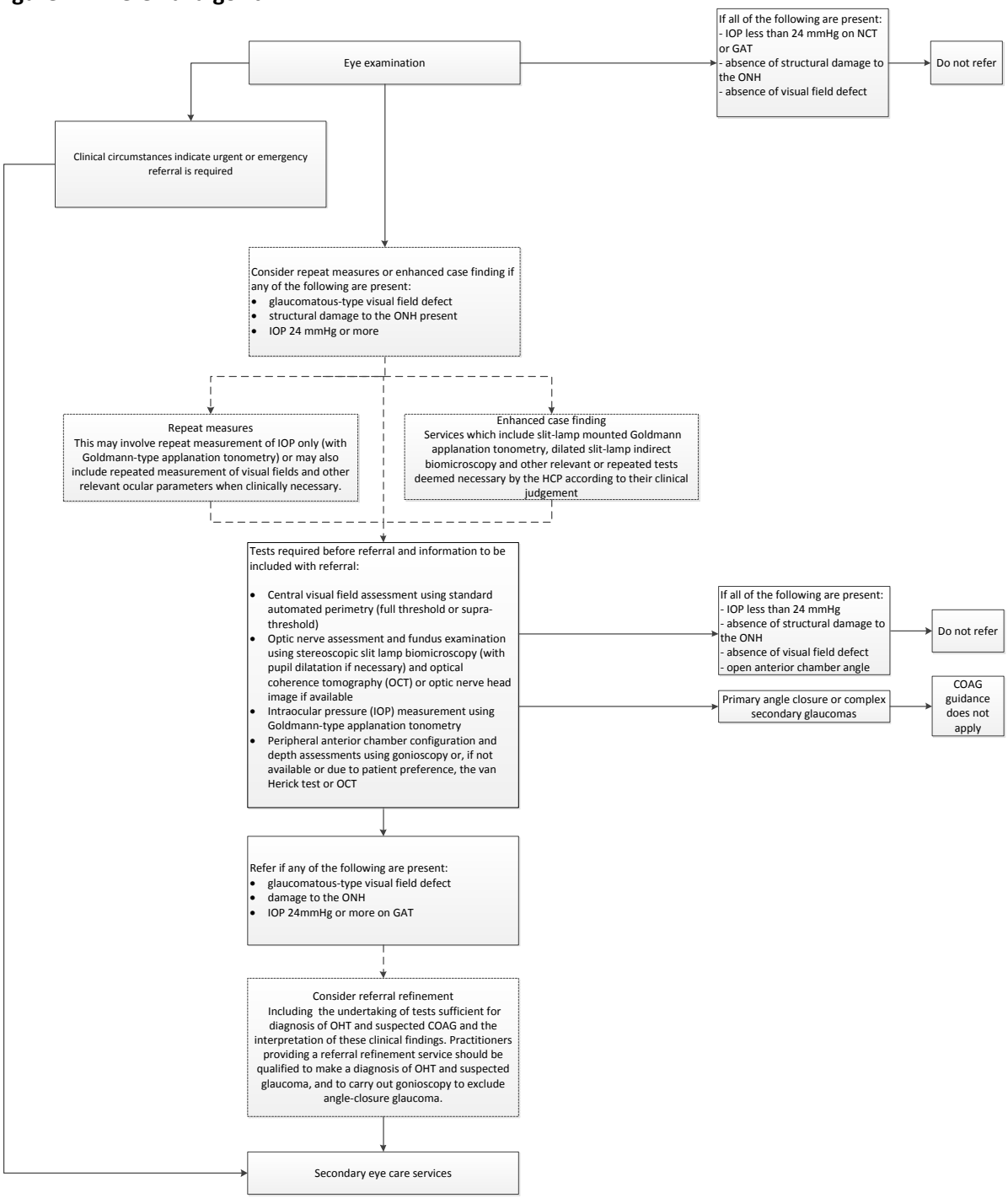


Figure 2: Diagnosis algorithm

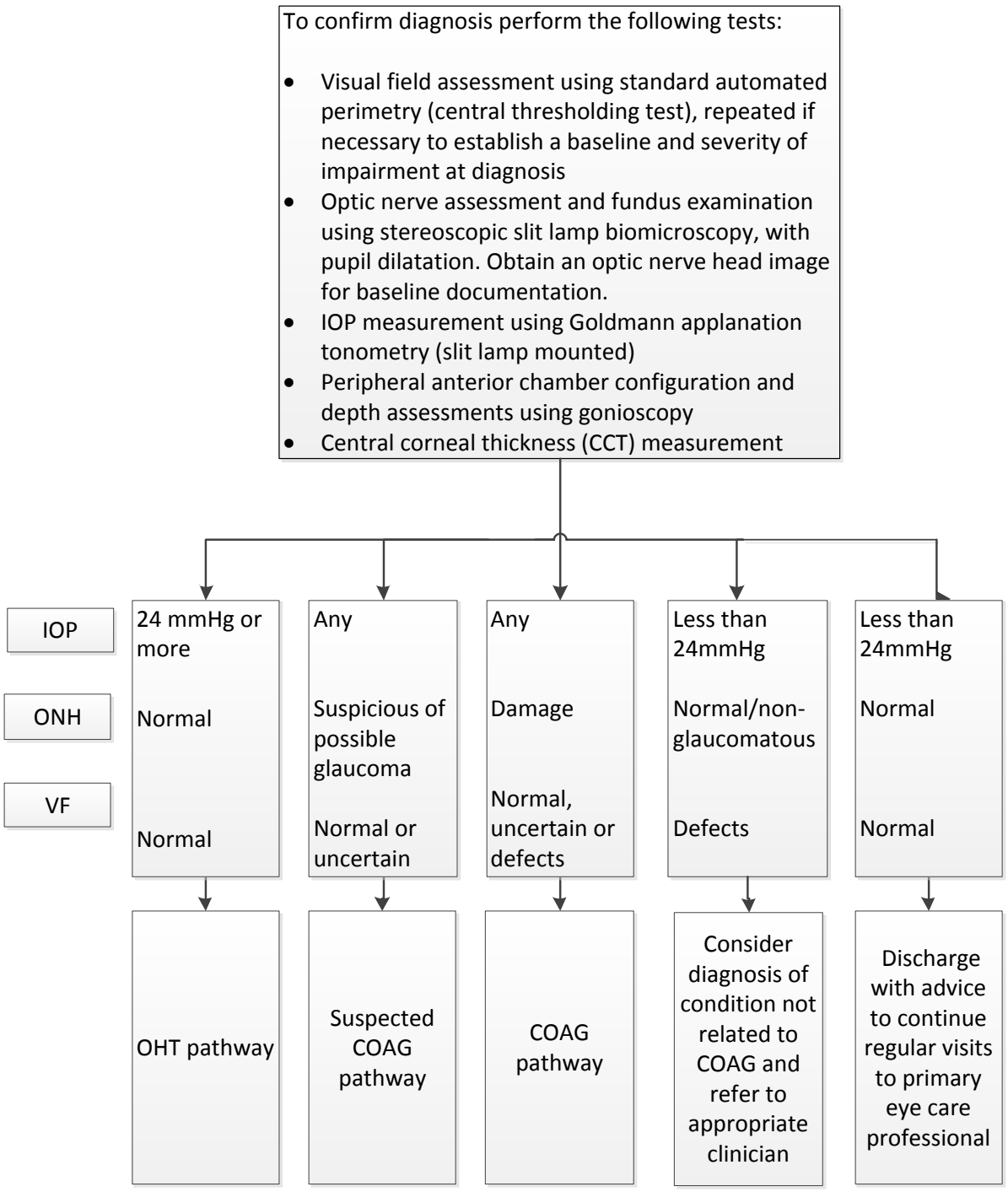


Figure 3: OHT management and reassessment algorithm

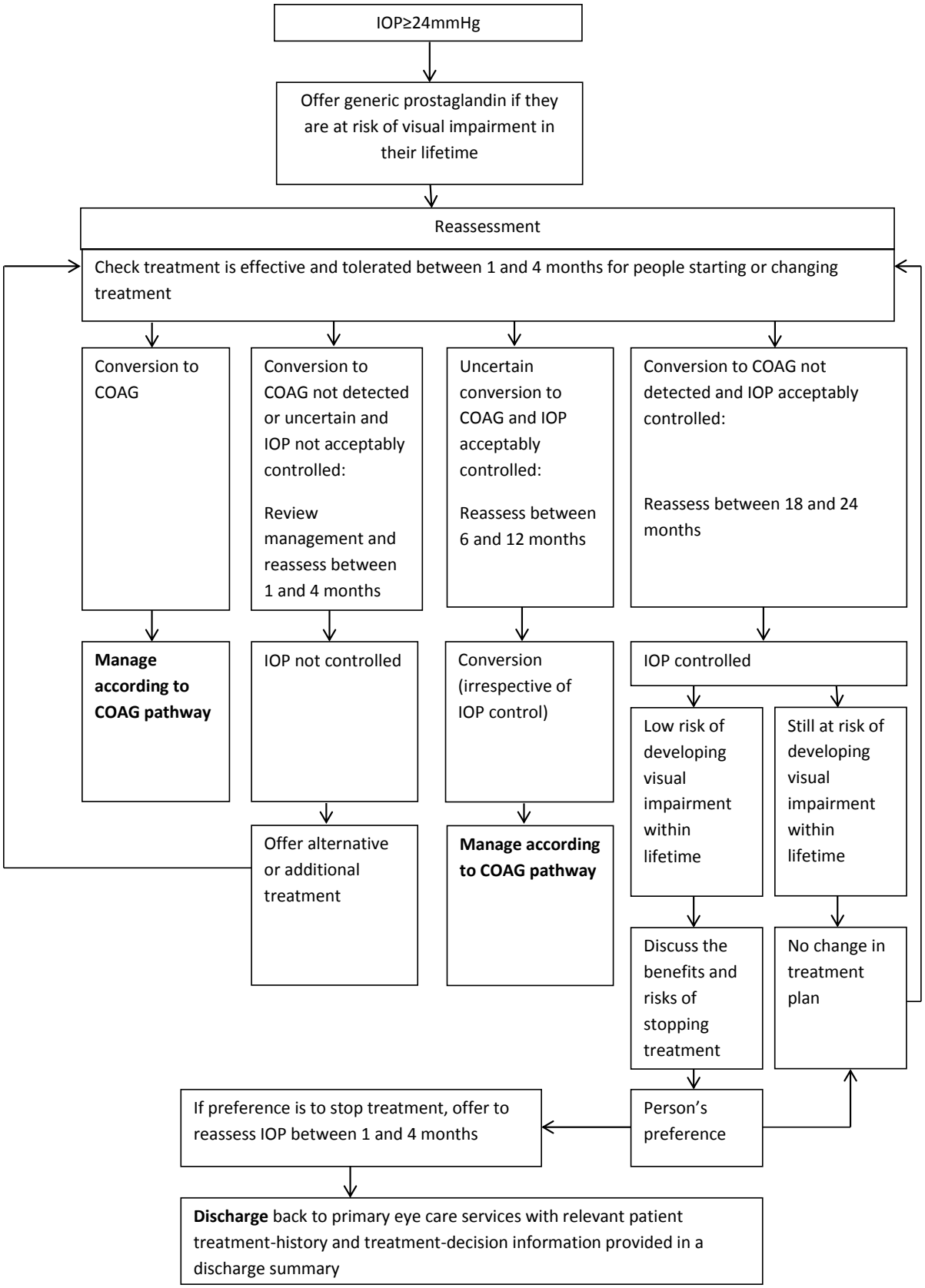


Figure 4: Suspected COAG management and reassessment algorithm

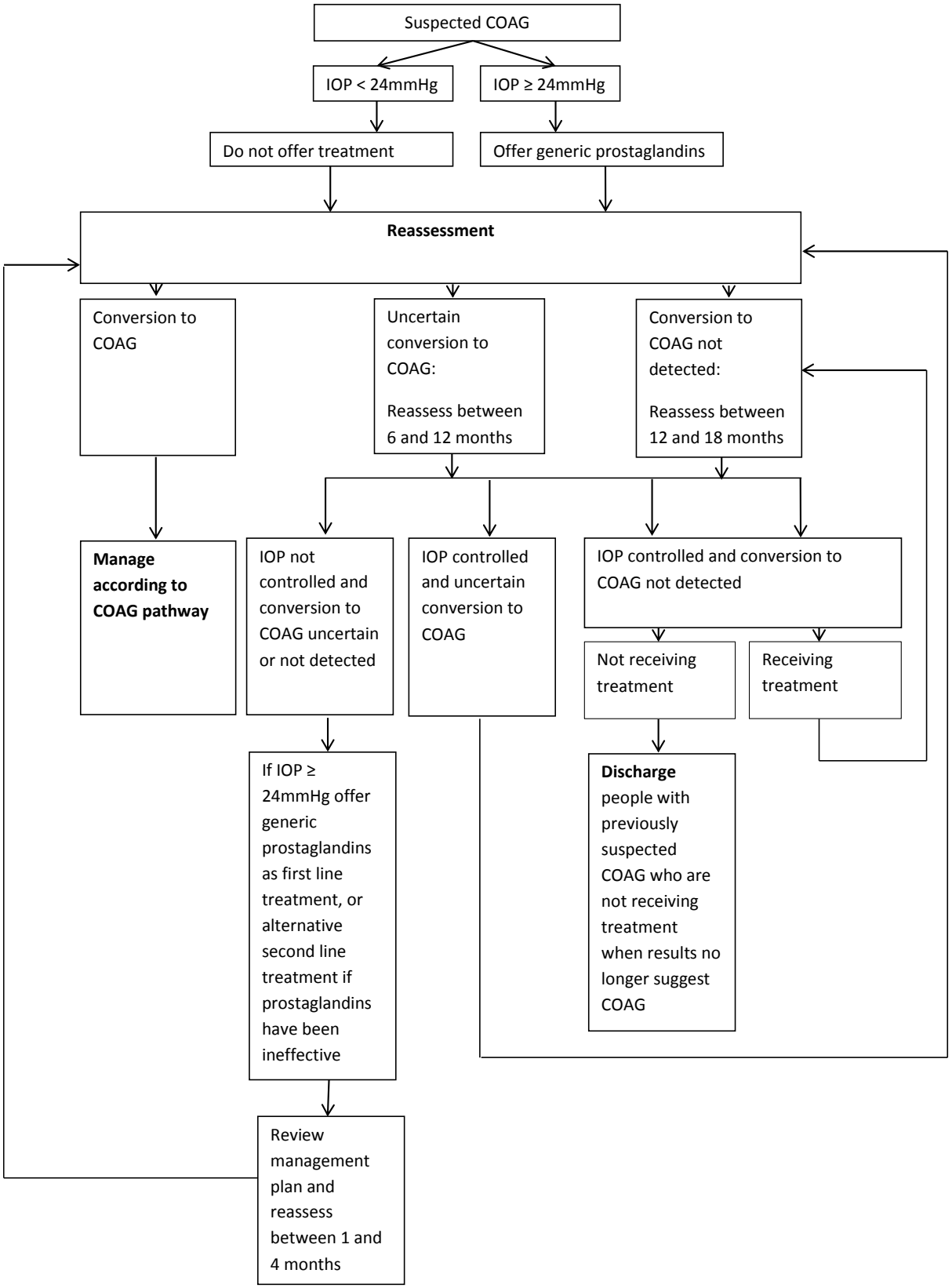
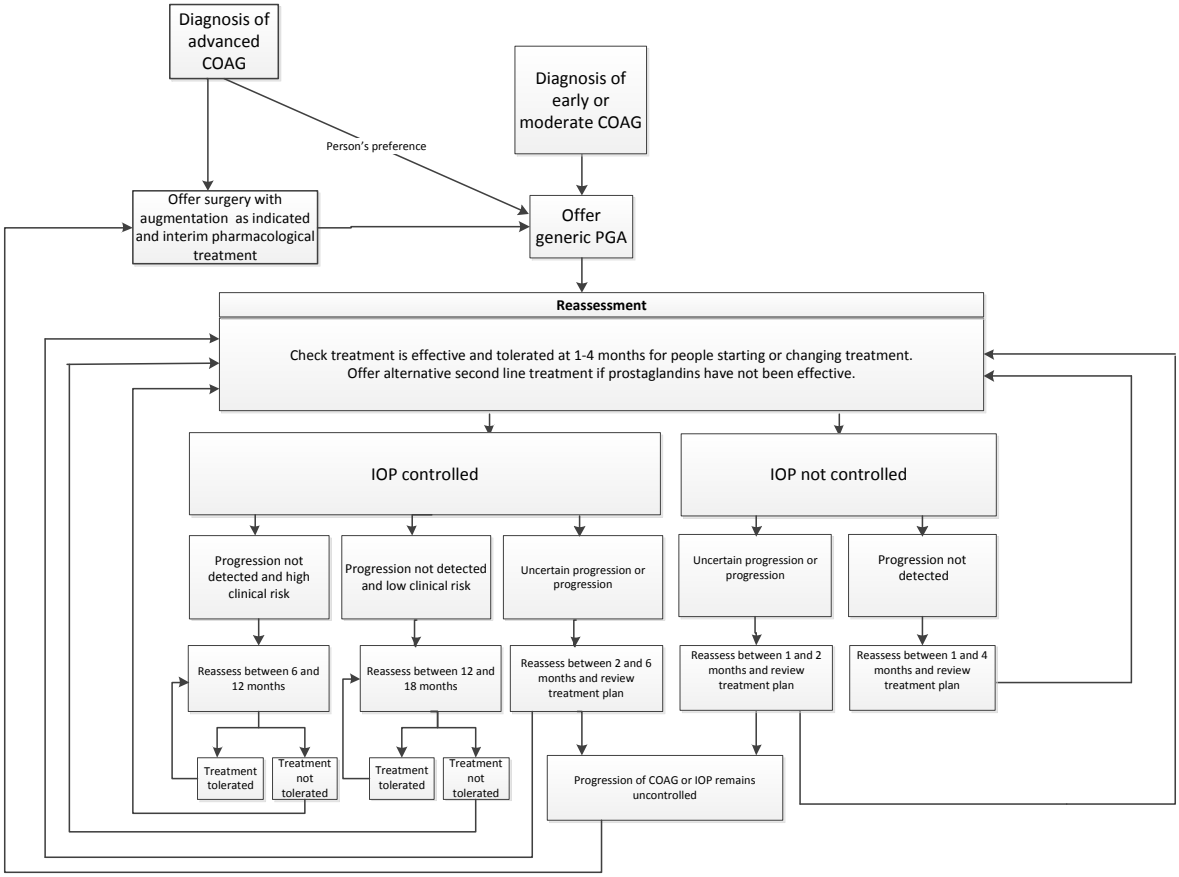


Figure 5: COAG algorithm



1.2 Full list of recommendations

1. Before referral for further investigation and diagnosis of COAG and related conditions, offer all of the following tests:
   - central visual field assessment using standard automated perimetry (full threshold or supra-threshold)
   - optic nerve assessment and fundus examination using stereoscopic slit-lamp biomicroscopy (with pupil dilatation if necessary), and optical coherence tomography (OCT) or optic nerve head image if available
   - intraocular pressure (IOP) measurement using Goldmann-type applanation tonometry
   - peripheral anterior chamber configuration and depth assessments using gonioscopy or, if not available or the patient prefers, the van Herick test or OCT. [2017]
2. Do not base a decision to refer solely on IOP measurement using non-contact tonometry. [2017]
3. Do not refer people who have previously been discharged from hospital eye services after assessment for COAG and related conditions unless clinical circumstances have changed and a new referral is needed. [2017]
4. Refer for further investigation and diagnosis of COAG and related conditions, after considering repeat measures as in recommendation 47, if:
   - there is optic nerve head damage on stereoscopic slit lamp biomicroscopy, or
   - there is a visual field defect consistent with glaucoma, or
   - IOP confirmed as 24 mmHg or more using Goldmann-type applanation tonometry. [2017]
5. Advise people with IOP below 24 mmHg to continue regular visits to their primary eye care professional. [2017]
6. Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:
   - records of all previous tests and images relevant to COAG and OHT assessment
   - records of past medical history which could affect drug choice
   - current systemic and topical medication
   - glaucoma medication record
   - drug allergies and intolerances. [2009]
7. Use alternative methods of assessment if clinical circumstances rule out standard methods (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]
8. Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturers' instructions. [2009]
9. To diagnose COAG and related conditions, offer all of the following tests:

- visual field assessment using standard automated perimetry (central thresholding test), repeated if necessary to establish severity at diagnosis
- optic nerve assessment and fundus examination using stereoscopic slit-lamp biomicroscopy, with pupil dilatation
- IOP measurement using Goldmann applanation tonometry (slit lamp mounted)
- peripheral anterior chamber configuration and depth assessments using gonioscopy
- central corneal thickness (CCT) measurement. [2017]

10. Obtain an optic nerve head image at diagnosis for baseline documentation (for example, a stereoscopic optic nerve head image or OCT). [2009, amended 2017]
11. After referral, consider an early assessment appointment when there is clinical concern based on the information provided. [2017]
12. At the time of diagnosis of ocular hypertension (OHT), assess risk of future visual impairment, taking account of risk factors such as:
    - level of IOP
    - CCT
    - family history
    - life expectancy. [2017]
13. Adopt professional[1]/ Department of Health[2] guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy. [2009]
14. Use the van Herick peripheral anterior chamber depth assessment if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]
15. At each assessment, offer the following tests to people with COAG, people suspected of having COAG and people with OHT:
    - Goldmann applanation tonometry (slit lamp mounted)
    - anterior segment slit lamp examination with van Herick peripheral anterior chamber depth assessment when clinically indicated. [2017]
16. When clinically indicated, repeat gonioscopy, for example, where a previous examination has been inconclusive or where there is suspicion of a change in clinical status of the anterior chamber angle. [2017]
17. 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 Table 35 and Table 39 for recommended reassessment intervals). [2009, amended 2017]
18. When clinically indicated, repeat visual field testing using either a central thresholding test or a supra-threshold test for people with OHT and those

[1] Royal College of Ophthalmologists (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2010_PROF_100_-CJD-Guidance-for-Ophthalmologists-joint-statement.pdf).
[2] See https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group

suspected of having COAG whose visual fields have previously been documented by standard threshold automated perimetry (central thresholding test) as being normal (see Table 34 and Table 35 for recommended reassessment interval). [2009, amended 2017]

19. When a visual field defect has previously been detected, use the same measurement strategy for each visual field assessment. [2009]

20. When clinically indicated, repeat assessment of the optic nerve head (for example, stereoscopic slit lamp biomicroscopy or imaging). [2017]

21. When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopy, obtain a new optic nerve head image for the person's records to provide a fresh benchmark for future assessments. [2009]

22. When an adequate view of the optic nerve head and surrounding area is unavailable at reassessment, people should have their pupils dilated before stereoscopic slit lamp biomicroscopy or optic nerve head imaging is repeated. [2009]

23. At each assessment, re-evaluate risk of conversion to COAG and risk of sight loss to set time to next assessment. [2017]

24. At each assessment, ask about general health and, if appropriate, factors affecting adherence to treatment, including cognitive impairment and any treatment side effects. [2017]

25. Discharge people back to primary eye care services if:

    - they were referred for OHT but do not need treatment
    - they were referred for suspected COAG but this is no longer suspected.

    Advise people that they should continue with regular visits to their primary eye care professional, at clinically appropriate intervals.[2017]

26. For people with treated OHT (baseline IOP of 24 mmHg or more) and a normal optic head and visual field at the most recent assessment:

    - use clinical judgement to assess control of IOP and risk of conversion to COAG, and
    - reassess according to Table 34. [2017]

27. For people with suspected COAG:

    - use clinical judgement to assess control of IOP and risk of conversion to COAG (optic nerve head damage and visual field defect), and
    - reassess according to Table 35. [2017]

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

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

    If a person decides to stop treatment after this discussion, offer to assess their IOP in 1 to 4 months with further reassessment if clinically indicated. [2009]

29. For people with COAG:

    - use clinical judgement to assess risk of COAG progression to sight loss, and

- reassess according to Table 39. [2017]

30. Take into account any cognitive and physical impairments when making decisions about management and treatment. [2017]

31. Offer a generic prostaglandin analogue (PGA)[3] to people with IOP of 24 mmHg or more (OHT) if they are at risk of visual impairment within their lifetime (see recommendation 12). [2017]

32. Do not offer treatment to people with OHT who are not at risk of visual impairment in their lifetime. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]

33. Offer another pharmacological treatment to people with an IOP of 24 mmHg or more who cannot tolerate their current treatment. The first choice should be an alternative generic PGA, if available, and if this is not tolerated, offer a beta-blocker. If none of these options is tolerated, offer non-generic PGA, carbonic anhydrase inhibitors, sympathomimetics, miotics or a combination of treatments. [2017]

34. Do not offer treatment to people with suspected COAG and IOP less than 24mmHg. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]

35. Offer a generic PGA[4] to people with suspected COAG and IOP of 24 mmHg or more, in line with the recommendations on treatment for people with OHT. [2017]

36. Offer a generic PGA[5] to people with COAG. [2017]

37. Check that there are no relevant comorbidities or potential drug interactions before offering pharmacological treatment. [2009]

38. Refer people whose IOP cannot be reduced sufficiently with pharmacological treatment to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options. [2009]

39. Offer people with advanced COAG, surgery with pharmacological augmentation (MMC[6]) as indicated. Offer them information on the risks and benefits associated with surgery. [2009, amended 2017]

40. Offer people who present with advanced COAG and who are listed for surgery, interim treatment with a generic PGA.[7] [2009, amended 2017]

[3] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[4] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[5] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[6] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[7] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision.

41. Encourage people to continue with the same pharmacological treatment unless:
    - their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss
    - there is progression of optic nerve head damage
    - there is progression of visual field defect
    - they cannot tolerate the drug. [2009]

42. Offer surgery with pharmacological augmentation (MMC[8]) 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. [2009, amended 2017]

43. Offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor[9] 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. [2009, amended 2017]

44. 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. [2009, amended 2017]

45. 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[10] 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[11]) as indicated.

Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[8] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[9] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[10] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[11] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

If the drug treatment option is chosen, after trying drugs from 2 therapeutic classes, consider offering surgery with pharmacological augmentation (MMC[12]) as indicated or laser trabeculoplasty. [2009, amended 2017]

46. Consider offering people with COAG who cannot tolerate a treatment:

- a drug from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor[13] 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[14]) as indicated or laser trabeculoplasty. [2009, amended 2017]

47. 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. [2009, amended 2017]

48. 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. [2009, amended 2017]

49. Before deciding to refer, consider repeating visual field assessment and IOP measurement on another occasion to confirm a visual field defect or IOP of 24 mmHg or more, unless clinical circumstances indicate urgent or emergency referral is needed. [2017]

50. People planning and providing eye care services should use a service model that includes Goldmann-type applanation tonometry before referral for diagnosis of COAG and related conditions. [2017]

51. People planning eye care services should consider commissioning referral-filtering services (for example, repeat measures, enhanced case finding, or referral refinement) for COAG and related conditions. [2017]

52. Provide results of all examinations and tests with the referral. [2017]

[12] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[13] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[14] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

53. Give a discharge summary to people who have been assessed and discharged to primary care. Send a copy to their GP and, with patient consent, copy the relevant information to the primary eye care professional nominated by the patient. Advise people to take their discharge summary with them when attending future sight tests. [2017]

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

- a specialist qualification and
- relevant experience. [2009, amended 2017]

55. Refer people with suspected optic nerve damage or repeatable visual field defect, or both, to a consultant ophthalmologist for consideration of a definitive diagnosis and formulation of a management plan. [2009]

56. Healthcare professionals involved in the diagnosis of OHT and COAG suspect status and preliminary identification of COAG should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the following:

- medical and ocular history
- differential diagnosis
- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry
- stereoscopic slit lamp biomicroscopic examination of anterior segment
- examination of the posterior segment using a slit lamp binocular indirect ophthalmoscopy
- gonioscopy
- van Herick peripheral anterior chamber depth assessment
- CCT measurement. [2009]

57. People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may have monitoring (but not treatment) from a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience and ability to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:

- Goldmann applanation tonometry (slit lamp mounted)
- standard automated perimetry (central thresholding test)
- central supra-threshold perimetry (this visual field strategy may be used for monitoring OHT or suspected COAG when the visual field is normal)
- stereoscopic slit lamp biomicroscopic examination of the anterior segment
- van Herick peripheral anterior chamber depth assessment

- examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy. [2009]

58. People with OHT, suspected COAG or COAG should have monitoring and treatment from a trained healthcare professional who has all of the following:
    - a specialist qualification
    - relevant experience
    - ability to detect a change in clinical status. [2009, amended 2017]
59. Be aware that holding an independent or non-medical prescribing qualification alone (without a specialist qualification relevant to the case complexity of glaucoma being managed) is insufficient for managing glaucoma and related conditions. [2017]
60. Healthcare professionals involved in the monitoring and treatment of OHT, suspected COAG and established COAG should be trained to make management decisions on all of the following:
    - risk factors for conversion to COAG
    - coexisting pathology
    - risk of sight loss
    - monitoring and detecting a change in clinical status (for example, visual field changes, stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)
    - pharmacology of IOP-lowering drugs
    - treatment changes for COAG, suspected COAG and OHT (with consideration given to relevant contraindications and interactions). [2009]
61. Healthcare professionals who diagnose, treat or monitor independently of consultant ophthalmologist supervision should take full responsibility for the care they provide. [2009]
62. 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 (see NICE's guideline on medicines optimisation).
- 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)
- 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. [2009, amended 2017]

1.3 Key research recommendations

1. What is the predictive value of risk tools for identifying people in the community who are at increased risk of developing COAG?
2. What is the predictive value of risk tools for identifying people with COAG who are at an increased risk of sight loss?
3. What is the effectiveness and cost effectiveness of using OCT for diagnosis and reassessment in glaucoma and related conditions?
4. What is the clinical and cost effectiveness of treating an intraocular pressure (IOP) of 22 or 23 mmHg?
5. What instrument should be used to measure health-related quality of life in people with glaucoma?

1.4 How this guideline was updated

Content from 2009 CG85 Glaucoma that has not been updated and retained in this guideline has been marked with grey highlighting throughout. Rationale for changes to recommendations can be found in the relevant linking evidence to recommendations sections and in the table in appendix R.

2 Introduction

2017 Update

The scope of this NICE guideline on diagnosing and managing chronic open-angle glaucoma has been extended to cover referral. This includes the most effective service models for referral-filtering schemes (repeat measures, enhanced case finding and referral refinement), the tests to be used for finding people with chronic open-angle glaucoma (COAG), suspected chronic open-angle glaucoma and ocular hypertension (OHT), and thresholds for onward referral. We have also updated the guidance on tests for diagnosis and reassessment, pharmacological treatments for lowering intraocular pressure and preserving visual field and reassessment intervals, which depend on prognosis.

The update has provided an opportunity to re-evaluate the clinical effectiveness, cost effectiveness and indications for treating OHT. Knowledge of corneal thickness is no longer needed to decide whether or not to treat OHT, and a single threshold of 24 mmHg is now recommended for both onward referral and treatment. Changes in the costs of pharmacological treatments, acknowledgement of short- and long-term variations in intraocular pressure and the uneven relationship between rising pressure and increased risk have allowed a simplification of the indications for OHT treatment.

Control of intraocular pressure remains critical to the therapeutic approach, with intensity of treatment and ongoing management being guided by disease severity and progression as shown by visual field change, morphological change in the optic disc, and the likelihood of progressive sight loss. Reassessment at each visit is emphasised, encouraging flexible clinical judgement about the frequency of visits and options for treatment, including stopping treatment when the perceived risk to a sighted lifetime is low.

Where fresh evidence was not found the guideline has not been updated, that is, accuracy of visual field tests, surgical interventions, laser procedures and information, education and support needed to achieve adherence to treatment.

Updating significant elements of the guideline has required an intensive effort from both the professional members of the National Guideline Centre and the guideline committee, who are thanked for their expertise, thoughtful work and in-depth discussions at and between guideline committee meetings.

Professor John Sparrow

Chair, Guideline Committee

CG85 Introduction

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

John Milton (1608–1674)

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

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

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

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

The main treatments covered in the guideline are pharmacological agents for topical use as eye drops, laser procedures and drainage surgery with or without pharmacological augmentation. Where multiple randomised controlled trials (RCT) of sufficient quality were found these were merged using

meta-analytical techniques in order to obtain a single result from all available evidence. Reporting of adverse events and patients' views from trials and other sources was considered and factored into the interpretation of evidence by the GDG. Evaluation of the cost effectiveness of the various treatment options for both COAG and OHT required the development of original cost effectiveness analyses carried out by the NCC-AC staff. For the clinicians and patient representatives of the GDG, this important aspect of the guideline was relatively unfamiliar territory at the outset. The professional staff of the centre, however, provided general and specific guidance which allowed the GDG not only to understand these complex analyses, but also to influence them with clinically relevant information. Thus, drainage surgery may appear to be the most cost-effective treatment when analysed, but this result needs to be interpreted in the context of relatively rare though serious complications, as well as patient preference, fear of surgery and personal risk averseness.

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

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

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

John Sparrow

Chair, Guideline Committee

2009

3 Development of the guideline

3.1 What is a NICE guideline?

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

NICE guidelines can:

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

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

We produce our guidelines using the following steps:

- A guideline topic is referred to NICE from NHS England.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Guideline Centre (NGC).
- The NGC establishes a Guideline Committee.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NGC and NICE produce a number of versions of this guideline:

- The 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence.
- The 'NICE guideline' lists the recommendations.
- 'Information for the public' is written using suitable language for people without specialist medical knowledge.
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from NHS England. NICE commissioned the NGC to produce the guideline.

The remit for this guideline is:

To update the existing guidance on the diagnosis and management of glaucoma.

3.3 Who developed this guideline?

A multidisciplinary Guideline Committee (GC) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Committee members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Guideline Centre (NGC) and thus supported the development of this guideline. The committee was convened by the NGC and chaired by John Sparrow in accordance with guidance from NICE.

The group met approximately every 5 to 6 weeks during the development of the guideline. At the start of the guideline development process, all committee members declared interests including consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. At all subsequent committee meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in appendix B.

Staff from the NGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers (research fellows), health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the committee.

3.3.1 What this guideline covers

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

For further details, please refer to the scope in appendix A and the review questions in Section 4.1.

3.3.2 What this guideline does not cover

Population-based screening programmes for glaucoma.

3.3.3 Relationships between the guideline and other NICE guidance

Related NICE technology appraisals:

- Ciclosporin for treating dry eye disease that has not improved despite treatment with artificial tears. NICE technology appraisal guidance TA369 (2015).

Related NICE interventional procedures guidance:

- Canaloplasty for primary open-angle glaucoma. NICE interventional procedure guidance 260 (2008).
- Trabecular stent bypass microsurgery for open-angle glaucoma. NICE interventional procedure guidance 396 (2011).
- Trabeculotomy ab interno for open-angle glaucoma. NICE interventional procedure 397 (2011).

Related NICE guidelines:

- Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. NICE guideline CG76 (2009).
- Medicines optimisation: the safe and effective use of medicines to enable the best possible outcomes. NICE guideline NG5 (2015).

Related NICE guidance currently in development:

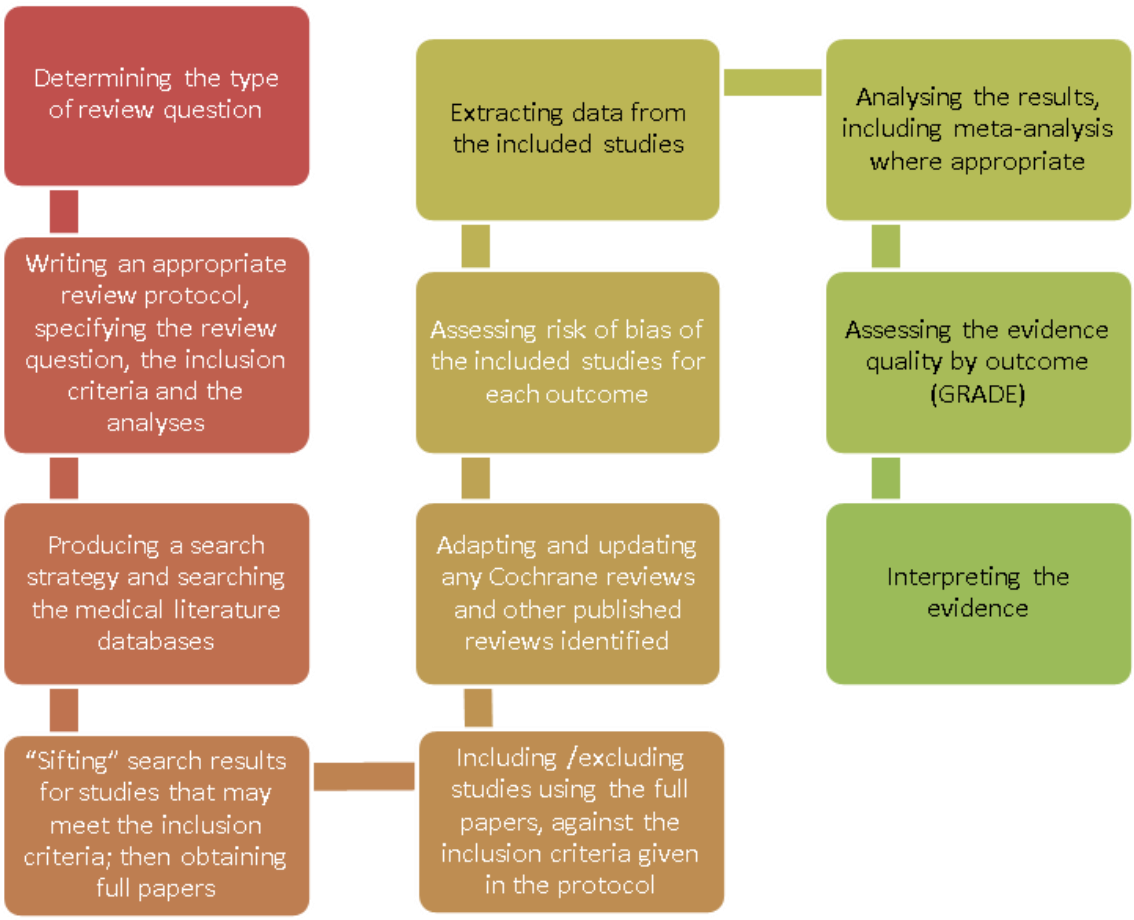
- Cataracts in adults: management. NICE guideline. Publication expected October 2017.
- Macular degeneration. NICE guideline. Publication expected November 2017.
- Glaucoma – lerdelimumab (CAT-152) [ID383]. Technology appraisal guidance. Publication TBC.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to develop the recommendations that are presented in subsequent chapters of this guideline. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual, 2012 and 2014 versions.[101,103]

Sections 4.1 to 4.2.1 describe the process used to identify and review clinical evidence (summarised in Figure 6), Sections 4.2 and 4.4 describe the process used to identify and review the health economic evidence, and Section 4.5 describes the process used to develop recommendations.

Figure 6: Step-by-step process of review of evidence in the guideline



4.1 Developing the review questions and outcomes

Review questions were developed using a PICO framework (population, intervention, comparison and outcome) for intervention reviews; using a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the committee. The NGC technical team drafted the review questions and the committee refined and validated them. The questions were based on the key clinical areas identified in the scope (appendix A).

A total of 9 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5.1	Prognostic risk tools	What is the accuracy of risk tools for identifying people in the community who are at increased risk of developing chronic open-angle glaucoma?	• 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
5.2	Prognostic risk tools	What is the accuracy of risk tools for identifying people with chronic open-angle glaucoma who are at an increased risk of vision loss?	• 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
6.1	Diagnostic test accuracy	What is the accuracy of tests for identifying closed or occludable anterior chamber angle?	• Specificity • Sensitivity • C-statistic (ROC curve or AUC)
6.2	Diagnostic test accuracy	What is the accuracy of tests for measuring IOP and monitoring changes in IOP, including repeat measures?	• Specificity • Sensitivity • C-statistic (ROC curve or AUC)
6.5	Diagnostic test accuracy	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)?	• Specificity • Sensitivity • C-statistic (ROC curve or AUC)
7.1	Intervention	What are the optimum intervals for monitoring people with ocular hypertension, suspected chronic open-angle glaucoma or both?	Critical outcomes: • 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) Important outcomes:

Chapter	Type of review	Review questions	Outcomes
			• 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)
7.2	Intervention	What are the optimum intervals for monitoring people with chronic open-angle glaucoma?	Critical outcomes: • 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) Important outcomes: • 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)
9.1	Intervention	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?	Critical outcomes: • Glaucomatous visual field loss (continuous; duration of study) • Normal visual field to visual field defect (dichotomous; confirmed by any method; duration of study) • Progression of glaucomatous visual field defect (confirmed by any method; 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) ○ Breathing difficulties ○ Cardiovascular events Important outcomes:

Chapter	Type of review	Review questions	Outcomes
			• 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 (duration of study) • Treatment adherence (duration of study) • Treatment discontinuation (duration of study)
11.2	Intervention	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?	Critical outcomes: • Appropriate referral (for OHT, suspected COAG, COAG) or non-referral • Missed OHT, suspected COAG, COAG • Vision loss as a result of incorrect non-referral Important outcomes: • 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)

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2014.[101] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

All searches were conducted in Medline, Embase, and The Cochrane Library. All searches were updated on 24 January 2017. No papers published after this date were considered.

Search strategies were quality assured by crosschecking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking committee members to highlight any additional studies. Searches were quality assured by a second information scientist before being run. The questions, the study types applied, the databases searched and the years covered can be found in appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

All references sent by stakeholders were considered. Searching for unpublished literature was not undertaken. The NGC and NICE do not have access to drug manufacturers' unpublished clinical trial results, so the clinical evidence considered by the committee for pharmaceutical interventions may be different from that considered by the MHRA and European Medicines Agency for the purposes of licensing and safety regulation.

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to glaucoma in the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment database (HTA), from 2008. (NHS EED ceased to be updated after March 2015). The search was run on Medline and Embase using a health economic filter, from January 2014, to ensure recent publications that had not yet been indexed by the economic databases were identified. Medline and Embase were searches from 2008 using quality of life and economic modelling filters. An additional search across all databases for the years 2000-2008 took place to find evidence relating to the service provision and prognostic risk tools questions that were not including in the original guideline. Where possible, searches were restricted to papers published in English. Studies published in languages other than English were not reviewed.

The health economic search strategies are included in appendix G. All searches were updated on 24 January 2017. No papers published after this date were considered.

4.3 Identifying and analysing evidence of effectiveness

Research fellows conducted the tasks listed below, which are described in further detail in the rest of this section:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population, and reported on outcomes of interest (review protocols are included in appendix C).
- Critically appraised relevant intervention, prognostic and diagnostic studies using the appropriate study design checklist as specified in the NICE guidelines manual.[101] Qualitative studies were critically appraised using the GRADE CERQual approach for rating confidence in the body of evidence as a whole and using an NGC checklist for the methodological limitations section of the quality assessment.
- Extracted key information about interventional study methods and results using 'EviBase', NGC's purpose-built software. EviBase produces summary evidence tables, including critical appraisal ratings. Key information about non-interventional study methods and results was manually

extracted onto standard evidence tables and critically appraised separately (evidence tables are included in appendix H).

- Generated summaries of the evidence by outcome. Outcome data were combined, analysed and reported according to study design:
  - Randomised data were meta-analysed where appropriate and reported in GRADE profile tables.
  - Data from non-randomised studies were presented as a range of values in GRADE profile tables or meta-analysed if appropriate.
  - Prognostic data were meta-analysed where appropriate and reported in modified GRADE profile tables.
  - Diagnostic data studies were meta-analysed where appropriate or presented as a range of values in adapted GRADE profile tables.
- A sample of a minimum of 10% of the abstract lists of the first 3 sifts by new reviewers and those for complex review questions (for example, prognostic reviews) were double sifted by a senior research fellow and any discrepancies were rectified. All of the evidence reviews were quality assured by a senior research fellow. This included checking:
  - papers were included or excluded appropriately
  - a sample of the data extractions
  - correct methods were used to synthesise data
  - a sample of the risk of bias assessments.

4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the criteria defined in the review protocols, which can be found in appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in appendix L. The committee was consulted about any uncertainty regarding inclusion or exclusion.

The key population inclusion criterion was:

- Adults (18 years and over) with, or at risk of, ocular hypertension (OHT), suspected chronic open-angle glaucoma (COAG) and COAG.

The key population exclusion criterion was:

- Children and young people under 18 years.
- 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.

Conference abstracts were not included in any of the reviews. Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

4.3.2 Type of studies

Randomised trials, non-randomised studies, and other observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that can produce an unbiased estimate of the intervention effects. Crossover RCTs were not appropriate for the question on appropriate pharmacological treatments. If non-randomised intervention studies were considered

appropriate for inclusion (for example, in prognostic risk tool and diagnostic reviews) the committee stated a priori in the protocol that either certain identified variables must be equivalent at baseline or else the analysis had to adjust for any baseline differences. If the study did not fulfil either criterion, it was excluded. Please refer to the review protocols in appendix C for full details on the study design of studies selected for each review question.

For diagnostic review questions, diagnostic RCTs, cross-sectional studies and prospective cohort studies were included. For prognostic review questions, prospective cohort studies were included. Case–control studies were not included.

Where data from non-randomised studies were included, the results for each outcome were presented separately for each study or meta-analysed if appropriate.

4.3.3 Methods of combining clinical studies

4.3.3.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted using Cochrane Review Manager (RevMan5)[123] software to combine the data given in all studies for each of the outcomes of interest for the review question.

4.3.3.1.1 Analysis of different types of data

Dichotomous outcomes

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate risk ratios (relative risk, RR) for the binary outcomes, which included:

- normal visual field to visual field defect
- vision loss
- adverse events
  - allergic reaction/intolerance (including red eye)
  - breathing difficulties
  - cardiovascular events
- normal/suspicious to abnormal optic nerve head
- treatment adherence
- treatment discontinuation
- appropriate referral
- missed OHT, suspected COAG or COAG
- vision loss as a result of incorrect non-referral
- development of glaucoma

The absolute risk difference was also calculated using GRADEpro[48] software, using the median event rate in the control arm of the pooled results.

For binary variables where there were zero events in either arm or a less than 1% event rate, Peto odds ratios, rather than risk ratios, were calculated. Peto odds ratios are more appropriate for data with a low number of events.

Continuous outcomes

Continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. These outcomes included:

- glaucomatous visual field loss
- long-term glaucomatous visual field loss
- progression of glaucomatous visual field defect
- health-related quality of life
- optic nerve head damage
- long-term optic nerve head damage
- progression of optic nerve head damage
- IOP level
- patient/carer satisfaction

Where the studies within a single meta-analysis had different scales of measurement, standardised mean differences were used (providing all studies reported either change from baseline or final values rather than a mixture of both); each different measure in each study was 'normalised' to the standard deviation value pooled between the intervention and comparator groups in that same study.

The means and standard deviations of continuous outcomes are required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals (95% CI) were reported, and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5[123] software). Where p values were reported as 'less than', a conservative approach was undertaken. For example, if a p value was reported as 'p≤0.001', the calculations for standard deviations were based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (version 5.1.0, updated March 2011) were applied.

4.3.3.1.2 Generic inverse variance

If a study reported only the summary statistic and 95% CI the generic-inverse variance method was used to enter data into RevMan5.[123] If the control event rate was reported, this was used to generate the absolute risk difference in GRADEpro.[48] If multivariate analysis was used to derive the summary statistic but no adjusted control event rate was reported, no absolute risk difference was calculated.

4.3.3.1.3 Heterogeneity

Statistical heterogeneity was assessed for each meta-analysis estimate by considering the chi-squared test for significance at $p<0.1$ or an I-squared (I^2) inconsistency statistic (with an I-squared value of more than 50% indicating significant heterogeneity) as well as the distribution of effects. Where significant heterogeneity was present, predefined subgrouping of studies was carried out for either as determined a priori in the protocols (appendix C).

If the subgroup analysis resolved heterogeneity within all of the derived subgroups, then each of the derived subgroups were adopted as separate outcomes (providing at least 1 study remained in each subgroup). Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. Any subgroup differences were interpreted with caution as separating the groups breaks the study randomisation and as such is subject to uncontrolled confounding.

For some questions, additional subgrouping was applied, and this is documented in the individual review question protocols (see appendix C). These additional subgrouping strategies were applied independently, so subunits of subgroups were not created, unlike the situation with strata. Other subgrouping strategies were only used if the age category subgroup was unable to explain heterogeneity; then, these further subgrouping strategies were applied in order of priority. Again, once a subgrouping strategy was found to explain heterogeneity from all derived subgroups, further subgrouping strategies were not used.

If all predefined strategies of subgrouping were unable to explain statistical heterogeneity within each derived subgroup, then a random effects (DerSimonian and Laird) model was employed to the entire group of studies in the meta-analysis. A random-effects model assumes a distribution of populations, rather than a single population. This leads to a widening of the confidence interval around the overall estimate, thus providing a more realistic interpretation of the true distribution of effects across more than 1 population. If, however, the committee considered the heterogeneity was so large that meta-analysis was inappropriate, then the results were described narratively.

4.3.3.2 Network meta-analysis

A network meta-analysis (NMA) was conducted to estimate the effectiveness of prostaglandin analogues and beta-blockers in lowering IOP to prevent conversion to COAG in people with OHT. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the probability of each antiviral treatment being the best for an outcome and as effect estimates for how much each treatment is better than the other treatments included in the network.

A hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4. We used statistical models for fixed and random effects that allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms. The model was based on original work from the University of Bristol.[164] The checklist 'Evidence Synthesis of Treatment Efficacy in Decision Making: A Reviewer's Checklist'[1] was completed.

As it is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed-effects or random-effects models. For pairwise meta-analysis, a fixed-effects model was used in the first instance. For the network set up in our NMA, both fixed- and random-effect models were performed. These models were then compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset that has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. However, if the difference in DIC between a fixed- and random-effect model was smaller than 5 points and the models made very similar inferences, then we reported the fixed-effects model results as that makes fewer assumptions than the random-effect model, contains fewer parameters and is easier to interpret clinically.

Heterogeneity was assessed in the results of the random-effects model by using the method described by Dias,[36] which compares the size of the treatment effect to the extent of between-trials variation. This method tries to answer the question of what is the reasonable confidence interval of the log odds ratio of an outcome for the prediction of the confidence interval of the log odds ratio of the same outcome of a future trial of infinite size.

Inconsistency in the networks was tested by comparing any available direct and indirect treatment comparison and testing the null hypothesis that the indirect evidence was not different from the direct evidence on the odds ratio scale using the normal distribution. Inconsistency was identified if

the mean estimates (mean odds ratios) of the direct comparisons were outside the confidence intervals of the odds ratios as generated from the NMA output.

There were 3 main outputs from the NMA:

- estimated log odds ratios (ORs; with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence
- the probability that each treatment was best, based on the proportion of Markov chain iterations in which each treatment had the highest probability of achieving the outcomes selected in the network
- a ranking of treatments compared to baseline groups (presented as the median rank and its 95% credible intervals).

4.3.3.3 Data synthesis for diagnostic test accuracy reviews

Two separate review protocols were produced to reflect the 2 different diagnostic study designs.

4.3.3.3.1 Diagnostic RCTs

Diagnostic RCTs (sometimes referred to as test and treat trials) are a randomised comparison of 2 diagnostic tests, with study outcomes being clinically important consequences of the diagnosis (patient-related outcome measures similar to those in intervention trials, such as mortality). Patients are randomised to receive test A or test B, followed by identical therapeutic interventions based on the results of the test (so someone with a positive result would receive the same treatment regardless of whether they were diagnosed by test A or test B). Downstream patient outcomes are then compared between the 2 groups. As treatment is the same in both arms of the trial, any differences in patient outcomes will reflect the accuracy of the tests in correctly establishing who does and does not have the condition. Data were synthesised using the same methods for intervention reviews (see Section 4.3.3.1.1 above).

4.3.3.3.2 Diagnostic accuracy studies

For diagnostic test accuracy studies, a positive result on the index test was found if the patient had values of the measured quantity above or below a threshold value, and different thresholds could be used. The thresholds were pre-specified by the committee including whether or not data could be pooled across a range of thresholds. Diagnostic test accuracy measures used in the analysis were the area under the receiver operating characteristics (ROC) curve (AUC) and, for different thresholds (if appropriate), sensitivity and specificity. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition. In practice, this varies amongst studies. If a test has a high sensitivity, then very few people with the condition will be missed (few false negatives). For example, a test with a sensitivity of 97% will only miss 3% of people with the condition. Conversely, if a test has a high specificity, then few people without the condition would be incorrectly diagnosed (few false positives). For example, a test with a specificity of 97% will only incorrectly diagnose 3% of people who do not have the condition as positive. For this guideline, sensitivity or specificity was considered more important depending on the context the test was being used in. For example, specificity was prioritised at case finding in order to reduce the number of unnecessary referrals to secondary care, and sensitivity was prioritised at diagnosis to minimise the number of missed cases (false negatives) that could have a detrimental impact on the vision of the patient. Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5.[123] In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given or else were derived from raw data or calculated from the set of test accuracy statistics.

Diagnostic meta-analysis was conducted where appropriate, that is, when 3 or more studies were available per threshold. Test accuracy for the studies was pooled using the bivariate method for the direct estimation of summary sensitivity and specificity using a random-effects approach in WinBUGS software.[164] The advantage of this approach is that it produces summary estimates of sensitivity and specificity that account for the correlation between the 2 statistics. Other advantages of this method have been described elsewhere.[122,156,157] The bivariate method uses logistic regression on the true positives, true negatives, false positives and false negatives reported in the studies. Overall sensitivity and specificity and confidence regions were plotted (using methods outlined by Novielli 2010.[108]) Pooled sensitivity and specificity and their 95% CIs were reported in the clinical evidence summary tables. For scores with fewer than 3 studies, each study's sensitivity and the paired specificity were reported where possible.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots and pooled diagnostic meta-analysis plots.

The following criteria were used for evaluating AUCs:

- ≤0.50: worse than chance
- 0.50–0.60: very poor
- 0.61–0.70: poor
- 0.71–0.80: moderate
- 0.81–0.90: good
- 0.91–1.00: excellent or perfect test.

4.3.3.4 Data synthesis for risk prediction rules

Evidence reviews on risk prediction rules or risk prediction tool results were presented separately for discrimination and calibration. The discrimination data were analysed according to the principles of data synthesis for diagnostic accuracy studies as outlined in Section 4.3.3.3.2. Calibration data such as r-squared (R^2), if reported, were presented separately to the discrimination data. The results were presented for each study separately along with the quality rating for the study and modified GRADE assessment.

4.3.4 Appraising the quality of evidence by outcomes

4.3.4.1 Intervention reviews

The evidence for outcomes from the included RCTs and, where appropriate, non-randomised intervention studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro[48]) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results.

Each outcome was first examined for each of the quality elements listed and defined in Table 2.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional or assessor) and attrition bias (due to

Quality element	Description
	missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example a result may be consistent with both clinical benefit AND clinical harm) and thus be imprecise.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an overestimate of the effectiveness of that outcome.
Other issues	Sometimes randomisation may not adequately lead to group equivalence of confounders, and if so, this may lead to bias, which should be taken into account. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Details of how the 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) were appraised for each outcome are given below. Publication or other bias was only taken into consideration in the quality assessment if it was apparent.

4.3.4.1.1 Risk of bias

The main domains of bias for RCTs are listed in Table 3. Each outcome had its risk of bias assessed within each study first. For each study, if there were no risks of bias in any domain, the risk of bias was given a rating of 0. If there was risk of bias in just 1 domain, the risk of bias was given a 'serious' rating of −1, but if there was risk of bias in 2 or more domains the risk of bias was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome, by taking into account the weighting of studies according to study precision. For example, if the most precise studies tended to each have a score of −1 for that outcome, the overall score for that outcome would tend towards −1.

Table 3: Principle domains of bias in randomised controlled trials

Limitation	Explanation
Selection bias (sequence generation and allocation concealment)	If those enrolling patients are aware of the group to which the next enrolled patient will be allocated, either because of a non-random sequence that is predictable, or because a truly random sequence was not concealed from the researcher, this may translate into systematic selection bias. This may occur if the researcher chooses not to recruit a participant into that specific group because of: • knowledge of that participant's likely prognostic characteristics, and • a desire for one group to do better than the other.
Performance and detection bias (lack of blinding of patients and healthcare professionals)	Patients, caregivers, those adjudicating or recording outcomes, and data analysts should not be aware of the arm to which patients are allocated. Knowledge of the group can influence: • the experience of the placebo effect • performance in outcome measures • the level of care and attention received, and • the methods of measurement or analysis

Limitation	Explanation
	all of which can contribute to systematic bias.
Attrition bias	Attrition bias results from an unaccounted for loss of data beyond a certain level (a differential of 10% between groups). Loss of data can occur when participants are compulsorily withdrawn from a group by the researchers (for example, when a per-protocol approach is used) or when participants do not attend assessment sessions. If the missing data are likely to be different from the data of those remaining in the groups, and there is a differential rate of such missing data from groups, systematic attrition bias may result.
Selective outcome reporting	Reporting of some outcomes and not others based on the results can also lead to bias, as this may distort the overall impression of efficacy.
Other limitations	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules. • Use of unvalidated patient-reported outcome measures. • Lack of washout periods to avoid carry-over effects in crossover trials. • Recruitment bias in cluster-randomised trials.

The assessment of risk of bias differs for non-randomised intervention studies, as they are inherently at high risk of selection bias. For this reason, GRADE requires that non-randomised evidence is initially downgraded based on study design, starting with a rating of –2. This accounts for selection bias and non-randomised intervention studies are not downgraded any further on that domain. Non-randomised evidence was assessed against the remaining domains used for RCTs in Table 3, and downgraded further as appropriate.

4.3.4.1.2 Indirectness

Indirectness refers to the extent to which the populations, interventions, comparisons and outcome measures are dissimilar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention. As for the risk of bias, each outcome had its indirectness assessed within each study first. For each study, if there were no sources of indirectness, indirectness was given a rating of 0. If there was indirectness in just 1 source (for example, in terms of population), indirectness was given a 'serious' rating of −1, but if there was indirectness in 2 or more sources (for example, in terms of population and treatment) the indirectness was given a 'very serious' rating of −2. A weighted average score was then calculated across all studies contributing to the outcome by taking into account study precision. For example, if the most precise studies tended to have an indirectness score of −1 each for that outcome, the overall score for that outcome would tend towards −1.

4.3.4.1.3 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. When estimates of the treatment effect across studies differ widely, this suggests true differences in the underlying treatment effect, which may be due to differences in populations, settings or doses. When heterogeneity existed within an outcome (chi-squared $p<0.1$, or $I^2>50\%$), but no plausible explanation could be found, the quality of evidence for that outcome was downgraded. Inconsistency for that outcome was given a 'serious' score of −1 if the I^2 was 50–74%, and a 'very serious' score of −2 if the I^2 was 75% or more.

If inconsistency could be explained based on pre-specified subgroup analysis (that is, each subgroup had an $I^2<50\%$), the committee considered this as well as whether to make separate recommendations on new outcomes based on the subgroups defined by the assumed explanatory

factors. In such a situation, the quality of evidence was not downgraded for those emergent outcomes.

Since the inconsistency score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

4.3.4.1.4 Imprecision

The criteria applied for imprecision were based on the 95% CIs for the pooled estimate of effect and the minimal important differences (MID) for the outcome. The MIDs are the threshold for appreciable benefits and harms, separated by a zone either side of the line of no effect where there is assumed to be no clinically important effect. If either end of the 95% CI of the overall estimate of effect crossed 1 of the MID lines, imprecision was regarded as serious and a 'serious' score of −1 was given. This was because the overall result, as represented by the span of the confidence interval, was consistent with 2 interpretations as defined by the MID (for example, both no clinically important effect and clinical benefit were possible interpretations). If both MID lines were crossed by either or both ends of the 95% CI then imprecision was regarded as very serious and a 'very serious' score of −2 was given. This was because the overall result was consistent with all 3 interpretations defined by the MID (no clinically important effect, clinical benefit and clinical harm). This is illustrated in Figure 7. As for inconsistency, since the imprecision score was based on the meta-analysis results, the score represented the whole outcome and so weighted averaging across studies was not necessary.

The position of the MID lines is ideally determined by values reported in the literature. 'Anchor-based' methods aim to establish clinically meaningful changes in a continuous outcome variable by relating or 'anchoring' them to patient-centred measures of clinical effectiveness that could be regarded as gold standards with a high level of face validity. For example, a MID for an outcome could be defined by the minimum amount of change in that outcome necessary to make patients feel their quality of life had 'significantly improved'. MIDs in the literature may also be based on expert clinician or consensus opinion concerning the minimum amount of change in a variable deemed to affect quality of life or health. For binary variables, many MIDs reported in the literature will inevitably be based on expert consensus, as such MIDs relate to all-or-nothing population effects rather than measurable effects on an individual, and so are often not amenable to patient-centred 'anchor' methods.

In the absence of values identified in the literature, the alternative approach to deciding on MID levels is the 'default' method, as follows:

- For categorical outcomes, the MIDs were taken to be RRs of 0.75 and 1.25. For 'positive' outcomes such as 'patient satisfaction', the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm, while the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit. For 'negative' outcomes such as 'bleeding', the opposite occurs, so the RR of 0.75 is taken as the line denoting the boundary between no clinically important effect and a clinically significant benefit, whilst the RR of 1.25 is taken as the line denoting the boundary between no clinically important effect and a clinically significant harm.
- For mortality, any change was considered clinically important and the imprecision was assessed based on the whether the confidence intervals crossed the line of no effect, that is, whether the result was consistent with both benefit and harm.
- For continuous outcome variables the MID was taken as half the median baseline standard deviation of that variable, across all studies in the meta-analysis. Hence the MID denoting the minimum clinically significant benefit was positive for a 'positive' outcome (for example, a quality of life measure where a higher score denotes better health) and negative for a 'negative' outcome (for example, a visual analogue scale [VAS] pain score). Clinically significant harms will be the

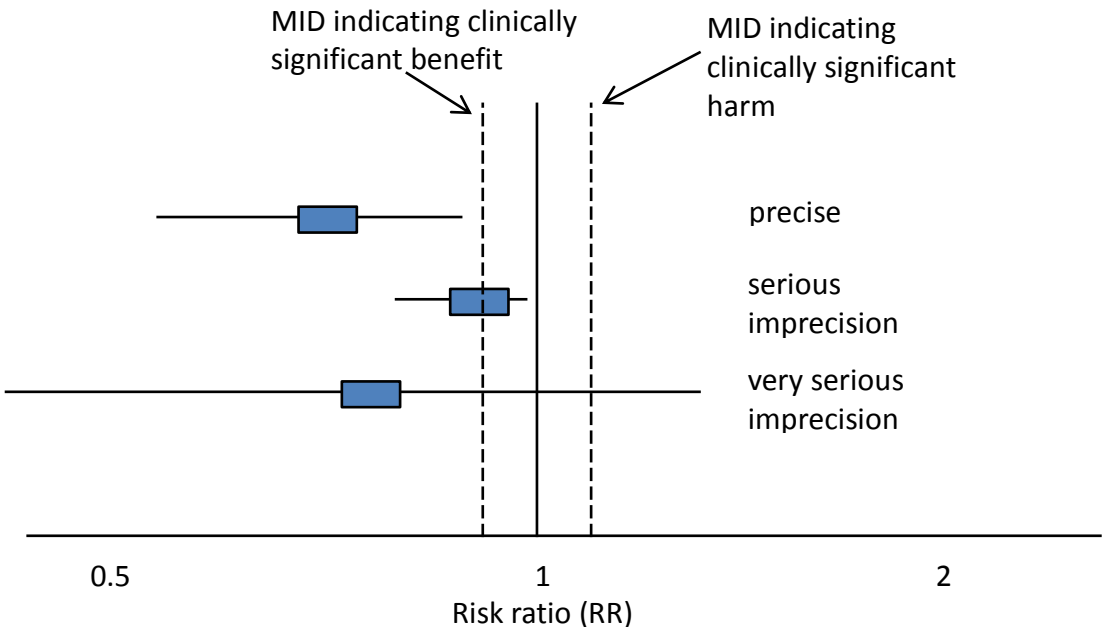
converse of these. If baseline values are unavailable, then half the median comparator group standard deviation of that variable will be taken as the MID.

- If standardised mean differences have been used, then the MID will be set at the absolute value of +0.5. This follows because standardised mean differences are mean differences normalised to the pooled standard deviation of the 2 groups, and are thus effectively expressed in units of 'numbers of standard deviations'. The 0.5 MID value in this context therefore indicates half a standard deviation, the same definition of MID as used for non-standardised mean differences.

The default MID value was subject to amendment after discussion with the committee. If the committee decided that the MID level should be altered, after consideration of absolute as well as relative effects, this was allowed, provided that any such decision was not influenced by any bias towards making stronger or weaker recommendations for specific outcomes.

For this guideline, no appropriate MIDs for continuous or dichotomous outcomes were found in the literature, and so the default method was adopted.

Figure 7: Illustration of precise and imprecise outcomes based on the 95% CI of dichotomous outcomes in a forest plot (Note that all 3 results would be pooled estimates, and would not, in practice, be placed on the same forest plot)



4.3.4.1.5 Overall grading of the quality of clinical evidence

Once an outcome had been appraised for the main quality elements, as above, an overall quality grade was calculated for that outcome. The scores (0, −1 or −2) from each of the main quality elements were summed to give a score that could be anything from 0 (the best possible) to −8 (the worst possible). However, scores were capped at −3. This final score was then applied to the starting grade that had originally been applied to the outcome by default, based on study design. All RCTs started as High and the overall quality became Moderate, Low or Very Low if the overall score was −1, −2 or −3 points respectively. The significance of these overall ratings is explained in Table 4. The reasons for downgrading in each case were specified in the footnotes of the GRADE tables.

Non-randomised intervention studies started at Low, and so a score of −1 would be enough to take the grade to the lowest level of Very Low. Non-randomised intervention studies could, however, be upgraded if there was a large magnitude of effect or a dose-response gradient.

Table 4: Overall quality of outcome evidence in GRADE

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

4.3.4.2 Prognostic reviews

Risk of bias and applicability of evidence for prognostic risk data were evaluated by study using the Prediction study Risk of Bias Assessment Tool (PROBAST) checklist (see appendix H in the NICE guidelines manual 2014[101]). Risk of bias and applicability in risk prediction studies in PROBAST consists of 4 domains:

- patient selection
- predictors
- outcome
- analysis

If data were meta-analysed, the quality for pooled studies was presented. If the data were not pooled, then a quality rating was presented for each study.

4.3.4.2.1 Inconsistency

Inconsistency was assessed as for intervention studies.

4.3.4.2.2 Imprecision

In meta-analysed outcomes, or for non-pooled outcomes, the position of the 95% CIs in relation to the null line determined the existence of imprecision. If the 95% CI did not cross the null line, then no serious imprecision was recorded. If the 95% CI crossed the null line, then serious imprecision was recorded.

4.3.4.2.3 Overall grading

Quality rating started at High for prospective studies, and each major limitation brought the rating down by 1 increment to a minimum grade of Very Low, as explained for interventional reviews. For prognostic reviews, prospective cohort studies with a multivariate analysis are regarded as the gold standard because RCTs are usually inappropriate for these types of review for ethical or pragmatic reasons. Furthermore, if the study were looking at more than 1 risk factor of interest, then randomisation would be inappropriate as it can only be applied to 1 of the risk factors.

4.3.4.3 Diagnostic studies

Risk of bias and indirectness of evidence for diagnostic data were evaluated by study using the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklists (see appendix H in the NICE guidelines manual 2014[101]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 8):

- patient selection
- index test
- reference standard
- flow and timing.

Figure 8: Summary of QUADAS-2 with list of signalling, risk of bias and applicability questions.

Domain	Patient selection	Index test	Reference standard	Flow and timing
Description	Describe methods of patient selection. Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2×2 table (refer to flow diagram). Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/ unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case–control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias; (high/low/ unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability (high/low/ unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

4.3.4.3.1 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results for an outcome across different studies. Inconsistency was assessed by inspection of the sensitivity and specificity (based on the primary measure) using the point estimates and 95% CIs of the individual studies on the forest plots. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and the threshold set by the committee (the threshold above which it would be acceptable to recommend a test). For example, the committee might have set a threshold of 90% as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual studies

varied across 2 areas (for example, 50–90% and 90–100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0–50%, 50–90% and 90–100%).

4.3.4.3.2 Imprecision

The judgement of precision was based on visual inspection of the confidence region around the summary sensitivity and specificity point from the diagnostic meta-analysis, if a diagnostic meta-analysis was conducted. Where a diagnostic meta-analysis was not conducted, imprecision was assessed according to the range of point estimates or, if only one study contributed to the evidence, the 95% CI around the single study. As a general rule (after discussion with the committee), a variation of 0–20% was considered precise, 20–40% serious imprecision, and >40% very serious imprecision. Imprecision was assessed on the primary outcome measure for decision-making.

4.3.4.3.3 Overall grading

Quality rating started at High for prospective and retrospective cross sectional studies, and each major limitation (risk of bias, indirectness, inconsistency and imprecision) brought the rating down by 1 increment to a minimum grade of Very Low, as explained for intervention reviews.

4.3.5 Publication bias

Funnel plots were constructed using RevMan5.[123] to assess against potential publication bias for outcomes containing more than 5 studies (appendix K). This was taken into consideration when assessing the quality of the evidence.

4.3.6 Assessing clinical importance

The committee assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro[48] software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies, which was standardised across the reviews. The committee considered for most of the outcomes in the intervention reviews that if at least 100 more participants per 1,000 (10%) achieved the outcome of interest in the intervention group compared to the comparison group for a positive outcome then this intervention was considered beneficial. The same point estimate but in the opposite direction applied for a negative outcome. For adverse events 50 events or more per 1,000 (5%) represented clinical harm. For continuous outcomes, if the mean difference was greater than the minimally important difference (MID), then this represented a clinical benefit or harm. For outcomes such as mortality, any reduction or increase was considered clinically important.

This assessment was carried out by the committee for each critical outcome, and an evidence summary table was produced to compile the committee's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.7 Clinical evidence statements

Clinical evidence statements are summary statements that are included in each review chapter, and which summarise the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- The number of studies and the number of participants for a particular outcome.

- An indication of the direction of clinical importance (if 1 treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments).
- A description of the overall quality of the evidence (GRADE overall quality).

4.4 Identifying and analysing evidence of cost-effectiveness

The committee is required to make decisions based on the best available evidence of both clinical effectiveness and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost.[101] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Health economic evidence was sought relating to the key clinical issues being addressed in the guideline. Health economists:

- undertook a systematic review of the published economic literature
- undertook new cost-effectiveness analysis in priority areas.

4.4.1 Literature review

The health economists:

- Identified potentially relevant studies for each review question from the health economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using economic evaluations checklists as specified in the NICE guidelines manual. [101]
- Extracted key information about the studies' methods and results into health economic evidence tables (included in appendix I).
- Generated summaries of the evidence in NICE health economic evidence profile tables (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost-utility, cost-effectiveness, cost-benefit and cost-consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as health economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. Studies published before 2001 and studies from non-OECD countries or the USA were also excluded, on the basis that the applicability of such studies to the present UK NHS context is likely to be too low for them to be helpful for decision-making.

Remaining health economic studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section. However, in this guideline, no economic studies were excluded on the basis that more applicable evidence was available.

For more details about the assessment of applicability and methodological quality, see Table 5 below and the economic evaluation checklist (appendix G of the 2012 NICE guidelines manual[103]) and the health economics review protocol in appendix D.

When no relevant health economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the committee to inform the possible economic implications of the recommendations.

4.4.1.2 NICE health economic evidence profiles

NICE health economic evidence profile tables were used to summarise cost and cost-effectiveness estimates for the included health economic studies in each review chapter. The health economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the NICE guidelines manual.[103] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio (ICER) for the base-case analysis in the study, as well as information about the assessment of uncertainty in the analysis. See Table 5 for more details.

When a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[112]

Table 5: Content of NICE health economic evidence profile

Item	Description
Study	Surname of first author, date of study publication and country perspective with a reference to full information on the study.
Applicability	An assessment of applicability of the study to this guideline, the current NHS situation and NICE decision-making:[(a)] • Directly applicable – the study meets all applicability criteria, or fails to meet 1 or more applicability criteria but this is unlikely to change the conclusions about cost-effectiveness. • Partially applicable – the study fails to meet 1 or more applicability criteria, and this could change the conclusions about cost-effectiveness. • Not applicable – the study fails to meet 1 or more of the applicability criteria, and this is likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study:[(a)] • Minor limitations – the study meets all quality criteria, or fails to meet 1 or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness. • Potentially serious limitations – the study fails to meet 1 or more quality criteria, and this could change the conclusions about cost-effectiveness. • Very serious limitations – the study fails to meet 1 or more quality criteria, and this is highly likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Other comments	Information about the design of the study and particular issues that should be considered when interpreting it.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects (usually in £ per QALY gained).

Item	Description
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in appendix G of the 2012 NICE guidelines manual[103]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published health economic literature for each review question, as described above, new health economic analysis was undertaken by the health economist in selected areas. Priority areas for new analysis were agreed by the committee after formation of the review questions and consideration of the existing health economic evidence.

The committee identified Pharmacological treatment as the highest priority area for original health economic modelling. In the original guideline two treatment models were conducted, one on a population with Ocular Hypertension (OHT) and one on a population with Chronic Open-Angle Glaucoma (COAG). The surveillance report highlighted the need for updating these models to take into account the decrease in the cost of prostaglandin analogues (PGA), which were identified as the most effective pharmacological treatment in the original guideline but not cost effective in OHT subgroups at lower risk of developing COAG. Due to the decrease in the cost of PGAs, the committee felt that that area of the guideline would benefit the most from original health economic modelling. The OHT treatment model was updated to reflect the changes in costs, and the results the OHT treatment model were extrapolated to a COAG population.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case for interventions with health outcomes in NHS settings.[101,104]
- The committee was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, the committee expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NGC.

Full methods for the cost-effectiveness analysis for the most cost-effective treatment option for Ocular Hypertension are described in appendix N.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money.[102] In general, an intervention was considered to be cost-effective (given that the estimate was considered plausible) if either of the following criteria applied:

- 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 cost less than £20,000 per QALY gained compared with the next best strategy.

If the committee recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision were discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[102]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of health economic evidence

When no relevant published health economic studies were found, and a new analysis was not prioritised, the committee made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the review of clinical effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the committee and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

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

- Evidence tables of the clinical and health economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summaries of clinical and health economic evidence and quality (as presented in Chapters 5–12).
- Forest plots and summary ROC curves (appendix K).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (appendix N).

Recommendations were drafted based on the committee's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net clinical benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the committee took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net clinical benefit was moderated by the importance placed on the outcomes (the committee's values and preferences), and the confidence the committee had in the evidence (evidence quality). Secondly, the committee assessed whether the net clinical benefit justified any differences in costs between the alternative interventions.

When clinical and health economic evidence was of poor quality, conflicting or absent, the committee drafted recommendations based on its expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through committee discussions. The committee also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 4.5.1 below).

The committee considered the appropriate 'strength' of each recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the committee believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the committee has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances, the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The committee focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weaker recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.2 in the 2014 NICE guidelines manual[101]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the committee considered making recommendations for future research. Decisions about the inclusion of a research recommendation were based on factors such as:

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

4.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited

here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Prognostic risk tools

5.1 Increased risk of conversion to chronic open-angle glaucoma (COAG)

5.1.1 Introduction

Chronic open-angle glaucoma (COAG) is diagnosed primarily by glaucomatous optic neuropathy (characteristic changes of the optic nerve head) and a compatible visual field defect, in the presence of an open, normal appearing, anterior chamber angle. The onset of COAG is insidious, and may go unrecognised by patients until considerable visual field has been lost. Early detection and thus access to treatment is associated with better outcomes, but early diagnosis is difficult as there is an overlap between normal and glaucomatous change.

Ocular hypertension (OHT) or high eye pressure is a risk factor for glaucoma. Around 1.3 million people aged 40 and over in the UK have OHT. Diagnosis and reassessment of OHT places considerable burden on eye care services and patients. General medical practitioners do not usually have the appropriate training or equipment to undertake this work. Case finding of people suspected of having OHT or COAG occurs opportunistically when people visit their optometrist for a sight test. Following referral, usual UK practice is to monitor COAG, OHT and related conditions in secondary care, or through a co-management model such as between a hospital eye department and community optometry.

To guide intervention and reassessment intervals for people at risk of developing glaucoma, there is a need for accurate and reliable risk assessment for conversion to COAG. Validated risk prediction tools have become useful in risk assessment for other chronic diseases, for example coronary heart disease. A simple and valid risk prediction tool has the potential to inform decisions on optimal management for those at increased risk of developing glaucoma. Glaucoma risk predictors have been identified, namely age, intraocular pressure (IOP), and eye specific variables including the central corneal thickness (CCT), a measure of visual field function called the pattern standard deviation (PSD) and a measure of optic nerve damage (the vertical cup to disc ratio; VCDR).

Evaluation of a risk prediction tool is required in a representative UK-based population, such that the tool is valid for use in clinical practice, allowing risk-stratification of presenting patients and opening up new possibilities for service redesign (for example, better triage and referral pathways and more efficient reassessment strategies).

Because the prevalence of COAG is just 2% in people of 40 or older, tools to identify such individuals in the community must have high specificity to avoid incorrect referral of people who are wrongly identified by the tool as being at increased risk. Such incorrect referrals cause unnecessary anxiety to people being referred and have the potential to flood the eye care services. Correct identification of those at increased risk of future development of COAG allows for more regular reassessment or more timely treatment to be provided later in the pathway where needed.

5.1.2 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?

For full details, see review protocol in appendix C.

Table 6: PICO characteristics of review question

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?**

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?
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 Adults (18 and over) with suspected COAG: people with possible visual field loss or optic neuropathy that suggest possible glaucomatous damage, regardless of the level of the IOP Adults (18 and over) who were not previously treated for OHT (exclude populations where <80% 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

5.1.3 Clinical evidence

Five studies evaluating five risk tools were included in the review.[62,90,109,148,161] The studies are summarised in Table 7, and the risk tools are summarised in Table 8 below. See also the study selection flow chart in appendix E, coupled sensitivity and specificity forest plots in appendix K, study evidence tables in appendix H, and excluded studies list in appendix L.

Table 7: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Alencar 2008[4]	Glaucoma Probability Score (GPS)	n=223 People with suspected glaucoma Age: 59.0 ± 12.7	Conversion to glaucoma (average follow-up 5 years). Defined as the development of 3 consecutive abnormal examinations during follow-up, or 2 consecutive abnormal examinations, when the last examination results available during	n=54 eyes (24.2%)	Prospective cohort Data from control arm of Diagnostic

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		Male to female ratio: not reported Family origin: not reported USA	follow-up were abnormal. An abnormal result followed by a normal result was not considered a conversion. An abnormal visual field was defined as a pattern standard deviation (PSD) with $p < 0.05$ and/or a Glaucoma Hemifield Test (GHT) with results outside normal limits. Two experienced glaucoma specialists verified that the visual field defects were consistent with glaucoma. C-statistic		Innovations in Glaucoma Study (DIGS)
Medeiros 2005[90]	OHTS predictive model OHTS predictive model, reduced	n=126 (252 eyes) People with OHT (baseline IOP ≥24mmHg in 1 eye and ≥21mmHg in the other eye; normal-appearing optic discs and retinal nerve fibre layer on baseline stereo photographs of both eyes; and normal visual field test results) Not receiving treatment Excluded people with pseudoexfoliation or pigment dispersion Age: mean 56.3±13.1 Male to female ratio 42:58 Family origin: White non-Hispanic: 93.6%; African	Conversion from OHT to glaucoma (5 years). 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 primary open-angle glaucoma (POAG) was defined as the end point for people 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 characterization of progression. When grading photographs for progression, each examiner was masked to the temporal sequence of the photographs. Discrepancies between the 2 graders were either resolved by consensus or by adjudication of a third experienced grader. Abnormality on SAP was defined as the presence of a GHT result outside normal limits or PSD with $p<.05$. A confirmed visual field defect required 3 consecutive, abnormal visual field test results. A glaucoma	n=31 (25%)	Prospective cohort Data from control arm of Diagnostic Innovations in Glaucoma Study (DIGS)

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		American: 3.3%; Hispanic: 1.6%; Asian: 1.6% USA	specialist, who excluded other causes of nonglaucomatous visual field loss or presence of visual field artefacts as possible causes of the visual field abnormality, also 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. C-statistic Calibration plot		
Takwoingi 2014[148]	OHTS-EGPS prediction model	n=879 from 3 cohorts People with OHT, some who are undergoing treatment for OHT Rotterdam Eye Hospital (n=393) Age: mean 56.0 (11.0); Male to female ratio: 187:206 Family origin: White: 100% Moorfields Eye Hospital (n=298) Age: mean 59.3 (10.2) Male to female ratio: 174:124 Family origin: White 82.6%; African ancestry: 6.4%; Asian: 1.6% Dunfermline Hospital (n=188) Age: mean 62.9	Conversion from OHT to glaucoma (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 person 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. Dunfermline: development of a	Rotterdam n=28/393 (7.1%) Moorfields n=44/298 (14.8%) Dunfermline n=28/188 (14.9%)	Data from 2 RCTs and 2 prospective cohort studies Data from 1 cohort study (Nottingham Queens Medical Centre) was excluded as 30.2% of people were treated.

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		(11.8), OAG 62.2 (9.2) Male to female ratio: 105:83 Family origin: White: 100%; Diabetes: 9%; Treated: 1.9% UK and the Netherlands	repeatable visual field defect or 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. C-statistic Calibration slope Calibration plot		
The Ocular Hypertension Treatment Study Group and the European Glaucoma Prevention Study (OHTS-EGPS) Group 2007 [109]	OHTS prediction model OHTS-EGPS prediction model	n=500 People with OHT, minority undergoing treatment for OHT (with beta-blockers 7.6%) Age: no POAG 57.2±10, POAG 61.1±9.9 Male to female ratio 241:259 Family origin: White, not Hispanic: 100% 18 centres, Europe	Conversion from OHT to glaucoma (5 year). Defined as the first abnormal visual field or optic disk that masked readers classified as meeting the definition for change. C-statistic Calibration plot	n=61 (12.2%)	Validated using data from control group arms of 1 RCT (EGPS)
Weinreb 2010 [161]	Glaucoma Probability Score (GPS) Moorfields Regression Analysis (MRA)	n=438 (857 eyes) People with OHT Age: mean 55.4 (95% CI 54.5 to 56.2) Male to female ratio 185:253 Family origin:	Development of confirmed visual field abnormality (unclear time point). Confirmed clinically significant stereograph-based optic disc deterioration attributed to POAG. Masked, certified readers at the Visual Field and/or Optic Disc Reading Centers identified the abnormalities independently. 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	n=64/828 eyes (7.7%)	Prospective cohort Data from Confocal Scanning Laser Ophthalmology (CSLO) Ancillary Study to the OHTS

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
		African-American: 17% Family history of glaucoma: 32% USA	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. Sensitivity Specificity C-statistic		

Table 8: Summary of risk tools included in the review

Risk tool	Description of tool
Glaucoma Probability Score (GPS)	The GPS was available with HRT 3.0 (or higher software). The GPS was obtained using a new automated analysis independent of either contour line tracing or a reference plane. The software analysed the optic disc and parapapillary retina topography and builds a 3-dimensional model using 5 shape-based measures: cup size, cup depth, rim steepness (referring to the optic disc), and vertical (superior to inferior) and horizontal (nasal to temporal) parapapillary nerve fibre layer curvatures. The values of the parameters were then fed into a machine-learning classifier analysis, a relevance vector machine (RVM), which compares the person's results to previously defined healthy and glaucomatous models. Glaucomatous eyes usually present with flatter RNFL curvature and increased cup size, depth, and slope (rim steepness). The final GPS was the probability that the model has structural differences from the normal model that were compatible with glaucomatous damage. The higher the GPS, the more similar it was to the glaucoma model. Risk of glaucoma classified as outside normal limits, borderline, or within normal limits.
Moorfields Regression Analysis (MRA)	Compares measured rim area to predicted rim area adjusted for disc size cup shape (scoring not reported). The risk of glaucoma was classified as outside normal limits, borderline, or within normal limits.
OHTS predictive model	Score calculated based on 6 risk factors. Interpretation 5 year risk of glaucoma based on score: Score <12: <1% Score 13 to 27: 1-5% Score 28 to 33: 6-10% Score 34 to 37: 11-15% Score 38 to 40: 16-20% Score 41 to 44: 21-30% Score 45 to 47: 31-40%

Risk tool	Description of tool
	Score 48 to 50: 41 to 50% Score >50: >50%
	Factor Age (years) 40-44=score 0 45-49=score 1 50-54=score 2 55-59=score 3 60-64=score 4 65-69=score 5 70-74=score 6 75-80=score 7 Diabetes mellitus Yes=score -9 No=score 0 Baseline IOP (mmHg) 23=score 0 24=score 1 25=score 2 26=score 3 27=score 4 28=score 5 29=score 6 30=score 7 31=score 7 32=score 8 CCT (micrometre) 450-469=score 30 470-489=score 27 490-509=score 24 510-539=score 21 530-549=score 19 550-569=score 16 570-589=score 13 590-609=score 11 610-629=score 8 630-649=score 5 650-669=score 3 670-689=score 0 Vertical cup/disc ratio 0.1=score 0 0.2=score 2

Risk tool	Description of tool
	0.3=score 5 0.4=score 7 0.5=score 10 0.6=score 12 0.7=score 15 0.8=score 17 0.9=score 20 PSD 1.00-1.19=score 0 1.20-1.39=score 2 1.40-1.59=score 4 1.60-1.79=score 6 1.80-1.99=score 8 2.00-2.19=score 10 2.20-2.39=score 12 2.40-2.59=score 14
OHTS predictive model (reduced)	Score calculated based on 4 risk factors (scoring not reported): • age • diabetes mellitus • baseline IOP • CCT Interpretation of score not reported.
OHTS-EGPS predictive model	Score calculated based on 4 risk factors (scoring not reported): • IOP • Cup/disc ratio • CCT • PSD Interpretation of score not reported.

5.1.4 Discrimination

Table 9: Clinical evidence profile: risk tools for predicting conversion to COAG

Risk tool	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity (%)	Specificity (%)	C-statistic	Quality
GPS global		HIGH	No serious inconsistency	No serious indirectness	No serious imprecision				MODERATE
Alencar 2008	223					-	-	0.732	
Weinreb 2010	438					0.28 (0.13–0.46)	0.73 (0.68–0.77)	0.75 (0.69–0.82)	
MRA	438	VERY HIGH	Not estimable	No serious indirectness	No serious imprecision	0.30 (0.15–0.47)	0.78 (0.74–0.82)	0.76 (0.70–0.82)	LOW
Weinreb 2010									
OHTS model		HIGH	No serious inconsistency	No serious indirectness	No serious imprecision				MODERATE
Medeiros 2005	126					-	-	0.68	
OHTS-EGPS 2007	500					-	-	0.72 (0.63–0.80)	
OHTS model (reduced)	126	HIGH	Not estimable	No serious indirectness	Not estimable				MODERATE
Medeiros 2005						-	-	0.73	
OHTS-EGPS model		HIGH	No serious inconsistency	No serious indirectness	No serious imprecision				MODERATE
OHTS-EGPS 2007	500					-	-	0.74 (0.70–0.78)	
Takwoingi 2014									
• Rotterdam	393					-	-	0.83 (0.75–0.91)	
• Moorfields	298					-	-	0.69 (0.59–0.78)	
• Dunfermline	188					-	-	0.72 (0.63–0.82)	

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias.

(b) Inconsistency was assessed by inspection of the point estimate and confidence intervals of the c-statistic. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and 70%, which the committee set as the acceptable threshold for recommending a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example, 50-70% and 70-100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0-50%, 50-70% and 70-100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability.

(d) Imprecision was assessed according to the range of point estimates of the specificity value, or when that was not reported, by the c-statistic. The evidence was downgraded by 1 increment when there was a >20% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%.

5.1.5 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the economic article selection flow chart in appendix F.

5.1.6 Evidence statements

Clinical

Moderate quality evidence was found for 2 studies (n=661) reporting on the GPS global risk tool which showed a sensitivity of 0.28 (0.13-0.46) and specificity of 0.73 (0.68-0.77), the second study reported a c-statistic of 0.73 with no associated uncertainty values reported. Moderate quality evidence was also found for 2 studies (n=626) reporting on the accuracy of the OHTS model, both studies only reported c-statistics of 0.68 and 0.72 (0.63-0.80). A further single study of moderate quality (n=126) reported on a reduced version of the OHTS model which also only reported a c-statistic of 0.73 with no associated uncertainty values reported. In addition to this, 2 studies of moderate quality reported on the OHTS-EGPS model. The smaller of these studies (n=500) reported a c-statistic of 0.74 (0.70-0.78). The larger study reported on 3 separate data sets from 3 hospitals all of which showed a moderate c-statistic. A single low quality study (n=438) reported on the MRA tool which showed a sensitivity of 0.30 (0.15-0.47) and specificity of 0.78 (0.74-0.82). Although 2 of the studies met the minimum specificity threshold, the sensitivity for both was very poor and the corresponding c-statistics showed only a moderate performance for predicting conversion to COAG.

Economic

No relevant economic evaluations were identified.

5.1.7 Recommendations and link to evidence

Recommendations	**No recommendation**
Research recommendation	**1. What is the predictive value of risk tools for identifying people in the community who are at increased risk of developing COAG?**
Relative values of different outcomes	The committee was interested in the prognostic accuracy of tools to predict conversion to COAG, as indicated by visual field loss or an abnormal optic nerve head appearance in people with OHT, or people with suspected COAG. The committee intended to use the tool to identify people who are at high risk of conversion to aid case finding in the community and to guide decision making for referral. People who are at high risk of conversion may benefit from more regular reassessment or treatment provided later in the pathway. The committee intended the tool to be used primarily to identify people who are at higher risk of conversion for additional care. The committee agreed that the priority of such a tool to identify individuals in the community is that it must have a high specificity to avoid incorrect referral of people who are wrongly identified as being at increased risk (alongside consideration of a reasonably acceptable corresponding sensitivity). The committee set minimum thresholds for the acceptability of a risk prediction tool in this population as sensitivity and specificity values above 60% and 90% respectively, and if no sensitivity and specificity information was available, a c-statistic value ≥70%.
Quality of the clinical	Evidence for 5 risk tools was identified for inclusion in the review. Overall, the

evidence	evidence was of moderate to low quality. All of the studies were of high to very high risk of bias, due to reasons such as not having a reasonable number of outcome events or a lack of reported calibration data. Some of the studies included people who had received treatment for IOP. The committee agreed that studies with these IOP treated populations could be included if the number of people receiving treatment was less than 20% of the full study population; these studies were still considered directly applicable and were not downgraded for indirectness.
Trade-off between clinical benefits and harms	All 5 of the tools showed moderate discrimination according to the c-statistic. However, for 3 of the tools evidence was not reported on their associated sensitivity and specificity. The committee noted that the c-statistic was important for comparing the overall accuracy of the tools, but in itself was unlikely to provide enough information to establish a recommendation, as it does not indicate the number of false positive or false negative classifications from the tool. Therefore, the committee decided against recommending a tool without sensitivity and specificity data. There was sensitivity and specificity data for 2 of the tools: Glaucoma Probability Score (GPS) and Moorfields Regression Analysis (MRA). Evidence for both tools showed specificity below the committee defined threshold and very poor sensitivity ratings well below the committee-defined threshold. Therefore, the committee agreed that the predicative ability of both tools was too poor to recommend their use in clinical practice. Therefore, the committee decided to make a research recommendation in this area.
Trade-off between net clinical effects and costs	No economic evidence was found for this question. The available clinical evidence did not show any tool to have acceptable predictive values and therefore none could be recommended. For people who do not have COAG, the use of prognostic tools is associated with an additional cost as further tests are necessary to complete the tool. There are also downstream costs associated with inaccurate tools if these lead to people being referred unnecessarily (from tools with a low specificity), or health benefits foregone if tools fail to identify people at high risk of developing COAG who would require further referral or reassessment (from tools with a low sensitivity), as these people could benefit from treatment or reassessment which could impact their progression pathway if they are not missed. The committee considered the available evidence to be insufficient to determine whether any of the available tools is cost effective.
Other considerations	The committee noted anecdotally that the OHTS-EGPS tool was already being utilised in a number of UK locations in clinical practice and therefore implementation would not be difficult if the research were to find good evidence for its use in the future. <u>Research recommendation</u> 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 at case finding which people are at high risk of conversion to COAG is important for guiding decisions about reassessment, 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. More information can be found in appendix Q for the research recommendation on prognostic tools for identifying risk of conversion to COAG and risk of sight loss.

5.2 Increased risk of COAG progression

5.2.1 Introduction

To guide intervention and reassessment intervals for people with glaucoma, there is a need for accurate and reliable risk assessment to identify those at risk of developing significant visual loss. A simple and valid risk prediction tool has the potential to inform decisions on optimal management for those at risk of developing visual loss, for example, possibly adjusting reassessment intervals or interventions according to risk.

5.2.2 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?

For full details, see the review protocol in appendix D.

Table 10: PICO characteristics of review question

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?
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 tool	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)
Statistical outcomes	Statistical outputs may include: • Discrimination (sensitivity, specificity, predictive values) • 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
Study types	Prospective and retrospective cohort studies, externally or temporarily validated

5.2.3 Clinical evidence

One study evaluating a single risk tool was included in the review. [7] The study is summarised in Table 11and the risk tool is summarised in Table 12 below. See also the study selection flow chart in appendix E, coupled sensitivity and specificity forest plots in appendix K, study evidence tables in appendix H, and excluded studies list in appendix L.

Table 11: Summary of studies included in the review

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
Anton 2013 [7]	Glaucoma guided progression	n=22 People with	Progression of glaucoma as defined by the	Overall progression: 9	Prospectiv e cohort

Study	Risk tool	Population	Outcomes	No of events (%)	Study design
	analysis event analysis (GPA I)	glaucoma (POAG, pigment dispersion and pseudoexfoliative) Mean age: 64.3±10.3 years Gender and family origin not reported Follow-up 3 years Spain	EMGTS study: All follow-up VFs were compared with 2 baseline tests from the same eye using glaucoma change probability maps (GCPMs). Definite progression was defined as at least 3 test points showing significant progression, as compared with baseline, at the same locations on 3 consecutive GCPMs. Specificity Sensitivity	With GPA I: 7	

Table 12: Summary of risk tools included in the review

Risk tool	Description of tool or model	Comments
Glaucoma progression analysis (GPA I)	Corresponds to number of visual field series obtained Change in VF series (baseline is established based on 2 initial tests with successive follow-up examinations compared point-to-point with the baseline score).	

5.2.4 Discrimination

5.2.4.1 Tools using linear regression models

Table 13: Clinical evidence profile: risk tools for predicting the progression of COAG

Risk tool	No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sensitivity (%)	Specificity (%)	C-statistic	Quality
Glaucoma progression analysis (GPA I)	1	22	VERY HIGH[e]	Not estimable	No indirectness	Serious imprecision	0.83 (0.42-1.00)	0.93 (0.68-1.00)	Not reported	VERY LOW

(a) Risk of bias was assessed using the PROBAST checklist items relating to risk of bias.

(b) Inconsistency was assessed by inspecting the point estimate and confidence intervals of the sensitivity and specificity forest plots, or the c-statistic. Particular attention was placed on values above or below 50% (diagnosis based on chance alone) and 70%, the threshold the committee set above, which is acceptable to recommend a test. The evidence was downgraded by 1 increment if the individual studies varied across 2 areas (for example, 50–70% and 70–100%) and by 2 increments if the individual studies varied across 3 areas (for example, 0–50%, 50–70% and 70–100%).

(c) Indirectness was assessed using the PROBAST checklist items relating to applicability.

(d) Imprecision was assessed according to the range of point estimates of the primary measure. The evidence was downgraded by 1 increment when there was more than 20% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of more than 40%.

(e) For the assessment of risk of bias relating to the reporting of outcomes, 1 domain was excluded from the PROBAST checklist due to its lack of applicability to the specific tools included in this review. This domain was: was the outcome determined without knowledge of predictor information.

5.2.5 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the economic article selection flow chart in appendix F.

New cost-effectiveness model

This area was not prioritised for new cost-effectiveness modelling.

5.2.6 Evidence statements

Clinical

Very low quality evidence was found for 1 small study (n=22) reporting on the GPA 1. The sensitivity was 0.83 with very large uncertainty around this result (0.42-1.00) and the specificity was 0.93 (0.68-1.00). The study did not report a c-statistic.

Economic

No relevant economic evaluations were identified.

5.2.7 Recommendations and link to evidence

Recommendations	**No recommendation**
Research recommendation	**2. What is the predictive value of risk tools for identifying people with COAG who are at an increased risk of sight loss?**
Relative values of different outcomes	The committee was interested in the prognostic accuracy of tools to predict progression of COAG, as indicated by visual field loss or abnormal optic nerve head, in people with confirmed COAG. The committee intended to use the tool to identify people who are at high risk of glaucoma progression who may require more frequent reassessment and people who are at low risk of progression who may be eligible for less frequent reassessment. The committee noted that sensitivity was deemed more important than specificity in people with confirmed COAG, as false negatives would be detrimental to the preservation of vision within these individuals. False positives would lead to unnecessary testing, but preservation of sight in patients with COAG is critical. The committee set minimum thresholds for the acceptability of a risk prediction tool in this population at ≥80% sensitivity, ≥70% specificity, and, of no sensitivity and specificity information was available, a c-statistic value ≥70%.
Quality of the clinical evidence	One tool was included in the review (Glaucoma/guided progression analysis event analysis, also known as GPA I). The evidence was of very low quality because of a very high risk of bias due to not having a reasonable number of outcome events, lack of calibration data, and attrition of study subjects. The tool was also subject to serious imprecision, which contributed to the very low quality rating.
Trade-off between clinical benefits and harms	While the point estimate for sensitivity of the GPA I tool seemed promising, there was very large uncertainty around this. Specificity was above the minimum acceptable threshold the committee set, although the uncertainty around the estimate dipped slightly below the threshold. The discrimination of the tool was based on low quality evidence from a single study with a very small sample size and

	no associated c-statistic for predictive value was reported. The committee agreed that this finding was not sufficient evidence to recommend use of the GPA I tool as a predictor of risk for glaucoma progression in clinical practice. The committee recognised the potential for the tool and decided to make a research recommendation in this area.
Trade-off between net clinical effects and costs	No economic evidence was found for this question. The available clinical evidence was of very low quality and covered only 1 tool so the committee could not derive the cost effectiveness of the prognostic tools. While the sensitivity is important for clinical reasons, the specificity of tools (that is, the minimisation of false positives) is important for economic reasons, as false positives are associated with the unnecessary costs of more frequent reassessment. For people who already have COAG, the use of prognostic tools is not associated with any immediate incremental cost, as the elements evaluated within the tools are already part of the standard assessment. However, there are downstream costs associated with inaccurate tools if these lead to people being monitored too frequently or health benefits foregone (in terms of benefit from treatment or reassessment) if tools fail to identify people at high risk who would require more intensive reassessment. The committee considered the available evidence to be insufficient to determine whether any of the available tools are cost effective.
Other considerations	The committee noted that the GPA I tool is used to identify people who are likely to progress at a greater rate and therefore its use is likely to have an impact on determining the frequency of reassessment intervals rather than potentially altering the treatment plan. The committee also discussed that GPA I is not currently used in clinical practice. The committee discussed that the tool would be relatively straightforward to implement, if future research were to find good evidence for its use, as the tests required (for example, visual field) are carried out routinely in practice. <u>Research recommendation</u> A risk 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. There was no evidence on cost effectiveness. More information can be found in appendix Q for the research recommendation on prognostic tools for identifying risk of conversion to COAG and risk of sight loss.

6 Tests used in case finding, diagnosis and reassessment

6.1 Introduction

The following chapter examines the evidence for the different tests used in case finding, diagnosis and reassessment. The evidence reviews are grouped by the type of test; however, the same tests can be used for case finding, diagnosis and reassessment and the evidence reflects this. Therefore, at the end of the chapter (Section 6.6.5) we bring together our conclusions on the use of the different tests in each scenario (case finding, diagnosis and reassessment). The intervals at which reassessment should be performed can be found in chapter 7.

6.1.1 Case finding

Cases of glaucoma and glaucoma-related conditions are most often identified through examination by a community optometrist at a routine NHS Sight Test or Private Eye Examination. The NHS Sight Test involves a range of tests to check the general health of the eye and the need for spectacles, but it is not a screening service for glaucoma. The term 'case finding' therefore indicates the opportunistic detection of eye signs suggestive of glaucoma and may imply further referral and investigation is warranted.

The 4 main examination techniques that may inform the presence of glaucoma are measurement of the visual field, assessment of the optic nerve head, intraocular pressure and examination of the anterior segment. Testing specifically for glaucoma is not mandated in the NHS Sight Test; however, it is normal practice for the intraocular pressure to be measured, the optic nerve to be assessed and the anterior segment examined as part of the routine. Visual field testing may be performed at the discretion of the optometrist but is not routinely undertaken on every occasion.

Cases of suspected glaucoma detected because of NHS Sight Tests or Private Eye examinations have traditionally been referred to the Hospital Eye Service for further investigation. Many cases are referred based on 1 suspicious or possibly abnormal test result. This approach is not sufficiently specific for detection of glaucoma; the accuracy of tests when measured on one occasion may be limited and many referrals are found not to have glaucoma when investigated further. These cases are termed 'false-positive' referrals.

6.1.2 Diagnosis

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

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

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

In the great majority of cases, a definite diagnosis of COAG should only be made when there is an irrefutable and consistently demonstrable abnormality of visual function in at least 1 eye. Usually this will be defined by a relative or absolute scotoma in the field of vision demonstrated by standard automated perimetry (SAP). When a person is unable to cooperate with SAP, alternative methods of defining a functional abnormality of the optic nerve should be used. This functional abnormality should be confidently attributed to glaucomatous optic neuropathy to the exclusion of any other cause and corroborated by demonstrable abnormality of the optic nerve in the affected eye(s). On occasion, there will be genuine uncertainty; for example, not all patients are able to perform visual function tests reliably. Depending on the level and source of uncertainty, other signs of COAG such as 'obvious' glaucomatous optic neuropathy may need to be given additional weight in arriving at a considered and accurate diagnosis. A period of observation with repeated clinical measurements may be required to confirm or refute an uncertain diagnosis.

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

6.1.3 Reassessment

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

People with ocular hypertension, or people who are suspected of having COAG, may develop COAG as time passes. Reassessment may therefore be required to detect conversion to COAG, at which point a different intervention strategy will become necessary. Interventions may be provided to reduce this risk of conversion and reassessment is then needed to gauge their effect. As a rule, a 'one stop' approach is easier for patients. Whenever possible, the tests necessary for reassessment should be undertaken during a single visit.

Reassessment requires the maintenance and availability of reliable and complete documentation of the patient's clinical record so that clinical findings over time can be traced and coherent continuity of care provided. A patient may not see the same practitioner at each visit but clear communication between each healthcare professional and the patient should ensure that the duration until the next assessment is agreed, including what will be done and why, with a clear understanding on the part of all concerned. This process should be stipulated by an agreed management plan owned by the patient and shared with the carers, appropriate to the severity of disease and prognosis and regularly reviewed by the management team authorised by the consultant responsible for the care of the

individual patient. It would be expected that clinicians use judgement in interpreting results, with tests being repeated as deemed clinically necessary, including when the accuracy, reliability or validity of a particular test result is in doubt.

6.2 Visual field evidence

6.2.1 Diagnostic visual field measurement

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

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

No studies were identified.

6.2.2.1 Clinical evidence

No studies were identified.

6.2.2.2 Economic evidence

No studies were identified.

6.2.2.3 Patient views evidence

No studies were identified.

2009

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

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

6.2.3 Monitoring visual field measurement

Data relating to the evidence for visual field measurement are presented in section 6.2.2 in the section on diagnosis.

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

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

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

6.3.1 Review question: 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)?

For full details, see review protocol in appendix C.

Table 14: Characteristics of review question

Population	Adults (18 and over)

Target condition	• Glaucoma damage:
	  ○ Optic nerve head or disc damage
	  ○ Macular and retinal nerve fibre layer damage
	• Progression of glaucoma damage

Index test(s)	• 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(s)	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 (receiver operating characteristic [ROC] curve or area under the curve [AUC])
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-sectional studies)

6.3.2 Clinical evidence

Ten studies were included in the review;[10,14,65,80,82,119,129,138,166,170] these are summarised in Table 15. All ten studies were identified in the update; no studies were included for this question in the original guideline. Evidence from these studies is summarised in the clinical evidence summary (Table 16). See also the study selection flow chart in appendix E, coupled sensitivity and specificity forest plots in appendix K, study evidence tables in appendix H, and excluded studies list in appendix L.

A variety of thresholds and index tests were used (see Table 15). The aim of all studies was to assess the diagnostic accuracy of the structural tests in identifying glaucomatous damage of the optic nerve head. Studies ranged from purely case-finding settings to specialist glaucoma clinic settings, and many involved mixed populations of both. No studies were included that provided accuracy of the structural tests for reassessing progression of existing damage. Some studies were identified at the early stages of the review, but the reference standard they relied on to identify progression was solely stereo photography rather than biomicroscopic slit lamp (with or without stereo photography) as specified in our review protocol; therefore, these studies were excluded from the review.

No relevant diagnostic test accuracy studies comparing stereo photography, monoscopic photography or direct ophthalmoscopy to the reference standard in people under investigation for glaucomatous damage were identified.

Structural index tests represented in the studies utilise 3D imaging devices and many of the papers presented accuracy based on different algorithms used by various software programs to analyse the images. Therefore, while there are only a few imaging devices covered by the studies included in the review, the evidence cannot be analysed together as it represents multiple different ways to analyse the image (some involving different levels of operator subjective judgement). The imaging devices and associated algorithms involved measuring different clinical parameters within the eye. There is a very wide range of parameters that can be investigated including the area or volume of the disc, cup or rim as well as the ratio of these, and can also include combinations of superior, inferior, nasal and temporal. Where studies reported 3 or more parameters for a test, the committee chose the 3 parameters with the best overall diagnostic performance for consideration in the review, as well as exploring any combinations of parameters.

Table 15: Summary of studies included in the review

Study	Population	Target condition	Index test	Reference standard
Azuara-Blanco 2016[10] and Banister 2016[14]	n=932 People referred from community optometrists to hospital eye services with a glaucoma-related finding that included high IOP, possible abnormalities in the optic disc or visual fields test, and possible narrow anterior chamber angle Age: 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% UK	Evidence of glaucomatous optic neuropathy and a characteristic VF loss in 1 hemifield that is different from the other hemifield that is across the horizontal midline	HRT-MRA HRT-GPS SD-OCT	Biomicroscopy of the appearance of the optic nerve head and evaluation of the visual field with SAP IOP and chamber angle were also measured
Kamdeu Fansi 2011[65]	n=232 (left eyes) People at high risk for development of COAG (defined as 1 or more of African	Definitive glaucoma based on optic disc appearance and FDT perimetry screening results	HRTII/MRA HRT3/MRA HRT3/GPS HRT3/MRA/GPS	Standard ophthalmologic examination including gonioscopy, IOP, slit-lamp examination, and observation of the optic

Study	Population	Target condition	Index test	Reference standard
	descent, older than 50 years and positive family history of COAG) examined as part of the mobile glaucoma screening clinic project Age: 61 (11) years Gender (F/M): 151/81 Family origin: African-Caribbean: 54; White: 178 Canada			disc, nerve fibre layer and retina after eye dilation
Lee 2013[80]	n=117 People referred to the glaucoma clinic of the hospital with borderline changes in morphology Age Glaucoma: 49.9 (12.8) No glaucoma: 48.9 (11.2) Gender and family origin not reported Korea	Glaucoma characterised by the presence of a glaucomatous optic disc and a glaucomatous visual field with or without IOP ≥21 mmHg	HRT3	Comprehensive ophthalmologic examination including BCVA, slit-lamp biomicroscopy, IOP, gonioscopy, funduscopic examination with stereoscopic optic disc photography and monoscopic red-free digital fundus photography
Li 2010[82]	n=210 (right eyes) People recruited 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 who were offered a free glaucoma screening	Definitive glaucoma based on optic disc appearance and FDT perimetry screening results	OCT	Ocular examination including pachymetry, gonioscopy, IOP, slit-lamp examination, and stereo examination of the optic nerve head, RNFL and retina

Study	Population	Target condition	Index test	Reference standard
	Age: 61.01 (8.73) years Gender (F/M): 157/53 Family origin: Black: 7.14%; White: 91.43%; Hispanic: 0.95%; Other: 0.48% Canada			
Pueyo 2009[119]	n=140 People aged between 18 and 80 Age, gender and family origin not reported Spain	IOP≥22mmHg, repeated abnormal visual fields defects and optic disc appearance consistent with glaucomatous optic neuropathy	HRT-II OCT	IOP measurement, automated perimetry and optic disc appearance (slit-lamp biomicroscopy and stereoscopic optic disc photography)
Rolle 2016[129]	n=113 People enrolled consecutively from the Glaucoma Centre of the Eye Clinic of the University of Torino Age: 62.1 (14.53) Gender (M/F): 61/52 Family origin not reported Italy	Glaucomatous eyes with abnormal VF or GHT and ONH changes, such as optic rim notch or diffuse loss of optic rim tissue, vertical cup and disc diameter ratio asymmetry >0.2, disc haemorrhages.	Spectralis SD-OCT	VF test using Humphrey Field Analyser and biomicroscopic slit-lamp examination. All subjects also underwent complete ophthalmic examination, including visual acuity, refraction, gonioscopy, Goldmann applanation tonometry and ultrasound pachymetry
Simavli 2015[138]	n=156 People recruited from the Glaucoma Service at Massachusetts Eye and Ear Infirmary as part of the prospective SD-OCT in Glaucoma Study Age	Glaucoma defined as characteristic changes of the ONH with corresponding abnormal VF defects	Spectralis SD-OCT Peripapillary retinal volume scan	VF testing with Humphrey Field Analyser, stereo disc photography and slit lamp biomicroscopy. All subjects also underwent a complete eye examination by a glaucoma specialist, which included history, visual acuity testing,

Study	Population	Target condition	Index test	Reference standard
	No glaucoma 62.6 (11.6) POAG: 66.0 (10.6) Gender and family origin not reported USA			refraction, Goldmann applanation tonometry, gonioscopy, ultrasonic pachymetry and dilated ophthalmoscopy
Wu 2012[166]	n=146 People from the Glaucoma Service at the Massachusetts Eye and Ear Infirmary Age No glaucoma: 63.5 (14.0) Glaucoma: 69.2 (13.0) Gender (% female): No glaucoma: 52.9 Glaucoma: 59 Family origin (% White): No glaucoma: 74.1 Glaucoma: 67.2 USA	Glaucoma defined as characteristic changes of the optic nerve head with corresponding abnormal VF defects	Spectralis SD-OCT Peripapillary Nerve Fibre Layer Measurement	VF testing with Humphrey Visual Field Analyser, stereo disc photography 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
Zheng 2010[170]	n=308 People recruited by the Singapore Ministry of Home Affairs of which a random age-stratified sample was used as the study sample. Age: Mean (SD) not reported. All participants between 40–80 years Family origin: Malay: 100% Gender not reported	Glaucoma defined according to the International Society for Geographic and Epidemiological Ophthalmology based on 3 categories: (1) Glaucomatous optic disc abnormality with a corresponding visual field defect	HRT-II	Optic disc evaluation using a +78 D lens at x16 magnification with a measuring graticule. Margins of the optic cup were defined stereoscopically as the point of maximal infection of vessels crossing the neuroretinal rim

Study	Population	Target condition	Index test	Reference standard
	Singapore	(2) Severely damaged optic disc in the absence of a visual field defect (3) Subjects without visual field or optic disc data who were blind and had previous glaucoma surgery or an IOP>99.5th percentile		

Table 16: Clinical evidence summary: diagnostic accuracy for structural tests to measure damage of the optic nerve head as well as macular and retinal nerve fibre layer in the context of case finding

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)		Specificity % (95% CI)	AUC (95% CI)
SD-OCT							
SD-OCT	1	883	MODERATE[c] Due to indirectness	0.77 (0.69, 0.83)		0.79 (0.75, 0.81)	0.84
SD-OCT RNFL thickness	1	140	LOW[a] Due to very serious risk of bias	Average	0.84	Specificity fixed at 0.85	0.93 (0.89, 0.97)
					0.70	Specificity fixed at 0.95	
				Inferior	0.76	Specificity fixed at 0.85	0.91 (0.8, 0.95)
					0.62	Specificity fixed at 0.95	
				Nasal	0.66	Specificity fixed at 0.85	0.89 (0.83, 0.94)
					0.49	Specificity fixed at 0.95	
SD-OCT cup diameter	1	210	MODERATE[a] Due to serious risk of bias	0.83 (0.36, 1.00)		0.84 (0.79, 0.89)	0.91 (0.82, 0.99)
SD-OCT cup or disc vertical ratio	1	210	MODERATE[a] Due to serious risk of bias	0.83 (0.36, 1.00)		0.82 (0.76, 0.87)	0.88 (0.80, 0.95)
SD-OCT cup area	1	210	MODERATE[a] Due to serious risk of bias	0.83 (0.36, 1.00)		0.81 (0.75, 0.86)	0.86 (0.78, 0.93)
Spectralis SD-OCT T-MRT	1	113	VERY LOW[a,d] Due to very serious risk of bias, serious imprecision	GHT	0.70 (0.59, 0.79)	0.73 (0.52, 0.90)	0.75 (0.63, 0.80)
				GSS2	0.61 (0.50, 0.71)	0.82 (0.61, 0.95)	0.73 (0.63, 0.82)
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA1	1	156	LOW[a,] Due to very serious risk of bias	Superior	0.80 (0.70, 0.88)	0.85 (0.74, 0.93)	Not reported
				Temporal	0.84 (0.75, 0.91)	0.76 (0.64, 0.86)	
				Inferior	0.93 (0.86, 0.98	0.88 (0.78, 0.95)	
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA2	1	156	LOW[a] Due to very serious risk of bias	Superior	0.85 (0.76, 0.92)	0.78 (0.66, 0.87)	Not reported
				Temporal	0.84 (0.74, 0.91)	0.78 (0.66, 0.87)	

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)		Specificity % (95% CI)	AUC (95% CI)
				Inferior	0.89 (0.80, 0.94)	0.90 (0.80, 0.96)	
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA3	1	118	LOW[a] Due to very serious risk of bias	Superior	0.90 (0.82, 0.96)	0.64 (0.51, 0.75)	Not reported
				Temporal	0.60 (0.48, 0.70)	0.78 (0.66, 0.87)	
				Inferior	0.80 (0.70, 0.88)	0.85 (0.74, 0.93)	
Spectralis SD-OCT Peripapillary Nerve Fibre Layer Measurement at different thresholds							
Overall global RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.80 (0.74, 0.87)		0.93 (0.89, 0.97)	Not reported
Overall global RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.67 (0.60, 0.75)		1.00 (0.96, 1.00)	Not reported
1 quadrants with RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.97 (0.94, 1.00)		0.86 (0.80, 0.92)	Not reported
1 quadrants with RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.89 (0.83, 0.94)		0.95 (0.92, 0.99)	Not reported
1 sectors of TS,TI,NS,NI with RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.98 (0.96, 1.00)		0.89 (0.84, 0.94)	Not reported
1 sectors of TS,TI,NS,NI with RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.93 (0.89, 0.98)		0.95 (0.92, 0.99)	Not reported
HRT							
HRT-2 Fisher's LDF	1	140	LOW[a] Due to very serious risk of bias	0.84		specificity set as 0.85	0.90 (0.85-0.95)
				0.73		specificity set as 0.95	
Vertical cup or disc ratio	1	140	LOW[a]	0.82		specificity set as 0.85	0.89 (0.84-0.95)

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
			Due to very serious risk of bias	0.74	specificity set as 0.95	
Cup disc area ratio or rim disc area ratio	1	140	LOW[a] Due to very serious risk of bias	0.87 0.76	specificity set as 0.85 specificity set as 0.95	0.89 (0.84-0.95)
HRT-2 LDF1	1	308	LOW[a] Due to very serious risk of bias	0.73 (0.64, 0.80)	0.78 (0.74, 0.82)	0.75 (0.71, 0.80)
HRT-2 LDF2	1	308	LOW[a] Due to very serious risk of bias	0.66 (0.57, 0.74)	0.85 (0.81, 0.88)	0.75 (0.71, 0.80)
HRT-2 LDF3	1	308	LOW[a] Due to very serious risk of bias	0.67 (0.60, 0.77)	0.84 (0.80, 0.87)	0.76 (0.72, 0.81)
HRT-3 MRA	2	932 232	MODERATE[c] Due to serious indirectness	0.87 (0.80, 0.92) 1.00 (0.4, 1.00)	0.64 (0.60, 0.67) 0.90 (0.86, 0.94)	0.79 Not reported
HRT-3 GPS	3	128 1	VERY LOW[c,d] Due to serious indirectness, very serious imprecision	0.75 (0.43, 0.94)[e]	0.70 (0.40, 0.91)	0.62 (0.49, 0.81)
HRT-3 H-RNFL	1	117	VERY LOW[a,d,c] Due to very serious risk of bias , serious indirectness and serious imprecision	Not reported	Not reported	0.60 (0.45, 0.73)
HRT-3 V-RNFL	1	117	VERY LOW[a,d,c] Due to very serious risk of bias , serious indirectness and serious imprecision	Not reported	Not reported	0.60 (0.43, 0.69)
HRT-3 cup depth	1	117	VERY LOW[a,d,c] Due to very serious risk of bias , serious indirectness and serious imprecision	Not reported	Not reported	0.59 (0.44, 0.66)
HRT-2 MRA at different thresholds						

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
Cut-off point 'borderline' or more	1	308	LOW[a] Due to very serious risk of bias	0.71 (0.62, 0.79)	0.86 (0.83, 0.90)	0.79 (0.74, 0.83)
Cut-off point 'out' or more	2	232 308	LOW[a] Due to very serious risk of bias	0.75 (0.22, 0.99) 0.44 (0.35, 0.53)	0.96 (0.90, 0.97) 0.97 (0.95, 0.99)	Not reported 0.70 (0.66, 0.75)
Combinations of parameters						
HRT-3 MRA + HRT-3 GPS	2	932 308	MODERATE[c] Due to serious indirectness	0.91 (0.85, 0.95) 1.0 (0.40, 1.00)	0.53 (0.49, 0.57) 0.73 (0.67, 0.79)	Not reported Not reported
HRT-3 MRA + SD-OCT	1	932	MODERATE[c] Due to serious indirectness	0.92 (0.86, 0.96)	0.54 (0.50, 0.58)	Not reported
SD-OCT ONH + RNFL parameters	1	210	MODERATE[a] Due to serious risk of bias	0.67 (0.22, 0.96)	0.85 (0.79, 0.90)	Not reported

The case-finding assessment was conducted with an emphasis on test specificity, as the committee identified this as the primary measure to guide its decision-making. The committee set the specificity threshold of 95% as an acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Please refer to clinical evidence tables for details on study limitations.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity plots as well as the summary area under the curve (AUC) plots. Particular attention was placed on the specificity threshold that the committee set as an acceptable level to recommend a test and on AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies were above or below 50%, or above or below the acceptable threshold*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies were above or below 50%, and above or below the acceptable threshold.*

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely specialist glaucoma clinic context.

(d) Imprecision was assessed based on inspection of the confidence region of specificity in the diagnostic meta-analysis; where diagnostic meta-analysis had not been conducted, assessed according to the range of confidence intervals in the individual study; or if specificity confidence intervals were not available, then on AUC. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%

(e) Pooled sensitivity and specificity from diagnostic meta-analysis

Table 17: Clinical evidence summary: diagnostic accuracy for structural tests to measure damage of the optic nerve head as well as macular and retinal nerve fibre layer in the context of diagnosis and reassessment

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)		Specificity % (95% CI)	AUC (95% CI)
SD-OCT							
SD-OCT	1	883	HIGH	0.77 (0.69, 0.83)		0.79 (0.75, 0.81)	0.84
SD-OCT RNFL thickness	1	140	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	Average	0.84	Specificity fixed at 0.85	0.93 (0.89, 0.97)
					0.70	Specificity fixed at 0.95	
				Inferior	0.76	Specificity fixed at 0.85	0.91 (0.8, 0.95)
					0.62	Specificity fixed at 0.95	
				Nasal	0.66	Specificity fixed at 0.85	0.89 (0.83, 0.94)
					0.49	Specificity fixed at 0.95	
SD-OCT cup diameter	1	210	VERY LOW[a,c,d] Due to serious risk of bias, serious indirectness and very serious imprecision	0.83 (0.36, 1.00)		0.84 (0.79, 0.89)	0.91 (0.82, 0.99)
SD-OCT cup or disc vertical ratio	1	210	VERY LOW[a,c,d] Due to serious risk of bias, serious indirectness and very serious imprecision	0.83 (0.36, 1.00)		0.82 (0.76, 0.87)	0.88 (0.80, 0.95)
SD-OCT cup area	1	210	VERY LOW[a,c,d] Due to serious risk of bias, serious indirectness and very serious imprecision	0.83 (0.36, 1.00)		0.81 (0.75, 0.86)	0.86 (0.78, 0.93)
Spectralis SD-OCT T-MRT	1	113	LOW[a] Due to very serious risk of bias	GHT	0.70 (0.59, 0.79)	0.73 (0.52, 0.90)	0.75 (0.63, 0.80)
				GSS2	0.61 (0.50, 0.71)	0.82 (0.61, 0.95)	0.73 (0.63, 0.82)

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)		Specificity % (95% CI)	AUC (95% CI)
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA1	1	156	LOW[a] Due to very serious risk of bias	Superior Temporal Inferior	0.80 (0.70, 0.88) 0.84 (0.75, 0.91) 0.93 (0.86, 0.98)	0.85 (0.74, 0.93) 0.76 (0.64, 0.86) 0.88 (0.78, 0.95)	Not reported
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA2	1	156	LOW[a] Due to very serious risk of bias	Superior Temporal Inferior	0.85 (0.76, 0.92) 0.84 (0.74, 0.91) 0.89 (0.80, 0.94)	0.78 (0.66, 0.87) 0.78 (0.66, 0.87) 0.90 (0.80, 0.96)	Not reported
Spectralis SD-OCT 3D peripapillary retinal volume scan OCA3		118	LOW[a] Due to very serious risk of bias	Superior Temporal Inferior	0.90 (0.82, 0.96) 0.60 (0.48, 0.70) 0.80 (0.70, 0.88)	0.64 (0.51, 0.75) 0.78 (0.66, 0.87) 0.85 (0.74, 0.93)	Not reported
Spectralis SD-OCT Peripapillary Nerve Fibre Layer Measurement at different thresholds							
Overall global RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.80 (0.74, 0.87)		0.93 (0.89, 0.97)	Not reported
Overall global RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.67 (0.60, 0.75)		1.00 (0.96, 1.00)	Not reported
1 quadrants with RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.97 (0.94, 1.00)		0.86 (0.80, 0.92)	Not reported
1 quadrants with RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.89 (0.83, 0.94)		0.95 (0.92, 0.99)	Not reported
1 sectors of TS,TI,NS,NI with RNFL thickness abnormal at <5% level	1	146	LOW[a] Due to very serious risk of bias	0.98 (0.96, 1.00)		0.89 (0.84, 0.94)	Not reported

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
1 sectors of TS,TI,NS,NI with RNFL thickness abnormal at <1% level	1	146	LOW[a] Due to very serious risk of bias	0.93 (0.89, 0.98)	0.95 (0.92, 0.99)	Not reported
HRT						
HRT-2 Fisher's LDF	1	140	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.84 0.73	specificity set as 0.85 specificity set as 0.95	0.90 (0.85-0.95)
Vertical cup or disc ratio	1	140	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.82 0.74	specificity set as 0.85 specificity set as 0.95	0.89 (0.84-0.95)
Cup disc area ratio or rim disc area ratio	1	140	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.87 0.76	specificity set as 0.85 specificity set as 0.95	0.89 (0.84-0.95)
HRT-2 LDF1	1	308	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.73 (0.64, 0.80)	0.78 (0.74, 0.82)	0.75 (0.71, 0.80)
HRT-2 LDF2	1	308	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.66 (0.57, 0.74)	0.85 (0.81, 0.88)	0.75 (0.71, 0.80)
HRT-2 LDF3	1	308	VERY LOW[a,c] Due to very serious risk of bias, serious indirectness	0.67 (0.60, 0.77)	0.84 (0.80, 0.87)	0.76 (0.72, 0.81)
HRT-3 MRA	2	932 232	HIGH	0.87 (0.80, 0.92) 1.00 (0.4, 1.00)	0.64 (0.60, 0.67) 0.90 (0.86, 0.94)	0.79 Not reported
HRT-3 GPS	3	128	VERY LOW[c,d]	0.75 (0.43, 0.94)[e]	0.70 (0.40, 0.91)	0.62 (0.49, 0.81)

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
		1	Due to serious indirectness, very serious imprecision			
HRT-3 H-RNFL	1	117	VERY LOW[a,d] Due to very serious risk of bias and serious imprecision	Not reported	Not reported	0.60 (0.45, 0.73)
HRT-3 V-RNFL	1	117	VERY LOW[a,d] Due to very serious risk of bias and serious imprecision	Not reported	Not reported	0.60 (0.43, 0.69)
HRT-3 cup depth	1	117	VERY LOW[a,d] Due to very serious risk of bias and serious imprecision	Not reported	Not reported	0.59 (0.44, 0.66)
HRT-2 MRA at different thresholds						
Cut-off point 'borderline' or more	1	308	VERY LOW[a] Due to very serious risk of bias, serious indirectness	0.71 (0.62, 0.79)	0.86 (0.83, 0.90)	0.79 (0.74, 0.83)
Cut-off point 'out' or more	2	232 308	VERY LOW[a] Due to very serious risk of bias, serious indirectness	0.75 (0.22, 0.99) 0.44 (0.35, 0.53)	0.96 (0.90, 0.97) 0.97 (0.95, 0.99)	Not reported 0.70 (0.66, 0.75)
Combinations of parameters						
HRT-3 MRA + HRT-3 GPS	2	932 308	HIGH	0.91 (0.85, 0.95) 1.0 (0.40, 1.00)	0.53 (0.49, 0.57) 0.73 (0.67, 0.79)	Not reported Not reported
HRT-3 MRA + SD-OCT	1	932	HIGH	0.92 (0.86, 0.96)	0.54 (0.50, 0.58)	Not reported

Index Test (Threshold)	No of studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
SD-OCT ONH + RNFL parameters	1	210	VERY LOW[a,c,d] Due to serious risk of bias, serious indirectness, and very serious imprecision	0.67 (0.22, 0.96)	0.85 (0.79, 0.90)	Not reported

The diagnosis and reassessment assessment was conducted with an emphasis on test sensitivity, as the committee identified this as the primary measure to guide its decision-making. The committee set the sensitivity threshold of 95% as an acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Please refer to clinical evidence tables for details on study limitations.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity plots as well as the summary area under the curve (AUC) plots. Particular attention was placed on the sensitivity threshold that the committee set as an acceptable level to recommend a test and on AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies were above or below 50%, or above or below the acceptable threshold*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies were above or below 50%, and above or below the acceptable threshold.*

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely case-finding context.

(d) Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis; where diagnostic meta-analysis had not been conducted, assessed according to the range of confidence intervals in the individual study; or if sensitivity confidence intervals were not available, then on AUC. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%

(e) Pooled sensitivity and specificity from diagnostic meta-analysis.

6.3.3 Economic evidence

Published literature

No relevant economic evaluations were identified. Note that the GATE study,[10] which has been included in the clinical review for this question, has an economic model; however, this has been included in the service model question, as it has a service delivery aspect of using different optic nerve head imaging technologies as part of a hospital triage model.

See also the economic article selection flow diagram in appendix F.

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 18 reports the unit costs that were presented to the committee to aid consideration of cost effectiveness. The costs include the capital cost of the diagnostic technology. This was micro-costed in the Azaura-Blanco (2016) study.[10] The study obtained the initial outlay costs from various commercial providers to the NHS. The initial outlay costs were annuitised over the useful working lifespan of the piece of equipment (assumed to be 10 years for all equipment) applying an annual discount factor of 3.5% to account for the opportunity cost of the investment overtime. The equivalent annual cost of each piece of equipment was divided by its estimated maximum number of uses per annum (from NHS providing units and expert opinion) to give cost per use estimates.[10]

Table 18: Unit costs of optic nerve head tests in a secondary care setting (OCT and HRT)

Item	Unit Cost	Source
Technician-led index test (for example, OCT, GDx or HRT)	£2.72	Agenda for change
Capital cost OCT diagnostic technology (per test)	£1.32	Azuara-Blanco 2016 [10] (micro-costed)
Capital cost of HRT-III (GPS and MRA) diagnostic technologies (per test)	£0.79	Azuara-Blanco 2016 [10] (micro-costed)
Total cost of OCT test	**£4.04**	
Total cost of HRT test	**£3.51***	

*the committee noted that HRT equipment has been discontinued and therefore new machines are no longer available to purchase.

The unit costs in Table 18 represent the costs of OCT and HRT tests conducted in a secondary care setting assuming the equipment is used to maximum capacity. The costs would not be the same and would be likely to be higher if conducted in a community or primary care setting as the equipment would probably not be used to full capacity and therefore the capital cost per test would increase.

6.3.4 Evidence statements

Clinical

The committee decided not to consider the evidence for the diagnostic accuracy of HRT as this technology is no longer a supported by the manufacturer and is becoming increasingly rarely used in practice. In the context of case finding, the tests that met the committee's pre-specified specificity threshold for consideration (95%) were SD-OCT retinal nerve fibre layer (RNFL) thickness where low quality evidence from one small study (n=140) showed that at a fixed specificity of 0.95 the sensitivities were 0.62 and 0.49 when measuring the inferior and nasal parameters respectively, and 0.70 when taking an average of the different parameter measurements. However, uncertainty could not be assessed as no confidence intervals were reported. Imprecision was therefore based on the reported AUC ratings associated with these estimates thresholds: 0.91 (0.80, 0.95); 0.89 (0.83, 0.94); and 0.93 (0.89, 0.97). There was also low quality evidence from another single small study (n=146) that the Spectralis SD-OCT peripapillary nerve fibre layer measurement met the pre-specified specificity threshold when considering that having one quadrant with RNFL thickness as abnormal at <1% level as the cut-off (sensitivity 0.89 [0.83, 0.94], specificity 0.95 [0.92, 0.99]) or when considering that 1 sector of temporal superior, temporal inferior, nasal superior, nasal inferior with RNFL thickness as abnormal at <1% level as the cut-off (sensitivity 0.93 [0.89, 0.98], specificity 0.95 [0.92, 0.99]).

Moderate quality evidence from one study (n=883) was also found for SD-OCT (sens 0.77 [0.69, 0.83], spec 0.79 [0.75, 0.81]) and from one study (n=210) for SD-OCT cup diameter (sens 0.83 [0.36, 1.00], spec 0.84 (0.79, 0.89]), SD-OCT cup or disc ratio (sens 0.83 [0.36, 1.00], spec 0.82 (0.76, 0.87]), SD-OCT cup area (0.83 [0.36, 1.00], spec 0.81 [0.75, 0.86]), although none of these estimates met the pre-specified specificity threshold. All the rest of the OCT evidence was at low to very low quality and did not meet the committee's specificity threshold for consideration of a test to be used in the case-finding setting, including evidence from the only paper looking at combinations of different OCT parameters (ONH + RNFL parameters).

In the context of diagnosis and reassessment high quality evidence from one study (n=883) suggested SD-OCT showed a sensitivity of 0.77 (0.69, 0.83) and specificity of 0.79 (0.75, 0.81) which did not meet the committee's pre-specified sensitivity threshold of 95%. A structural test that did meet the committee's pre-specified sensitivity threshold was the Spectralis SD-OCT peripapillary nerve fibre layer measurement for two particular parameters. Low quality evidence from one small study (n=146) suggested that when considering that having one quadrant with RNFL thickness as abnormal at 5% level as the cut-off, sensitivity was 0.97 (0.94, 1.00) and specificity was 0.86 (0.80, 0.92); or when considering that 1 sector of temporal superior, temporal inferior, nasal superior, nasal inferior with RNFL thickness as abnormal at 5% level as the cut-off, sensitivity was 0.98 (0.96, 1.00) and specificity was 0.89 (0.84, 0.94). All the rest of the OCT evidence was at low to very low quality and did not meet the committee's sensitivity threshold for consideration of a test to be used in the diagnosis and reassessment setting, including evidence from the only paper looking at combinations of different OCT parameters (ONH + RNFL parameters).

Economic

No relevant economic evaluations were identified.

6.4 Accuracy of intraocular pressure (IOP) tests

6.4.1 Review question: What is the accuracy of tests for measuring IOP and monitoring changes in IOP, including repeat measures?

For full details, see review protocol in appendix C.

Table 19: Characteristics of review question

Population	Adults (18 and over)
Target condition	Detection of any level of IOP
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 (ORA) • 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) by trained clinician, slit lamp mounted
Statistical measures	• 2x2 tables • Specificity • Sensitivity • C-statistic (ROC curve or AUC)
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-sectional studies)

6.4.2 Clinical evidence

Four studies were included in the review.[8,17,21,95] Three studies[17,21,95] were added to the previous study included in CG85;[8] these are summarised in Table 26 below. This evidence is summarised in the clinical evidence profile below. See also the study selection flow chart in appendix E, coupled sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in appendix K, study evidence tables in appendix H, and excluded studies list in appendix L.

The 4 studies compared the reference standard of Goldmann applanation tonometry with Pulsair non-contact tonometry, Reichert Tono-Pen AVIA, Icare rebound tonometry. Studies ranged from purely case-finding settings to specialist glaucoma clinic settings, and many involved mixed populations of both.

Table 20: Summary of studies included in the review

Study	Population	Target condition	Index test	Reference standard	Comments
Atkinson 1992[8]	n=not reported (403 eyes) People from general ophthalmolog	Detection of IOP ≥21mmHg	Pulsair non-contact tonometry	Goldmann applanation tonometry	Study presented as 3 studies, 3 machines used in 2 centres

Study	Population	Target condition	Index test	Reference standard	Comments
	y outpatient departments and glaucoma clinics Age, gender and family origin not reported UK				
Billy 2015[17]	n=100 (198 eyes) People attending the ophthalmology clinic at the Eric Williams Medical Sciences Complex who were having their routine visit Age: 21-50 years: 33% 51-70 years: 51% >71 years: 26% Gender (M:F):39:61 Family origin: Indo-Trinidadian: 55%; African-Trinidadian: 36%; Mixed: 8%; White: 1% Trinidad	Detection of IOP ≥ 21mmHg	Reichert Tono-Pen AVIA carried out by trained medical students	Goldmann applanation tonometry	Prospective cross-sectional
Cagatay 2014[21]	n=40 (40 eyes) Adults with no ocular pathology other than having myopia	Detection of IOP above 21mmHg	Icare rebound tonometer	Goldmann applanation tonometry	Prospective randomised

Study	Population	Target condition	Index test	Reference standard	Comments
	of 6 dioptres or over Age: 35.73 ± 12.97 years Gender and family origin not reported Turkey				
Moreno-Montanes 2015[95]	n=150 (150 eyes) People with IOPs in the normal range and no glaucoma and those with ocular hypertension or glaucoma Age: 57.0 ± 18.13 years Gender (M/F): 55 (36.7%)/95 (63.3%) Family origin not reported Spain	Detection of IOP ≥ 21mmHg	Icare rebound tonometry PRO	Goldmann applanation tonometry	Prospective cross-sectional

Table 21: Clinical evidence summary: diagnostic test accuracy for Pulsair non-contact tonometry, Reichert Tono-Pen AVIA and Icare rebound tonometry in the context of case finding

Index Test (Threshold)	studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
Pulsair non-contact tonometry (21mmHg threshold)	3	403	HIGH	0.52 (0.19, 0.87)[c]	0.94 (0.81, 0.98)[c]	-
Reichert Tono-Pen AVIA (21mmHg threshold)	1	100	MODERATE[b] due to serious indirectness	0.56 (0.30, 0.80)	0.98 (0.94, 0.99)	-
Icare rebound tonometry (21mmHg threshold)	2	40 150	LOW[a,b] due to serious inconsistency, serious indirectness	0.83 (0.36, 1.00) 0.79[d]	0.97 (0.85, 1.00) 0.74[d]	- 0.88 (0.82, 0.93)

The assessment was conducted with an emphasis on test specificity for case finding within the community as the committee identified these as the primary measures to guide decision-making. The committee set the specificity threshold for case finding at 95% as an acceptable level to recommend a test.

(a) Inconsistency was assessed by inspection of the sensitivity and specificity plots as well as the summary area under the curve (AUC) plots. Particular attention was placed on the specificity threshold for case finding that the committee set as acceptable levels to recommend a test as well as the AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies were above or below 50% or above or below the acceptable threshold 95%*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies were above or below 50% and above or below the acceptable threshold 95%.*

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely specialist glaucoma clinic context.

(c) Pooled sensitivity and specificity from diagnostic meta-analysis

(d) Unable to judge imprecision as the study did not report confidence intervals or provide sufficient data to calculate these.

Table 22: Clinical evidence summary: diagnostic test accuracy for Pulsair non-contact tonometry, Reichert Tono-Pen AVIA and Icare rebound tonometry in the context of diagnosis and reassessment

Index Test (Threshold)	studies	n	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)

Pulsair non-contact tonometry (21mmHg threshold)	3	403	LOW[e] due to very serious imprecision	0.52 (0.19, 0.87)[c]	0.94 (0.81, 0.98)[c]	-
Reichert Tono-Pen AVIA (21mmHg threshold)	1	100	LOW[e] due to very serious imprecision	0.56 (0.30, 0.80)	0.98 (0.94, 0.99)	-
Icare rebound tonometry (21mmHg threshold)	2	40 150	VERY LOW[a,b,c] due to serious inconsistency, serious indirectness, very serious imprecision	0.83 (0.36, 1.00) 0.79[d]	0.97 (0.85, 1.00) 0.74[d]	- 0.88 (0.82, 0.93)

The assessment was conducted with an emphasis on test sensitivity for diagnosis and reassessment, as the committee identified these as the primary measures to guide decision-making. The committee set the sensitivity threshold for diagnosis and reassessment at 95% as an acceptable level to recommend a test.

(a) Inconsistency was assessed by inspection of the sensitivity and specificity plots as well as the summary area under the curve (AUC) plots. Particular attention was placed on the sensitivity for diagnosis and reassessment that the committee set as acceptable levels to recommend a test as well as the AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies were above or below 50% or above or below the acceptable threshold 95%*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies were above or below 50% and above or below the acceptable threshold 95%.*

(b) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely case-finding context.

(c) Pooled sensitivity and specificity from diagnostic meta-analysis

(d) Unable to judge imprecision as the study did not report confidence intervals or provide sufficient data to calculate these.

(e) Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis; where diagnostic meta-analysis had not been conducted, assessed according to the range of confidence intervals in the individual study; or if sensitivity confidence intervals were not available, then on AUC. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%

6.4.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

Unit costs

Relevant unit costs have been provided below to aid consideration of cost-effectiveness.

In the previous guideline, a cost analysis to calculate the unit costs was conducted to compare the cost of contact (Goldmann Applanation Tonometry) versus non-contact tonometry (Pulsair). Elements included in the analysis were capital costs, life span and consumables. The necessary time to complete the tests and the consequences of false positives and false negatives were excluded from the analysis. This costing of tests was updated here with costs that are more recent and the medicine more commonly used in current practice.

The following assumptions were used in the unit cost analysis:

- the same test would be used for both diagnosis and reassessment
- life span of machines is 5 years unless available data state differently
- reference standard tests are the most accurate within the same group
- interest rate for calculating the annual cost of machines is 3.5%
- medicines used specifically for the test were the only consumables.

The number of people referred every year to a clinic for confirmation or exclusion of COAG was estimated by averaging the estimates the committee experts provided. The same method was applied to estimate the number of follow-up visits per year. On average, 3 people per day undergo tests for the diagnosis of COAG and 33 people per day are followed up, totalling 1,000 people per year for diagnosis and 12,000 people per year for reassessment in an average clinic.

The capital cost of a Goldmann Tonometer is composed of the cost of the actual tonometer, the slit lamp on which it is mounted, and the lenses. However, as most optometrists would have a slit lamp for other eye examinations, the capital cost of this equipment has been excluded in a scenario analysis. Experts estimated the overall cost, which was later confirmed by data provided by the UK supplier (personal communication). The latter also provided the average life span of the machine. The cost of a non-contact tonometer was obtained from the website of the UK distributor of Keeler Pulsair tonometer. The average life span was not available and therefore subject to assumption. Annual costs of equipment were calculated as:

$$E = \frac{K}{\frac{1-(1+r)^{-n}}{r} + 1}$$

where E=annual cost of the machine

K=capital outlay (cost of purchasing the machine)

r=interest rate 3.5%

n=life span

Other resources considered in the cost analysis were medicine and disposables used in order to perform the test. One unit of Lidocaine and Fluorescein was used before Goldmann tonometry and 1 disposable prism was used per test. The cost of medicine and disposables per test is reported below.

Table 23: Cost of medicine for tests

Medicine	Cost Per Pack (a)	Units	Cost Per Unit (£)
Lidocaine hydrochloride 4%, fluorescein sodium 0.25%	£11.24	20	0.6
Tonojet L900 disposable prism	£75.00	100	0.75

Source: BNF November 2016

Based on this, the total cost per person was calculated as:

$$TC = \frac{ac}{p} + d + e$$

where

TC=total cost per person

ac=annual cost of equipment

p=diagnosis and reassessment population

d=cost of medicine unit

e=cost of disposable

The total cost per person and the difference in costs between strategies are reported in Table 24 below.

Table 24: Total cost and cost difference – Goldmann versus non-contact tonometry

Test	Capital outlay (K)	Life span (n)	Interest rate (r)	Annual cost	Cost per person (b)
Goldmann tonometry – equipment not available	£10,000	15 (a)	3.5%	£799	£1.41
Goldmann tonometry – equipment already available	-	-	3.5%	£799	£1.35
Non-contact tonometry	£5,000	5	3.5%	£907	£0.07
Difference – Goldmann versus non-contact (equipment not available or					**£1.34/£1.28**

Test	Capital outlay (K)	Life span (n)	Interest rate (r)	Annual cost	Cost per person (b)
available)					

(a) Life span of slit lamp alone is 30 years; however, the UK supplier of the Goldmann tonometer indicated its life span is 15 years.

(b) Annual cost of equipment per person + cost of medicine for each test.

6.4.4 Evidence statements

Clinical

High quality evidence from 1 study (n=403) reporting on 3 different Pulsair non-contact tonometry machines showed a pooled sensitivity of 0.52 (0.19, 0.87) with a pooled specificity of 0.94 (0.81, 0.98) when using a threshold of 21mmHg, not quite meeting the pre-specified case-finding specificity threshold for case finding. Moderate quality evidence from another smaller study (n=100) showed sensitivity 0.56 (0.30, 0.80) and specificity 0.98 (0.94, 0.99) when using the Reichert Tono-Pen AVIA at the 21mmHg threshold, meeting the pre-specified specificity threshold of 95% for consideration at case finding. Two studies reported on the sensitivity and specificity of Icare rebound tonometry at the threshold of 21mmHg. Evidence from these studies suggested sensitivities of 0.79 (no 95% CI reported) and 0.83 (0.36, 1.00) and paired specificities of 0.74 (no 95% CI) and 0.97 (0.85, 1.00). While one set of paired results for this index test reached the pre-specified specificity threshold for consideration at case finding, the quality of this evidence was low and the diagnostic accuracy was based on a very small sample size (n=40).

When assessing the evidence from a diagnosis and reassessment perspective, all the evidence was of low to very low quality based largely on the uncertainty around the sensitivity estimates, all of which failed to reach the pre-specified threshold for consideration of a non-contact test used in the diagnosis and reassessment context.

Economic

No relevant economic evaluations were identified.

6.5 Accuracy of tests for identifying closed or occludable anterior chamber angle

6.5.1 Review question: What is the accuracy of tests for identifying closed or occludable anterior chamber angle?

For full details, see review protocol in appendix C.

Table 25: Characteristics of review question

Population	Adults (18 and over)
Target condition	Closed or occludable anterior chamber angle
Index test(s)	• 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)
Study design	Single-gate studies (including prospective and retrospective cohort studies; cross-sectional studies)

6.5.2 Clinical evidence

Five studies were included in the review,[16,34,50,71,98] which assessed the accuracy of tests of identifying closed or occludable anterior chamber angles. One of these was included in the previous guideline (CG85).[16] Two studies from the previous guideline were excluded, as they did not meet the definition of the target condition in the protocol.[107,151] The included studies are summarised in Table 26 below. Studies ranged from purely case-finding settings to specialist glaucoma clinic settings, and many involved mixed populations of both. Evidence from these is summarised in the clinical evidence profile below (Table 16). See also the study selection flow chart in appendix E, coupled sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in appendix K, study evidence tables in appendix H, and excluded studies list in appendix L.

Table 26: Summary of studies included in the review

Study	Population	Target condition	Parameter(s)	Index test	Reference standard
Baskaran 2007[16]	n=120 (120 eyes) People who were recruited from glaucoma and general ophthalmology clinics who were also phakic Age: mean 62.1±11.3 Gender (male to female ratio): 52/68 Family origin: Chinese: 73%; Malaysian: 7%; Indian: 20% Singapore	Narrow angle Gonioscopy: narrow angle defined as the presence of a Schaffer grade of up to 1 (10° iridotrabecular angle) for at least 180° of the angle on gonioscopy with or without peripheral anterior synechiae van Herick test: using van Herick cut off ≤25% corneal thickness Prevalence 44.16% (53/120 eyes)	Peripheral ACD < 25% corneal thickness	Modified van Herick's grade	Gonioscopy by a 'single observer'
Dabasia 2015 [34]	n=78 (145 eyes) Adults from glaucoma and general ophthalmology clinics	Narrow angle Gonioscopy: Narrow or occludable angle defined as an ACA in which the posterior (usually pigmented)	Grade 2 (modified LACD ≤25%) nasal and temporal Youden Index derived ACA cut-	van Herick test: the width of the corneal section was compared with the adjacent	Gonioscopy by a consultant glaucoma subspecialist ophthalmologist with

Study	Population	Target condition	Parameter(s)	Index test	Reference standard
	Age: median (IQR) 66 (53-79) Gender (male to female ratio): 34/44 Family origin: White: 56%; South Asian: 35% UK	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	off of 20.7° and central ACD measurement of ≤2.50mm	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: ACA cut-off 20.7° and ACD 2.50mm	extensive experience
Grewal 2011[50]	n=265 (265 eyes) People attending comprehensive ophthalmology clinic Age: ≥40 years, mean 55.2±5.1 Gender (male to female ratio): 49:51 Family origin: not reported USA	Occludable anterior chamber angle Gonioscopy: Shaffer grade ≤1 (10^{o}) in all quadrants Prevalence: 10.6% (28/265 eyes)	Angle opening distance 500 micrometres from scleral spur (AOD500) - temporal quadrant; nasal quadrant ACD Anterior chamber volume (ACV) Trabecular Iris space area, 500 micrometres from scleral spur (TISA500), temporal quadrant; nasal quadrant	Spectral domain (SD) AS-OCT Scheimpflug	Gonioscopy by a glaucoma specialist
Khor 2010[71]	n=2,104 (1,853 eyes) People seeking treatment for non-ophthalmic	Angle closure Gonioscopy. Closed angles in at least 1 quadrant. Posterior TM could not be seen	≥1 quadrants of the angle closed quadrants	AS-OCT	Gonioscopy by a 'single examiner'

Study	Population	Target condition	Parameter(s)	Index test	Reference standard
	reasons at a community clinic Gender (male to female ratio): 48:52 Family origin: Chinese: 89.5%; Malaysian: 2.1%; Indian: 7.3% Singapore	in the primary position without indentation (Scheie grade 3 or 4) Prevalence: 28.2% (522/1,853 eyes)			
Narayanaswamy 2010[98]	n=1,465 People attending a government run polyclinic mostly for general medical problems Age: Mean (SD) 62.7±7.7, range 50-93 Gender (male to female ratio): 46:54 Family origin: Chinese: 90%; Malaysian: 1.8%; Indian: 7% Singapore	Angle closure Gonioscopy: when posterior pigmented trabecular meshwork was not visible for at least 180^{o} Prevalence 21.5% (315/1,465 people)	AOD500 – temporal quadrant; nasal quadrant TISA500 – temporal quadrant; nasal quadrant	AS-OCT	Gonioscopy by a trained ophthalmologist

Table 27: Clinical evidence summary: diagnostic test accuracy for angle closure or occludable angles in the context of case finding

Index Test (Threshold)	No of studies	n eyes	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
OCT						
≥2 quadrants of the angle closed	1	1,853	HIGH	0.93 (0.90, 0.95)	0.52 (0.49, 0.55)	0.72 (0.70, 0.74)
AOD500, temporal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.68 (0.45, 0.84) 0.89 (0.85, 0.92)	0.88 (0.83, 0.92) 0.75 (0.72, 0.77)	0.81 (0.75, 0.85) 0.82 (0.79, 0.84)
AOD500, nasal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.79 (0.59, 0.92) 0.85 (0.81, 0.89)	0.71 (0.65, 0.77) 0.76 (0.74, 0.79)	0.76 (0.70, 0.81) 0.81 (0.78-0.83)
ACA ≤ 20.7°	1	78	VERY LOW [a,d] due to very serious risk of bias, serious imprecision	0.87 (0.73, 0.96)	0.87 (0.72, 0.96)	-
ACD ≤ 2.50mm	1	78	VERY LOW [a,d] due to very serious risk of bias, serious imprecision	0.72 (0.55, 0.85)	0.85 (0.69, 0.94)	-
TISA500, temporal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.71 (0.51, 0.87) 0.88 (0.85, 0.92)	0.81 (0.75, 0.86) 0.59 (0.56, 0.62)	0.74 (0.68, 0.79) 0.74 (0.71-0.76)
TISA500, nasal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.64 (0.44, 0.81) 0.73 (0.68, 0.78)	0.79 (0.73, 0.84) 0.75 (0.73, 0.78)	0.76 (0.70, 0.81) 0.74 (0.71-0.77)
Scheimpflug						
ACD	1	265	MODERATE [a] due to serious risk of bias	0.89 (0.72, 0.98)	0.73 (0.66, 0.78)	0.88 (0.83, 0.92)
ACV	1	265	MODERATE [a] due to serious risk of bias	0.89 (0.72, 0.98)	0.88 (0.83, 0.92)	0.93 (0.90, 0.96)
van Herick's						
Peripheral ACD <25% corneal thickness	2	120 78	HIGH	0.85 (0.72, 0.93) 0.79 (0.65, 0.89)	0.90 (0.80, 0.96) 0.92 (0.79, 0.97)	- -

The assessment was conducted with an emphasis on test specificity, as the committee identified this as the primary measure in guiding decision-making. The committee set the specificity threshold(s) of 95% as an acceptable level to recommend a test.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias. Please see clinical evidence tables for details of study limitations.

(b) Inconsistency was assessed by inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention was placed on the specificity threshold the committee set as an acceptable level to recommend a test (95%) and on AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies are above or below 50%, or above or below the acceptable threshold 95%*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies are above or below 50%, and above or below the acceptable threshold 95%*

(c) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely specialist glaucoma clinic context.

(d) Imprecision was assessed based on inspection of the confidence region of specificity in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, it was assessed according to the range of confidence intervals in the individual study. The evidence was downgraded by 1 increment when there was a >20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

Table 28: Clinical evidence summary: diagnostic test accuracy for angle closure or occludable angles in the context of diagnosis and reassessment

Index Test (Threshold)	No of studies	n eyes	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
OCT						
≥2 quadrants of the angle closed	1	1,853	MODERATE[c] due to serious indirectness	0.93 (0.90, 0.95)	0.52 (0.49, 0.55)	0.72 (0.70, 0.74)
AOD500, temporal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.68 (0.45, 0.84) 0.89 (0.85, 0.92)	0.88 (0.83, 0.92) 0.75 (0.72, 0.77)	0.81 (0.75, 0.85) 0.82 (0.79, 0.84)
AOD500, nasal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.79 (0.59, 0.92) 0.85 (0.81, 0.89)	0.71 (0.65, 0.77) 0.76 (0.74, 0.79)	0.76 (0.70, 0.81) 0.81 (0.78-0.83)
ACA ≤ 20.7°	1	78	VERY LOW [a,d] due to very serious risk of bias, serious imprecision	0.87 (0.73, 0.96)	0.87 (0.72, 0.96)	-
ACD ≤ 2.50mm	1	78	VERY LOW [a,d] due to very serious risk of bias, serious imprecision	0.72 (0.55, 0.85)	0.85 (0.69, 0.94)	-

Index Test (Threshold)	No of studies	n eyes	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)
TISA500, temporal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.71 (0.51, 0.87) 0.88 (0.85, 0.92)	0.81 (0.75, 0.86) 0.59 (0.56, 0.62)	0.74 (0.68, 0.79) 0.74 (0.71-0.76)
TISA500, nasal quadrant	2	265 1,465	MODERATE [a] due to serious risk of bias	0.64 (0.44, 0.81) 0.73 (0.68, 0.78)	0.79 (0.73, 0.84) 0.75 (0.73, 0.78)	0.76 (0.70, 0.81) 0.74 (0.71-0.77)
Scheimpflug						
ACD	1	265	LOW[a,d] due to serious risk of bias, serious imprecision	0.89 (0.72, 0.98)	0.73 (0.66, 0.78)	0.88 (0.83, 0.92)
ACV	1	265	LOW[a,d] due to serious risk of bias, serious imprecision	0.89 (0.72, 0.98)	0.88 (0.83, 0.92)	0.93 (0.90, 0.96)
van Herick's						
Peripheral ACD <25% corneal thickness	2	120 78	MODERATE[d] due to serious imprecision	0.85 (0.72, 0.93) 0.79 (0.65, 0.89)	0.90 (0.80, 0.96) 0.92 (0.79, 0.97)	- -

The assessment was conducted with an emphasis on test sensitivity, as the committee identified this as the primary measure in guiding decision-making. The committee set the sensitivity threshold(s) of 95% as an acceptable level to recommend a test.

(e) Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

(f) Inconsistency was assessed by inspection of the sensitivity and specificity plots and summary area under the curve (AUC) plots. Particular attention was placed on the sensitivity threshold the committee set as an acceptable level to recommend a test (95%) and on AUC values above or below 50% (where diagnosis is based on chance alone). The evidence was:

- *downgraded by 1 increment if the individual study values varied across 2 areas, where AUC values of individual studies are above or below 50%, or above or below the acceptable threshold 95%*
- *downgraded by 2 increments if the individual study values varied across 3 areas, where AUC values of individual studies are above or below 50%, and above or below the acceptable threshold 95%*

(g) Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded if the majority of evidence was from studies in a purely case-finding context.

(h) Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, it was assessed according to the range of confidence intervals in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.

6.5.3 Economic evidence

Published literature

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix F.

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

Unit costs

Relevant unit costs are provided below to aid consideration of cost-effectiveness.

In the previous guideline, a cost analysis to estimate unit costs was conducted to compare the cost of different anterior chamber angle tests (gonioscopy, OCT, van Herick's). Elements included in the analysis were capital costs, life span and consumables, while time necessary to complete the tests and the consequences of false positives and false negatives were excluded from the analysis. Time and expertise necessary to complete the tests were not included as they were felt to be too difficult to pin down as different levels of staff will complete the tests in different clinics and settings, and the time necessary to complete will depend on who is undertaking the test and their level of experience. It was also felt that the time necessary to complete the tests were not likely to differ too much between the different tests as although OCT imaging takes much less time than a gonioscopy, it also requires interpretation of the image. As these elements were excluded from the analysis, the estimated costs below are lower than actual costs to the NHS of performing the tests (NHS reference costs).

The following assumptions were used in the cost analysis:

- the same test would be used for both diagnosis and reassessment
- reference standard tests are the most accurate within the same group
- interest rate for calculating the annual cost of machines is 3.5%
- medicine used specifically for the test was the only consumable.

The number of people referred every year to a clinic for confirmation or exclusion of COAG was estimated by averaging the estimates the committee experts provided. The same method was applied to estimate the number of follow-up visits per year. On average 3 people per day undergo tests for the diagnosis of COAG and 33 people per day are followed up, totalling 1,000 people per year for diagnosis and 12,000 people per year for reassessment in an average clinic.

We obtained cost and life-span data for gonioscopy, A-scan, B-scan and OCT from the supplier. The van Herick's test is performed by means of a slit lamp, so only its cost was accounted for. However, as most optometrists would have a slit lamp for other eye examinations, the capital cost of this equipment has been excluded in a scenario analysis. Annual costs of equipment were calculated as:

$$E = \frac{K}{\frac{1-(1+r)^{-n}}{r} + 1}$$

where E=annual cost of the machine

K=capital outlay (cost of purchasing the machine)

r=interest rate 3.5%

n=life span

Other resources considered in the cost analysis was the medicine used in order to perform the test. One unit of Oxybuprocaine was used before gonioscopy and Viscotears coupling fluid used for gonioscopy lens, whereas 1 unit of Tropicamide was used before OCT; the cost of medicine per test is reported below.

Table 29: Cost of medicine for tests

Medicine	Cost Per Pack (a)	Units	Cost Per Unit (£)
Oxybuprocaine (benoxinate)	£10.15	20	0.5
Tropicamide 0.5%	£10.75	20	0.5
Viscotears	£2.80	5	0.56

Source: BNF November 2016

Based on this, the total cost per person was calculated as:

$$TC = \frac{ac}{p} + d$$

where

TC=total cost per person

ac=annual cost of equipment

p=diagnosis and reassessment population

d=cost of medicine unit

The total cost per person and the difference in costs between strategies are reported in Table 30 below.

Table 30: Total cost and cost difference versus gonioscopy

Test	Capital outlay (K)	Life span (n)	Interest rate (r)	Annual cost	Cost per person	Difference vs reference standard
Gonioscopy – slit lamp not available (a)	200 (b) + 10,000 (c)	3 (b) / 30 (c)	3.5%	£569	£1.10	-
Gonioscopy – slit lamp available (a)	200 (b)	3 (b)	3.5%	£53	£1.06	-
OCT	28,000	7	3.5%	£3,936	£0.80	Saves £0.30
van Herick - slit lamp not available	10,000 (c)	30	3.5%	£516	£0.04	Saves £1.06
van Herick - slit lamp available	£0	-	-	£0	£0	Saves £1.06

(a) Reference standard
(b) Gonioscope
(c) Slit lamp

6.5.4 Evidence statements

Clinical

In the case-finding context none of the three tests (OCT, Scheimpflug, van Herick test) met the pre-specified specificity threshold (95%). High quality evidence from 2 studies (n=198) suggested that the van Herick test was the closest to meeting this threshold with the two studies reporting specificities of 0.90 (0.80, 0.96) and 0.92 (0.79, 0.97) with corresponding sensitivities of 0.85 (0.72, 0.93) and 0.79 (0.65, 0.86), when using peripheral anterior chamber depth of <25% corneal thickness as the cut-off.

When considering the evidence from a diagnosis and case-finding perspective, moderate to low quality evidence suggested that none of the three tests (OCT, Scheimpflug, van Herick test) performed above the 95% sensitivity threshold. Moderate quality evidence from one large study (n=1853) suggested that OCT came closest to meeting the sensitivity requirement reporting sensitivity of 0.93 (0.90, 0.95) and corresponding specificity of 0.52 (0.49, 0.55) when using >2 quadrants of the angle closed as the cut-off.

Economic

No relevant economic evaluations were identified.

6.6 Central corneal thickness measurement evidence

6.6.1 Central corneal thickness measurement

Central corneal thickness was identified as a risk factor of converting from OHT to COAG (appendix U Section 7.4). A variety of options exist for measurement of central corneal thickness. There is no universally accepted reference standard. The GDG did not consider it necessary to investigate in detail comparisons between the various machines available. The GDG decided it was important to consider assessing CCT. 2009

6.6.1.1 Clinical evidence

In appendix U section7.4, we identify central corneal thickness as a risk factor of converting from OHT to COAG.

6.6.1.2 Economic evidence

CCT measurement was taken into account in the updated health economic modelling. In section 9.1.4, we define the most cost-effective treatment strategy for patients with OCT. This is based on risk factors for conversion to COAG, which include central corneal thickness. The results report that the same treatment is cost-effective irrespective of central corneal thickness therefore its measurement is not necessary to select the most appropriate and cost-effective treatment option.

6.6.1.3 Patient views evidence

No studies were identified.

6.6.1.4 Evidence statements - Central corneal thickness measurement vs. no measurement 2009

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

Economic The most cost-effective strategy for treating OHT patients does not depend on the results of the central corneal thickness measurement. This evidence is directly applicable with potentially serious limitations.

6.7 Recommendation and link to evidence

6.7.1.1 Case finding

Recommendations	**1. Before referral for further investigation and diagnosis of COAG and related conditions, offer all of the following tests:** • **central visual field assessment using standard automated perimetry (full threshold or supra-threshold)** • **optic nerve assessment and fundus examination using stereoscopic slit-lamp biomicroscopy (with pupil dilatation if necessary), and optical coherence tomography (OCT) or optic nerve head image if available** • **intraocular pressure (IOP) measurement using Goldmann-type applanation tonometry** • **peripheral anterior chamber configuration and depth assessments using gonioscopy or, if not available or the patient prefers, the van Herick test or OCT. [2017]** **2. Do not base a decision to refer solely on IOP measurement using non-contact tonometry. [2017]** **3. Do not refer people who have previously been discharged from hospital eye services after assessment for COAG and related conditions unless clinical circumstances have changed and a new referral is needed. [2017]** **4. Refer for further investigation and diagnosis of COAG and related conditions, after considering repeat measures as in recommendation 47, if:** • **there is optic nerve head damage on stereoscopic slit lamp biomicroscopy, or** • **there is a visual field defect consistent with glaucoma, or** • **IOP confirmed as 24 mmHg or more using Goldmann-type applanation tonometry. [2017]** **5. Advise people with IOP below 24 mmHg to continue regular visits to their primary eye care professional. [2017]**
Relative values of different outcomes	Structural tests to identify glaucoma damage (damage of the optic nerve head [ONH] and macular and retinal nerve fibre layer [RNFL]) The committee was interested in the diagnostic accuracy of these tests to identify people for referral to secondary care eye services, to diagnose people and to assess progression (that is, monitor changes in glaucoma damage). The committee intended to use these tests (along with others) for case finding, for diagnosis and for reassessing progression. The committee noted that specificity was more important than sensitivity for case finding, as reducing the number of unnecessary referrals (false positives) to

	secondary eye care services would reduce patient anxiety associated with further hospital visits and further unpleasant tests being carried out. In addition, this would allow people at higher risk of conversion to COAG or progression of COAG to be seen in a timelier manner. As ONH damage is also a diagnostic marker of possible glaucoma rather than a risk factor, the committee noted that the sensitivity of the test also needed to be satisfactory at this stage of the patient pathway, as missing cases with damage to the ONH might be detrimental to the vision of the patient. The committee set a threshold for the minimum acceptability of a test in this context as 95% specificity (with a consideration of the accompanying sensitivities of any tests that met the specificity thresholds). Test to measure intraocular pressure (IOP) The committee was interested in the diagnostic accuracy of tests for measuring IOP to identify people for referral to secondary care eye services, to diagnose people with OHT, and to monitor changes in IOP in order to determine the risk of conversion to COAG or progression of diagnosed COAG and the effectiveness of treatment. The tests (along with others) are used prior to onward referral to secondary eye care services for diagnosis, as well as for reassessment in OHT, COAG suspects, and people with COAG. The committee noted that specificity was deemed more important than sensitivity prior to onward referral. The risk associated with a small proportion of people with slightly raised IOP being missed (false negatives) was outweighed by the negative impact that the incorrect referral of people with low IOP (false positives) would have on the patient, as these referrals can cause much anxiety for the patient and the tests can be unpleasant. The committee set a threshold for the acceptability of a test in this context as 95% specificity (with a consideration of the accompanying sensitivities of any tests that met the specificity thresholds). Tests to identify closed or occludable anterior chamber angle (closed angle) The committee was interested in the accuracy of tests for measuring the anterior chamber angle. In order to identify COAG, the clinician must first rule out closed or occludable angle. If the test results suggest angle closure then the management of the patient is no longer covered within the scope of this guideline The committee noted that specificity was deemed more important than sensitivity for measuring the anterior chamber angle prior to onward referral as it wished to reduce the number of unnecessary referrals (false positives) to secondary care services, which it highlighted led to a significant degree of anxiety for the patient. The committee set a threshold for the minimum acceptability of a test in this context as 95% specificity (with a consideration of the accompanying sensitivities of any tests that met the specificity thresholds). The committee noted that anterior chamber angle measurements alone, in the absence of any other significant ophthalmic abnormality or symptoms suggestive of possible angle closure, were not sufficient to refer to hospital eye services; however, information regarding the anterior chamber angle along with the other recommended tests at this point in the patient pathway is helpful to ensure appropriate referrals.
Quality of the clinical evidence	ONH & RNFL damage Evidence for OCT, HRT and combinations of both tests were identified. The evidence for all tests ranged from moderate to very low quality because the studies were at serious or very serious risk of bias, some evidence came from purely specialist glaucoma service populations so was downgraded for indirectness, and for a minority of the evidence, imprecision around the specificity result also lead to further downgrading. IOP The included studies covered mixed populations that contained both individuals attending outpatient clinics and those attending monitoring appointments for OHT

	and COAG. The committee noted that 1 of the included studies looking at the accuracy of the Icare rebound tonometer was indirect due to the study population having high myopia and a low mean age, and the specificity estimates between the two Icare papers varied widely so the evidence was further downgraded due to inconsistency. Evidence from the study exploring Pulsair non-contact tonometry was rated high quality and evidence for Reichert Tono-Pen AVIA was rated moderate having been downgraded for indirectness as it was based in a purely specialist context. Data was only available for 1 IOP threshold (21mmHg); the committee expressed concern that the data did not reflect the accuracy of the tests at other thresholds and noted that this was particularly problematic, as these tests would be used in clinical practice to measure IOP at higher thresholds. <u>Closed angle</u> Evidence for 3 tests was identified: van Herick, OCT and Scheimpflug. The evidence for the van Herick test was high quality. The evidence for OCT was high quality for one large study, and ranged from moderate to very low for many of the other parameter measures, due to contributing studies being at serious or very serious risk of bias and some uncertainty around the specificity estimates. The evidence for Scheimpflug was moderate quality due to serious risk of bias. <u>Visual field assessments</u> The diagnostic accuracy of visual field assessments was not assessed in this update. The committee considered the evidence identified in CG85 review of the diagnostic accuracy of different visual field assessments. No evidence was identified comparing other perimetric tests against the reference standard Humphrey 24-2 SITA Standard.
Trade-off between clinical benefits and harms	<u>ONH & RNFL damage</u> The committee discussed that although evidence for HRT showed moderate to high sensitivity and specificity in several of the studies, this technology was becoming less widely used. Several parameters of the SD-OCT and Spectralis SD-OCT showed specificity at or over 95% for various parameters including RNFL thickness and 3D peripapillary retinal volume scan OCA2. Only 1 parameter (1 sector of TS, TI, NS, NI with RNFL thickness abnormal at <1% level) had a corresponding high sensitivity. One study also showed a high overall discrimination according to the c-statistic for RNFL thickness. Dilation for optic disc examination can affect patients' ability to drive afterwards. The committee considered that using OCT combined with biomicroscopic slit-lamp examination may not always be practical in the clinical setting but believed that it would provide a benefit if possible (this would affect patient time in the clinic). <u>IOP</u> Evidence for 3 tests for measuring IOP were identified: Pulsair non-contact tonometry, Reichert Tono-Pen AVIA, and Icare rebound tonometry. No overall measure of discrimination (c-statistic) was reported for Pulsair non-contact tonometry or the Reichert Tono-Pen AVIA, but both tests showed poor sensitivity and high specificity at the 21mmHg threshold. Icare rebound tonometry showed moderate overall discrimination according to the c-statistic and moderate sensitivity and moderate-to-high specificity at the 21mmHg threshold. The committee noted that referrals based on inaccurate IOP measurements were currently a major issue for secondary care eye services. Furthermore, the committee noted that, in some cases, IOP measurements were used in isolation to trigger a referral. Several of the tools (Reichert Tono-Pen AVIA and Icare rebound tonometry) met the minimum acceptable threshold of 95% specificity to recommend the test prior to onward referral. While the corresponding sensitivity for Icare rebound tonometry was high, this evidence was of low quality and based on a very small sample size that the committee felt was too low to represent the population. The committee noted that the corresponding sensitivity for the Tono-pen was almost no

better than chance. This made it difficult to recommend these tests over the reference standard (Goldmann applanation tonometry or GAT); therefore, the committee agreed to recommend Goldmann-type applanation tonometry for measuring IOP before a referral could be made. The committee noted that this should be conducted alongside a visual field and optic nerve measurement to determine if the person should be referred to secondary eye services. The committee discussed that IOP measurements from Goldmann-type applanation tonometry alongside other tests were likely to decrease the number of false positive test results, reduce unnecessary anxiety to the patient and avoid the completion of further unpleasant tests.

Due to the questionable diagnostic accuracy of these tests and small sample sizes of the evidence, the committee felt it necessary to recommend that referral not be based on non-contact tonometry alone, as this may lead to a high number of people being referred based on false positive test results, again leading to unnecessary anxiety to the patient and further unpleasant procedures. While the non-contact tonometry may be used at initial testing, the referral cannot be made without a Goldmann-Type applanation tonometry measurement. The committee decided it was important to note that if a primary eye care provider does not have access to Goldmann-Type applanation tonometry, that provider would first need to refer to a primary care practitioner who did have access to this equipment before a referral to secondary eye care services could be accepted. Furthermore, it may be beneficial to repeat the IOP measurement before deciding to refer to secondary care, as IOP is associated with a high level of variation throughout the day, which can lead to spurious results if measured on a single occasion. The committee noted that people planning or commissioning eye care services should consider providing a service model that includes Goldmann applanation tonometry before referral for diagnosis to facilitate this change in practice.

Threshold for IOP

The committee felt that it was important to consider not only the test used to measure IOP but also the threshold required for referral to secondary eye care services. The previous guideline did not refer to a referral threshold but gave a diagnostic threshold of greater than 21 mmHg. The committee noted that an unintended interpretation of the previous guideline had led services to refer patients with a threshold of 21mmHg. The evidence underpinning the threshold of 21mmHg for referral is lacking and this historic threshold had contributed to a significant number of unnecessary referrals that led to patient anxiety and further tests being carried out which some patients find unpleasant. In addition to this, due to the high number of referrals, people with currently undiagnosed or diagnosed glaucoma potentially had to wait longer for an appointment thereby increasing the risk of potential progression to sight loss or visual field impairment in these people. Although this review did not find any evidence for the accuracy of diagnostic tests at thresholds other than 21mmHg, the treatment review and economic model (appendix N) give additional rationale for the decision to change the IOP threshold required for referral to 24 or above.

The committee wished to note that people with an IOP below 24 mmHg should be advised to continue visiting their primary eye care practitioner to ensure any changes in the health of the eye could be detected and dealt with appropriately.

Closed angle

The evidence for a van Herick test showed moderate sensitivity and high specificity but not high enough to meet the committee pre-determined threshold for consideration. No c-statistic values were reported. The evidence for OCT showed moderate overall discrimination according to the c-statistic for one parameter only: AOD500 in the temporal quadrant. However, this parameter did not reach the committee's pre-specified specificity threshold. Neither the sensitivity nor the specificity values met the minimum acceptable threshold to recommend a test. Gonioscopy allows comprehensive visualisation of the anterior chamber angle and

	related structures. However, it is invasive, involves anaesthetic drops and has the potential to damage the surface of the eye if used incorrectly. The importance of knowing the angle details outweighs the potential harms and risks. However, if this test is not possible or desirable to a patient, then van Herick's test or OCT if available, were considered to be an adequate alternatives. Visual field assessments The diagnostic accuracy of visual field assessments was not assessed in this update. However, the committee felt it was reasonable to pull forward the recommendation from the diagnosis setting of the original guideline and recommend using standard automated perimetry at the case-finding stage as it is standard practice. Referral of those previously discharged from hospital eye care services In circumstances where people may have been treated for OHT or COAG and there has been a patient-led decision to no longer continue treatment (for example, if they are at low risk of developing visual impairment in their lifetime) and these people have been discharged back to primary eye care services, the committee wanted to avoid a 'revolving door' situation where such people are referred straight back in to HES following their first post-discharge sight test assessment. Therefore, alongside the treatment recommendations that cover when treatment may no longer be indicated, the committee included a 'do not refer' recommendation at the case-finding stage for those who had previously been discharged from HES. The recommendation specifies not referring unless clinical circumstances have changed and referral is required. Other abnormalities such as primary angle closure may be identified using the above tests but are outside the scope of the guideline and should be managed according to usual practice. CCT The health economic analysis illustrated that it is cost effective to treat people regardless of their CCT measurement. Nevertheless, the committee felt that CCT measurements provide useful information regarding the assessment of risk of the patient and their likely prognosis. The committee has added an additional recommendation to clarify that treatment decisions should be based on risk assessment and in discussion with the patient and their preferred choice of action. This new recommendation states, 'at the time of diagnosis of OHT a risk assessment should be made acknowledging risk factors for future vision loss such as levels of IOP, CCT, family history, and life expectancy'.
Trade-off between net clinical effects and costs	The diagnostic accuracy of a test has consequences in terms of health outcomes as well as costs to the NHS. If a test produces a high number of false positives (low specificity), then resources will be wasted on overtreatment. People might be put on unnecessary treatment that could also negatively affect their quality of life. If a test produces a high number of false negatives (low sensitivity), then signs of COAG conversion or progression might be missed with the consequent quality of life detriment for the patient if they do not receive appropriate treatment in a timely manner in order to slow down progression. This could increase costs to the NHS in the end, as false negatives would likely progress faster. If their diagnoses are eventually corrected, they may require more intensive and expensive treatment. ONH & RNFL damage No economic evidence was identified for this question. The unit costs of performing OCT and HRT tests in a Hospital Eye Services (HES) setting were presented to the committee (£4.04 and £3.51 respectively) however these costs do not reflect the cost of performing these tests in a community setting where they would be likely to be used to less frequently. Although an HRT test would have a lower unit cost than an OCT test (as capital outlay for equipment is lower), the committee discussed the issue that HRT technology has become less widely used due to manufacturing and maintenance issues and is likely to be disestablished in the near future.

As the clinical evidence for SD-OCT showed high sensitivity and specificity for some parameters, the committee believed that while not being appropriate to base a referral on, the image derived from SD-OCT might add important information about structural damage of the optic nerve head. While the committee prioritised specificity in the case-finding context, the high associated sensitivities for the peripapillary nerve fibre layer measurement parameters highlight the potential for SD-OCT to identify absence of glaucoma structural damage (potential to be used as a rule out test to ensure people without structural damage can be excluded from referral). Therefore, the committee chose to recommend SD-OCT as an adjunct to the reference standard (stereoscopic slit lamp biomicroscopy) if clinics already have access to the equipment. As no evidence was identified on the cost effectiveness of the use of SD-OCT in a case-finding setting, the committee was not able to make a stronger recommendation ensuring providers invest in the equipment if not already available. As providers are not currently actively asked to invest in the equipment if not already available, there is no definitive cost impact of the recommendation. Many providers at the case-finding or referral-filtering stages of the pathway are not NHS run, and for private providers, costs of investment in equipment are not borne by the NHS.

Should regions decide to set up an enhanced case-finding stage in the pathway, the area would have to set up a funding mechanism to ensure providers are reimbursed for repeat tests, which would increase costs to the NHS. There is evidence that these types of schemes reduce the number of onward referrals (see service models review), so although they would require an investment to set up (for example, staff training costs, equipment costs and reimbursement costs), they could lead to a reduction in cost, as fewer people would reach the diagnosis stage of the pathway.

IOP

No economic evidence was identified for this question. Unit costs were presented to the committee, which estimated that the Goldmann Applanation tonometry test costs an estimated £1.41 per test if a slit lamp is not available, and £1.35 if a slit lamp is already available, compared to an estimated £0.07 for a non-contact tonometry test. Therefore, the non-contact tonometry test costs at least £1.28 less per test compared to the Goldmann Applanation tonometry test.

The specificities of the 2 of the non-contact tonometry tests reported were above the acceptable threshold of 0.95 that the committee set for tests completed at the case-finding stage of the pathway. For 1 of the tests, the specificity was also very close at 94%. The high specificities mean that assuming the tests were used correctly, the non-contact tests would not produce a significantly larger proportion of false positives compared to the Goldmann test. This, in turn, means that the use of non-contact tonometry, at case finding, would not result in significantly more people inappropriately referred on to the diagnosis stage. Of greater concern is the level of false negatives that would arise from the use of non-contact tonometry at case finding due to the low sensitivity of the non-contact tests. Although sensitivity was considered less important at case finding (as it is assumed that false negatives would be correctly diagnosed at future appointments), a significantly large proportion of people who have OHT would receive a negative result and therefore would not be referred on for a definitive diagnosis and appropriate treatment. It is difficult to quantify the effect this would have on costs to the NHS, as we do not know how long it would take false negative diagnoses to be corrected.

The committee was not confident in the diagnostic accuracy of the non-contact tests (specifically the low sensitivities), and therefore decided to recommend that referrals to HES must not be based on IOP measurements using a non-contact test alone but that anyone referred on to HES must receive a Goldmann-type applanation test, unless an expedited referral is considered necessary. This does not mean that all community optometrists must invest in Goldmann-type applanation equipment (in fact, the committee noted that a large proportion already has the equipment). However, it does require that the service model in any particular area provide the

	necessary service to ensure that Goldmann-type applanation tests are performed on people suspected of OHT or COAG, prior to referral to HES. This could be in the form of repeat measure schemes or enhanced case finding (please see the service models linking evidence to recommendations table). Currently, a large proportion of primary care practitioners use non-contact or rebound tonometry to measure IOP and refer people onward based on the results of the non-contact tests. Following the updated recommendations, in order to refer people onward for a diagnosis, these clinics will need to either invest in Goldmann applanation tonometry equipment or refer to somewhere that can perform a Goldmann test prior to onward referral. Closed angle No economic evidence was identified for this question, but estimates of the unit costs of the tests were presented to the committee to aid consideration of cost effectiveness (see unit costs section of section 1.4 of the review of the accuracy of tests for identifying closed or occludable anterior chamber angle). The van Herick and OCT tests were estimated to save £1.06 and £0.30 per test respectively compared to gonioscopy. The cost of an OCT imaging test to image the optic nerve head was estimated in Azuara-Blanco (2016)[10] using a micro-costing approach, and their estimated costs were presented to the committee for the question regarding the accuracy of structural tests for identifying and monitoring progression of glaucoma damage (damage of optic nerve head, macula and retinal nerve fibre layer). The difference in costs of OCT imaging (£4.04 compared to £0.80) is due to different methods used to estimate costs (one taken from the literature see 6.3.3 and the other costed as in 6.5.3, as well as because the imaging test is being used for different purposes; therefore, the demand differs causing the cost per person to differ as well. The committee discussed both costs for the relevant questions. The evidence for the van Herick and OCT tests showed moderate sensitivity and high specificity. However, the committee noted that as gonioscopy (the reference standard) was not always available in a pre-referral setting and that many community optometrists do not have the necessary skills and training to perform gonioscopy tests, the use of the van Herick or OCT test (if available) was recommended if gonioscopy is not available. This will not have significant cost implications as performing the van Herick test is a core competency that is widely used and available. Visual field assessments As the visual field evidence was not updated in the current guideline, the committee considered the economic evidence included in CG85. No economic evidence was identified for inclusion. As the recommendation has not changed, the committee did not anticipate any implementation costs associated with pulling through the reference standard recommendation for case finding.
Other considerations	ONH & RNFL damage The committee discussed at length which test would be most appropriate to specify as a reference standard. The consensus opinion was that biomicroscopic slit-lamp examination was the most appropriate as it was accepted as the current clinical standard. The committee also discussed that the published literature in the area was most likely going to use biomicroscopic slit-lamp examination, and the committee was not aware that there was evidence of any superiority of other imaging devices at this time. Imaging devices remain under development and represent an unstable technology, which limits their validity as a reference standard when considering a condition that may require monitoring over time periods of up to 30 years. All of the structural index tests investigated are 3D imaging devices and many of the papers presented accuracy based on different algorithms used by various software programs to analyse the images. Therefore, while there are only a few imaging devices covered by the studies included in the review, the evidence cannot be analysed together as it represents multiple different ways to analyse the image

	(some involving different levels of operator subjective judgement). The committee discussed that although some primary eye care services would have access to SD-OCT, this was not currently a widely available technology at the case-finding stage of the patient pathway. The committee discussed the high specificity associated with this device but concluded that where this equipment was available it might be of value for obtaining a baseline ONH image; for case finding, it is not appropriate to base a referral on an SD-OCT image alone. This was due to the variability in the type of OCT practitioners would have access to and the variability in the ability of eye care professionals to interpret these images. Furthermore, these machines measure a high number of parameters that may not all be associated with the same accuracy when diagnosing damage to the optic nerve head. When advanced damage to the optic nerve head is revealed at case finding, an urgent referral should be considered to reduce the risk to the patient. The committee also noted that a high false-positive rate and unnecessary referrals place increased demand on secondary eye care services, which will have a detrimental impact on the timely assessment of those true positive cases that would benefit from earlier diagnosis and management. <u>IOP</u> The committee noted that the previous misinterpretation of CG85 had led to a significant number of referrals from single non-contact IOP measurements over 21mmHg. This had placed significant demand on secondary eye care services and led to a high volume of unnecessary referrals. The GC noted that increasing the threshold for referral to 24mmHg or above would reduce the unnecessary referral of people at low risk and allow patients at higher risk of conversion to COAG or progression of COAG to be seen in a timelier manner. The committee noted that Goldmann-type applanation tonometry refers to both measurements using GAT and Perkins applanation tonometry. While GAT was the preferred test for measuring IOP prior to referral, the committee believed that for those settings where GAT was not appropriate, a referral based on Perkins would be acceptable. Situations where GAT may not be appropriate include where a physical barrier exists such as mobility issues with approaching the slit-lamp or possibly learning or co-operation difficulties. <u>Closed angle</u> The committee noted that gonioscopy was not always available in the pre-referral setting. Although SD-OCT did not meet the committee's determined threshold, the committee felt that within a pre-referral context this test would still be beneficial to rule out a closed or occludable angle and was relatively easy to interpret. The committee also noted that the van Herick test was close to the threshold and a core competency for optometrists. Therefore, the committee chose to recommend the reference standard gonioscopy, but if this was not available, then the van Herick test, or if already easily accessible, OCT imaging.

Standard practice for all assessments

The committee thought it appropriate to pull through some of the consensus supporting recommendations made in the original guideline that are relevant to the case finding and diagnosis sections that have been updated. These are detailed in the following tables.

Recommendation	**6. Ensure that all of the following are made available at each clinical episode to all healthcare professionals involved in a person's care:** • **records of all previous tests and images relevant to COAG and OHT assessment** • **records of past medical history which could affect drug choice** • **current systemic and topical medication** • **glaucoma medication record** • **drug allergies and intolerances. [2009]**
Trade off between clinical benefits and harms	The GDG considered it important to ensure the continuity of care that all information is available to healthcare professionals when assessing a patient, particularly if the patient was previously seen by a different healthcare professional.
Economic considerations	There are costs associated with the delivery of care at multiple sites.
Other considerations	None

Recommendation	**7. Use alternative methods of assessment if clinical circumstances rule out standard methods (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]**
Trade off between clinical benefits and harms	The GDG considered it important to get a diagnosis in the interest of providing the correct management plan for all individuals. If the best test is not possible or desirable for a patient then an alternative method of assessment should be offered, even if it is less accurate.
Economic considerations	None.
Other considerations	None

Recommendation	**8. Ensure that all machines and measurement instruments are calibrated regularly according to the manufacturers' instructions. [2009]**
Trade off between clinical benefits and harms	Machines need to be regularly calibrated to ensure the correct measurements are being obtained.
Economic considerations	There are costs associated with the machines calibration but an accurate measurement of clinical parameters could offset these costs.
Other considerations	None

2009

6.7.1.2 Diagnosis

Recommendations	**9. To diagnose COAG and related conditions, offer all of the following tests:**

	• **visual field assessment using standard automated perimetry (central thresholding test), repeated if necessary to establish severity at diagnosis** • **optic nerve assessment and fundus examination using stereoscopic slit-lamp biomicroscopy, with pupil dilatation** • **IOP measurement using Goldmann applanation tonometry (slit lamp mounted)** • **peripheral anterior chamber configuration and depth assessments using gonioscopy** • **central corneal thickness (CCT) measurement. [2017]** **10. Obtain an optic nerve head image at diagnosis for baseline documentation (for example, a stereoscopic optic nerve head image or OCT). [2009, amended 2017]** **11. After referral, consider an early assessment appointment when there is clinical concern based on the information provided. [2017]** **12. At the time of diagnosis of ocular hypertension (OHT), assess risk of future visual impairment, taking account of risk factors such as:** • **level of IOP** • **CCT** • **family history** • **life expectancy. [2017]**
Research recommendation	**3. What is the effectiveness and cost effectiveness of using OCT for diagnosis and reassessment in glaucoma and related conditions?**
Relative values of different outcomes	<u>Structural tests to identify glaucoma damage (damage of the optic nerve head [ONH] and macular and retinal nerve fibre layer [RNFL])</u> The committee noted that sensitivity was more important than specificity for diagnosis as missing cases (false negatives) could have a detrimental impact on the vision of the patient. The committee set a threshold for the acceptability of a test in this context at 95% sensitivity (with a consideration of the accompanying specificities of any tests that met the sensitivity thresholds). <u>Test to measure intraocular pressure (IOP)</u> The committee noted that sensitivity was deemed more important than specificity for definitively diagnosing individuals with OHT, or confirmed COAG as the risk associated with not accurately detecting a raised IOP (false negatives) is much greater in this context. People with raised IOP have a higher risk of conversion to COAG and progression of COAG to visual field loss. Detection ensures that an optimal management plan can be initiated. The committee set a threshold for the acceptability of a test in this context as 95% sensitivity (with a consideration of the accompanying specificities of any tests that met the sensitivity thresholds). <u>Tests to identify closed or occludable anterior chamber angle (closed angle)</u> The committee noted that sensitivity was deemed more important than specificity for diagnosing COAG, as at the secondary care stage, it is important to minimise missed cases (reduce false negatives) and prioritise capturing those with angle-closure glaucoma and primary angle closure so that they may then be placed on the correct treatment pathway (outside the scope of the current guidance). The committee set a threshold for the acceptability of a test in this context as 95%

	sensitivity (with a consideration of the accompanying specificities of any tests that met the sensitivity thresholds).
Quality of the clinical evidence	ONH & RNFL damage Evidence for OCT, HRT and combinations of both tests were identified. The evidence for all tests ranged from high to low quality. Studies were at serious or very serious risk of bias. Evidence for some SD-OCT parameters was downgraded for indirectness as the source papers were based in a purely case-finding setting. Imprecision around the sensitivity estimates also caused further downgrading for some of the SD-OCT parameters. IOP Four studies were included in the review. The quality of the evidence ranged from high to low. Two of the studies relating to the Icare rebound tonometer were downgraded for inconsistency due to heterogeneity in the data. Overall, the included studies had mixed populations that contained both individuals attending outpatient clinics and those attending monitoring appointments for OHT and COAG. The committee noted that 1 of the included studies looking at the accuracy of the Icare rebound tonometer was indirect due to the study population having high myopia and a low mean age. Evidence from studies for Pulsair non-contact tonometry and the Reichert Tono-Pen AVIA were rated as low quality due to imprecision around the sensitivity estimates. Data was only available for 1 IOP threshold (21mmHg); the committee expressed concern that the data did not reflect the accuracy of the tests at other thresholds and noted that this was particularly problematic, as these tests would be used in clinical practice to measure IOP at higher thresholds. Closed angle Evidence for 3 tests was identified: van Herick, OCT and Scheimpflug. The evidence for the van Herick test was moderate quality due to imprecision around the sensitivity estimate. The evidence for OCT was of moderate to very low quality, due to contributing studies being at serious or very serious risk of bias, imprecision around some the of sensitivity estimates and 1 large study being based in a purely case-finding, indirect population. The evidence for Scheimpflug was low quality due to serious risk of bias and imprecision around the sensitivity estimates. Visual field assessments The diagnostic accuracy of visual field assessments was not assessed in this update. The committee considered the recommendation made in CG85 based on the review of the diagnostic accuracy of different visual field assessments. No evidence was identified comparing other perimetric tests against the reference standard Humphrey 24-2 SITA Standard. Central Corneal Thickness (CCT) measurement CCT measurement was taken into account in the updated health economic modelling (see section 9.1.4) which found that the same treatment is cost-effective irrespective of central corneal thickness. Therefore, the committee chose not to prioritise a review on the most effective test to measure CCT and instead pulled through the recommendation from the previous guideline. No clinical evidence was identified in the previous guideline and the committee agreed to include the broad recommendation to measure CCT (with no instruction on the preferred measurement method) due to the impact the CCT can have on IOP measurement, and therefore is of value in interpreting IOP measurements.
Trade-off between clinical benefits and harms	ONH & RNFL damage The committee discussed that although evidence for HRT showed moderate to high sensitivity and specificity in several of the studies, this technology was becoming less widely used.

Several parameters of the SD-OCT and Spectralis SD-OCT showed high sensitivity at various thresholds including RNFL thickness and 3D peripapillary retinal volume scan OCA1 and OCA3. Only 1 parameter (1 sector of TS, TI, NS, NI with RNFL thickness abnormal at <1% level) had a corresponding high specificity.

The committee therefore recommended optic nerve assessment using stereoscopic slit lamp biomicroscopy, with pupil dilation and fundus examination. Dilation for optic disc examination can affect a patients' ability to drive afterwards.

Baseline optic nerve head image

CG85 featured a supporting consensus recommendation on obtaining an optic nerve head image at diagnosis for baseline documentation. The committee considered that it is important to have a baseline image of the optic disc from which to determine if there has been a change in its appearance. Without this image, the clinician may not be able to make an accurate assessment of progression of optic nerve damage over time. The current guideline update committee agreed with this consensus and added the clarification that this image may be acquired by a stereoscopic optic nerve head picture (leaving it open to either biomicroscopy slit lamp examination or stereo photography) or OCT, whichever is more readily available at the time of diagnosis.

IOP

Evidence for 3 tests for measuring IOP were identified: Pulsair non-contact tonometry, Reichert Tono-Pen AVIA, and Icare rebound tonometry. None of the tests meet the pre-specified sensitivity threshold for consideration.

The committee noted that tests for IOP would not be used in isolation to diagnose COAG. The committee agreed that GAT would still be recommended, as there was not sufficient evidence to alter previous recommendations made in CG85.

Closed angle

The evidence for a van Herick test showed high specificity but not high enough to meet the committee determined threshold for consideration. No c-statistic values were reported. The evidence for OCT showed moderate overall discrimination according to the c-statistic for one parameter only: AOD500 in the temporal quadrant. However, this parameter did not meet the committee's defined threshold. The evidence for Scheimpflug, ACD parameter, showed moderate discrimination according to the c-statistic, But neither the sensitivity nor the specificity values met the minimum acceptable threshold to recommend a test; therefore, gonioscopy was recommended.

Gonioscopy allows comprehensive visualisation of the anterior chamber angle and related structures. However, it is invasive, involves anaesthetic drops and has the potential to damage the surface of the eye if used incorrectly. The importance of knowing the angle details outweighs the potential harms and risks. No technique was considered a suitable alternative to gonioscopy in describing the status of the drainage angle. For exclusion of angle closure and accurate diagnosis, the reference standard was therefore required.

Visual field assessments

The diagnostic accuracy of visual field assessments was not reviewed in this update. There was no clinical evidence identified that compared other perimetric tests with the reference standard of Humphrey 24-2 SITA Standard. This committee agreed that the updated reference standard of standard automated perimetry should be recommended as it was in the previous consensus recommendation in CG85.

CCT

While the previous guideline recommended different treatments based on CCT measurement (beta-blockers for people with an untreated IOP of >25 to 32mmHg and a CCT of 555-590 micrometres until the age of 60; PGA for people with a CCT of less than 555 micrometres until the age of 65 for people with an untreated IOP of >21 to 25mmHg and until the age of 80 years for an untreated IOP of >25 to 32mmHg), the updated health economic model showed that the same treatment

	(generic PGA) is cost-effective for all levels of CCT. The committee agreed that it is no longer meaningful to base treatment decisions on CCT and therefore did not prioritise exploring the diagnostic accuracy of tests to measure CCT. However, the committee agreed it would still be useful to retain the CCT recommendation from CG85, that a CCT measurement be completed. The current guideline committee agreed with the consensus of the CG85 committee that CCT can act as a confounder of IOP measurement and is therefore of value in interpreting IOP (in terms of what a clinically acceptable IOP is once treatment is underway). They also believed that it offers important information that will affect a clinician's choice on when to reassess, as it is a factor to consider (alongside others such as age, family history and visual fields) when assessing risk of progression to sight loss. CCT can be measured by contact or non-contact methods. Contact methods may be quicker and more accurate but require corneal anaesthesia and are associated with potential corneal injury or transmission of infection. <u>Priority assessment</u> The committee noted that in some instances clinicians within the hospital eye services may receive urgent referrals (for example, for those with highly elevated IOP ≥32mmHg at case finding) and that in these cases it would be important to prioritise assessment of these individuals to reduce the risk to the patient. However it may be the case that not all urgent referrals are automatically prioritised as the HES clinicians may re-evaluate the urgency based on the information provided with the referral. Therefore the committee felt it was important to provide room for clinician expert judgement and suggested a consider recommendation.
Trade-off between net clinical effects and costs	The diagnostic accuracy of a test has consequences in terms of health outcomes as well as costs to the NHS. If a test produces a high number of false positives (low specificity), then resources will be wasted on overtreatment. People might be put on unnecessary treatment, which could also negatively affect their quality of life. If a test produces a high number of false negatives (low sensitivity), then signs of COAG conversion or progression might be missed with the consequent quality of life detriment for the patient if they do not receive appropriate treatment in a timely manner in order to slow down progression. This could increase costs to the NHS in the end, as false negatives would be likely to progress faster. If their diagnoses are eventually corrected, they may require more intensive and expensive treatment. <u>ONH & RNFL damage</u> No economic evidence was identified for this test. The unit costs of performing OCT and HRT tests in a Hospital Eye Services (HES) setting were presented to the committee (£4.04 and £3.51 respectively). Although an HRT test has a lower unit cost than an OCT test, the committee discussed the issue that HRT technology was becoming less widely used due to manufacturing and maintenance issues and was likely to be disestablished in the near future. The recommendations have not changed regarding the use of the reference standard test for examination of the optic nerve head at diagnosis and at each reassessment visit; therefore, there are no changes in cost to the NHS. That said, the threshold for referral for IOP is now specified as 24mmHg; therefore, fewer people should reach the diagnosis stage of the pathway, and in turn, fewer people should need to be seen by HES. This means fewer optic nerve head examination tests will be required. The committee recommended obtaining an image of the optic nerve head at diagnosis if necessary equipment is available. The committee agreed that obtaining a baseline image is useful for future assessments. As no capital costs would be required, the only affect this would have on costs would be if the increased number of images undertaken led to increased staff required. <u>IOP</u> No economic evidence was identified for this test. Unit costs were presented to the committee estimated that the Goldmann Applanation tonometry test costs an

	estimated £1.41 per test if a slit lamp is not available, and £1.35 if a slit lamp is already available, compared to an estimated £0.07 for a non-contact tonometry test. Therefore, the non-contact tonometry test costs at least £1.28 less per test compared to the Goldmann Applanation tonometry test. All settings where diagnoses of OHT or COAG can be made will already have access to Goldmann applanation tonometry, as an IOP test using GAT is currently required to make a diagnosis. This means there would be no impact to costs at the diagnosis stage of the pathway. That said, the threshold for referral for IOP is now specified as 24mmHg; therefore, fewer people should reach the diagnosis stage of the pathway, and in turn, fewer people should be treated and reassessed. This means fewer IOP tests will be required in these settings. Closed angle No economic evidence was identified for this test but estimates of the unit costs of the tests were presented to the committee to aid consideration of cost effectiveness (see unit costs section of section 1.4 of the review of the accuracy of tests for identifying closed or occludable anterior chamber angle). The van Herick and OCT test was estimated to save £1.06 and £0.30 per test respectively. The recommendations are not being changed regarding the anterior chamber tests completed at diagnosis or reassessment; therefore, there are no changes in costs to the NHS at these stages. That said, the threshold for referral of increased IOP is now specified as 24mmHg; thus, fewer people will reach the diagnosis stage of the pathway. In turn, fewer people will be monitored. This means fewer anterior chamber tests will be required.
Other considerations	ONH & RNFL damage The committee discussed at length which test would be most appropriate to specify as a reference standard. The consensus opinion was that biomicroscopic slit-lamp examination was the most appropriate, as it was accepted as the current clinical standard. The committee also discussed that the published literature in the area was most likely going to use biomicroscopic slit-lamp examination, and the committee was not aware that there was evidence of any superiority of other imaging devices at this time. Imaging devices remain under development and represent an unstable technology, which limits their validity as a reference standard when considering a condition that may require monitoring over time periods of up to 30 years. All of the structural index tests investigated is 3D imaging devices and many of the papers present accuracy based on different algorithms used by various software programmes to analyse the images. Therefore, while there are only a few imaging devices covered by the studies included in the review, the evidence cannot be analysed together as it represents multiple different ways to analyse the image (some involving different levels of operator subjective judgement). The committee noted that although a number of secondary eye care services have access to SD-OCT, this equipment is not always available to clinicians at diagnosis. Therefore, even though there was evidence showing a high sensitivity of SD-OCT, the implementation cost associated with acquiring this technology made it impractical to recommend. In addition to this, the level of skill and expertise associated with assessing the ONH images varies from clinician to clinician. Therefore, the committee discussed the recommendations made in the previous guideline (CG85) and agreed that the majority of these recommendations were still applicable. The committee noted that if a hospital already has access to SD-OCT that considering its use for imaging the ONH for aiding glaucoma diagnosis may be beneficial. This equipment may be used by different areas within secondary eye care such as medical retina (macular) services. Where capacity is available, these machines could also be used by glaucoma services within these settings. Update to diagnosis recs since CG85 The diagnosis recommendations from CG85 did not go through any substantial

	changes based on the new evidence identified in the update. All the tests recommended for diagnosis remain the same. The only minor change is the clarification that the baseline image of the optic nerve head may be obtained by stereoscopic slit lamp, stereo photography or OCT, allowing clinics room to work within their current resources. Therefore, the updated diagnosis recommendations are unlikely to present any implementation difficulties. Research recommendation 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 than when visual field testing is used alone. 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 for the diagnosis and reassessment of glaucoma and related conditions.

The committee thought it appropriate to retain some of the consensus supporting recommendations made in the original guideline that are relevant to diagnosis. These are detailed in the following tables.

Recommendation	**13. Adopt professional[15]/ Department of Health[16] guidance to reduce the risk of transmitting infective agents via contact tonometry or gonioscopy. [2009]**
Trade off between clinical benefits and harms	There is a potential trade off between getting an accurate measurement of intraocular pressure and the risk of infection from contact tonometry.
Economic considerations	Not addressed.
Other considerations	The GDG decided not to duplicate work carried out by the Department of Health and other professional bodies therefore we refer to any guidance they provide[13,53,110,111]
Recommendation	**14. Use the van Herick peripheral anterior chamber depth assessment if clinical circumstances rule out gonioscopy (for example, when people with physical or learning disabilities are unable to participate in the examination). [2009]**
Relative values of different outcomes	As indicated above, the GDG considered precision of the test to be the most important issue. Although van Herick's test is not as accurate as gonioscopy, the GDG considered it an adequate alternative for use where gonioscopy was not possible.

2009

[15] Royal College of Ophthalmologists (https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2010_PROF_100_-CJD-Guidance-for-Ophthalmologists-joint-statement.pdf).

[16] See https://www.gov.uk/government/publications/guidance-from-the-acdp-tse-risk-management-subgroup-formerly-tse-working-group

Trade off between clinical benefits and harms	The GDG considered it important to get a diagnosis in the interest of providing the correct management plan for all individuals. If the best test is not possible for or desirable to a patient then van Herick's test is a suitable alternative.
Economic considerations	Other non-gonioscopic methods are more expensive than van Herick's test without adding any useful information.
Quality of evidence	Low quality clinical evidence in an indirect population. The economic evidence has partial applicability because not direct to a population with physical or learning disabilities. It has serious limitations as it is not a full economic evaluation and the summary of effectiveness was based on expert opinion.
Other considerations	None

2009

6.7.1.3 Reassessment

Recommendations	**15. At each assessment, offer the following tests to people with COAG, people suspected of having COAG and people with OHT:** • **Goldmann applanation tonometry (slit lamp mounted)** • **anterior segment slit lamp examination with van Herick peripheral anterior chamber depth assessment when clinically indicated. [2017]** **16. When clinically indicated, repeat gonioscopy, for example, where a previous examination has been inconclusive or where there is suspicion of a change in clinical status of the anterior chamber angle. [2017]** **17. 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 Table 35 and Table 39 for recommended reassessment intervals). [2009, amended 2017]** **18. 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 Table 34 and Table 35 for recommended reassessment interval). [2009, amended 2017]** **19. When a visual field defect has previously been detected, use the same measurement strategy for each visual field assessment. [2009]** **20. When clinically indicated, repeat assessment of the optic nerve head (for example, stereoscopic slit lamp biomicroscopy or imaging). [2017]**
Relative values of different outcomes	<u>Tests to identify closed or occludable anterior chamber angle (closed angle)</u> The committee was interested in the accuracy of tests for measuring the anterior chamber angle. The committee intended to use the tests for identifying people with closed, occludable or open angles (as part of case finding) for diagnosis of people with closed-angle glaucoma as opposed to COAG and for reassessing any changes in

	the angle over time. The committee noted that sensitivity was deemed more important than specificity for reassessing COAG progression, as at the secondary care stage, it is important to minimise missed cases (reduce false negatives) and prioritise capturing those with newly developed COAG or progressive COAG so that they may then be placed on the correct treatment pathway. The committee set a threshold for the acceptability of a test in this context as 95% sensitivity (with a consideration of the accompanying specificities of any tests that met the sensitivity thresholds). Structural tests to identify glaucoma damage (damage of the optic nerve head [ONH] and macular and retinal nerve fibre layer [RNFL]) The committee was interested in the diagnostic accuracy of structural tests for measuring glaucoma damage (damage to the optic nerve head or retinal nerve fibre layer) to identify people for referral to secondary care eye services, to diagnose people and assess progression, and for reassessing any changes in glaucoma damage. The committee intended to use the tests for diagnosis as part of a cohort of other diagnostic tests and for reassessing progression. The committee noted that sensitivity was more important than specificity for diagnosis and reassessment, as missing progression of COAG damage (false negatives) could have a detrimental impact on the vision of the patient. The committee set a threshold for the acceptability of a test in this context as 95% sensitivity (with a consideration of the accompanying specificities of any tests that met the sensitivity thresholds). Test to measure intraocular pressure (IOP) The committee was interested in the diagnostic accuracy of tests for measuring IOP to identify people for referral to secondary care eye services, to diagnose people with OHT, and to monitor changes in IOP in order to determine the risk of conversion to COAG or progression of diagnosed COAG and the effectiveness of treatment. The committee intended to use the tests prior to onward referral to secondary eye care services, for diagnosis as part of a cohort of other diagnostic tests, as well as for reassessment in OHT, COAG suspects, and people with COAG. The committee noted that sensitivity was deemed more important than specificity for reassessing individuals with OHT, COAG suspects and confirmed COAG, as the risk associated with not accurately detecting a raised IOP (false negatives) is much greater in this context. The committee also noted the importance of obtaining an accurate IOP at reassessment intervals to ensure that treatment could be adjusted accordingly and to minimise the risk of conversion to COAG or progression of COAG. The committee set a threshold for the acceptability of a test in this context as 95% sensitivity.
Quality of the clinical evidence	Closed angle, ONH & RNFL damage and IOP None of the evidence focused on the diagnostic accuracy of tests for anterior chamber angle, optic nerve head, or intraocular pressure in the specific context of reassessing progression in those already diagnosed with OHT, suspected COAG or COAG. As the relative value of the diagnostic accuracy outcomes (sensitivity and specificity) for the tests at the reassessment stage were prioritised by the committee in the same way as for the diagnosis context, please refer to the section linking evidence to recommendations for diagnosis with respect for the quality of evidence found. Visual field assessments Tests to ensure the accurate location and quantification of any visual field defects in reassessment for conversion to COAG and progression of established glaucoma was not assessed in this update. The committee considered the evidence identified in

	CG85 review of the accuracy of different visual field tests to use during reassessment. No evidence was identified comparing other perimetric tests against the reference standard Humphrey 24-2 SITA Standard.
Trade-off between clinical benefits and harms	<u>Closed angle</u> The committee discussed the recommendations made in the previous guideline (CG85). The committee agreed that the previous recommendations were still applicable. For the purposes of reassessment, the van Herick test was the most appropriate, as it is more accessible and may cause less distress to the patient. Although the van Herick test is not as accurate as gonioscopy, the committee considered it an adequate alternative for use where gonioscopy has previously been undertaken to establish configuration and condition of the anterior chamber angle. In the absence of uncertainty or suspicion of a change, the van Herick test is sufficient as a rapid check of the anterior chamber angle in the context of reassessment. As the reference standard, gonioscopy offers comprehensive visualisation of the anterior chamber angle and related structures in a way that is not possible with other tests. However, it is invasive, involves anaesthetic drops and has the potential to irritate the surface of the eye if used incorrectly. Therefore, the committee agreed to pull forward the CG85 recommendation that gonioscopy should be repeated during reassessment only when deemed clinically necessary (such as when there is uncertainty or a suspicion of change) as it will provide the clearest information on the state of the chamber angle. <u>ONH & RNFL damage</u> The committee decided that although the previous guideline suggested imaging of the optic nerve head at every reassessment visit, this might not always be necessary or clinically indicated. Therefore, the committee decided to recommend examining the optic nerve head only when clinically indicated at reassessment visits. The committee decided to pull forward 2 of the supporting recommendations from CG85 on optic nerve head imaging. The committee agreed that when a change in optic nerve head status is detected, obtaining a new baseline image facilitates future detection of further changes that may arise and is therefore essential for identification of ongoing optic disc damage. The committee also agreed that when an adequate view of the optic nerve head and surrounding area is unavailable during reassessment, people should have their pupils dilated before the assessment. Small pupil size may exclude a stereoscopic view of the optic disc thereby preventing adequate assessment. People should be alerted to possible consequences of having their pupils dilated as it may affect their ability to drive afterwards. However, obtaining an accurate view outweighs the minor inconvenience. <u>IOP</u> The committee decided to carry over the recommendations made in CG85 for measuring IOP at reassessments. Since important treatment decisions are based on IOP measurements, it is imperative to obtain a reliable IOP reading. The available evidence at case finding and diagnosis suggest that non-contact tonometry does not provide an accurate measure for IOP. The committee decided that there was not sufficient evidence to recommend any tool over the reference standard of Goldmann applanation tonometry. <u>Visual field assessments</u> The diagnostic accuracy of visual field assessments in the context of reassessment was considered outside the scope of the current guideline update. Therefore, the committee pulled forward the visual field recommendations from the monitoring

	section of the original guideline, which matched the recommendations for visual field testing at diagnosis. To be able to compare test results in order to detect a change in visual field, it is necessary to use the same field-testing strategy at reassessment visits as at diagnosis. The committee agreed that for those with COAG standard automated perimetry with central thresholding test should be offered, and for those with OHT or suspected standard automated perimetry with either central thresholding or supra-threshold could be offered, when deemed clinically necessary during reassessment visits. The committee also agreed to pull forward the recommendation that when a defect has been previously detected, the same visual field measurement strategy should be used each time visual field testing is undertaken. Using the same strategy minimises the inter-test variability, which is important to optimise detection of progression.
Trade-off between net clinical effects and costs	No economic evidence was identified with respect to tests for anterior chamber angle, optic nerve head, or intraocular pressure in the context of reassessing progression or reassessment in those already diagnosed with OHT, suspected COAG or COAG. No economic evidence was identified in the original guideline with respect to visual field assessments in the context of reassessment. The trade-off between net clinical effects and costs detailed in the discussion of the diagnosis recommendations are equally as relevant at the reassessment stage.
Other considerations	No new evidence was identified for inclusion in the update on tests appropriate for use for reassessment of IOP, optic nerve head or anterior chamber angle. Therefore, the majority of the recommendations remained unchanged from CG85. The only edits that the guideline update committee made related to what used to be a single recommendation about visual field examinations, which the new committee split into 2 recommendations to improve clarity. Where the previous recommendation advised to offer VF testing for people with COAG, the update committee amended this to 'when clinically indicated'. Where the previous recommendation relating to people with OHT and suspected COAG stated monitoring with supra-threshold perimetry, the update committee amended to this to 'when clinically indicated' and broadened tests to include either supra-threshold or central thresholding tests. The committee wished to make it clearer that there was room for clinician discretion as to when visual field testing would need to be repeated in a reassessment session. The committee also wished to clarify that for those with OHT and COAG suspect, either the supra-threshold test or the superior central thresholding test would be acceptable depending on clinical context and availability. None of these small amendments to the previous recommendations will affect resources or add additional implementation costs.

The committee thought it appropriate to retain some of the consensus supporting recommendations made in the original guideline that are relevant to reassessment. These are detailed in the following tables.

Recommendation	**21. When a change in optic nerve head status is detected by stereoscopic slit lamp biomicroscopy, obtain a new optic nerve head image for the person's records to provide a fresh benchmark for future assessments. [2009]**
Trade off between clinical benefits and harms	Having a fresh baseline image following a change in optic disc appearance facilitates future detection of further changes that may arise. Detection of such changes is essential in terms identification of ongoing optic disc damage. Pupil dilatation is needed for stereoscopic disc photography.
Economic considerations	Adding stereo photography to biomicroscopy slit lamp examination increases costs, therefore is should be done only after a detection of change in optic disc status. The economic evidence has serious limitations, as it was not a full economic evaluation. It is partially applicable as stereo photography is not commonly available in current practice.
Other considerations	Patient views: Patients should be alerted to possible consequences of having their pupils dilated. Dilatation for optic disc photography is required, which may affect a patient's ability to drive afterwards. Obtaining accurate information outweighs the minor inconvenience caused by pupil dilatation.

2009

Recommendation	**22. When an adequate view of the optic nerve head and surrounding area is unavailable at reassessment, people should have their pupils dilated before stereoscopic slit lamp biomicroscopy or optic nerve head imaging is repeated. [2009]**
Trade off between clinical benefits and harms	Small pupil size may exclude a stereoscopic view of the optic disc thereby preventing adequate assessment. Pupil dilatation in the presence of open angles carries low risk provided there are no specific contraindications to dilatation (e.g. iris-supported implants).
Economic considerations	Dilatation increases the cost of the assessment in terms of the cost of drops and clinician's time taken.
Other considerations	Patient views: Patients should be alerted to possible consequences of having their pupils dilated. Dilatation for optic disc examination may affect a patient's ability to drive afterwards. Obtaining accurate information outweighs the minor inconvenience caused by pupil dilatation.

7 Reassessment intervals

7.1 Optimum intervals for ocular hypertension, suspected chronic open-angle glaucoma or both

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

For full details, see review protocol in appendix C.

Table 31: PICO characteristics of review question

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
Comparison	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

7.1.2 Clinical evidence

No relevant clinical studies comparing monitoring intervals for people with OHT, suspected COAG or both were identified in this update. Similarly, no studies were identified for inclusion in the original guideline. See also the study selection flow chart in appendix E and excluded studies list in appendix L.

7.1.3 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review.[20] The study is summarised in the health economic evidence profile below (Table 32) and the health economic evidence table in appendix I.

See also the health economic study selection flow chart in appendix F.

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

7.1.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

One cost-utility analysis found that monitoring according to the most intensive frequencies recommended in the NICE guideline CG85 was not cost-effective (ICER: £2,220,000 per QALY gained) compared to monitoring according to the most conservative frequencies recommended in the NICE guideline CG85. This analysis was assessed as partially applicable with very serious limitations.

Table 32: Health economic evidence profile: NICE guidelines (conservative) versus NICE guidelines (intensive)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Burr 2012[20]] (UK)	Partially applicable [(a)]	Potentially serious limitations[(b)]	Discrete event simulation model with 20-year time horizon. Five interventions (surveillance pathways) were compared in the model but only the comparison of 2 of the interventions is relevant to this review question. Please see appendix I for details on the interventions that were being compared.	£1,776	0.0008 QALYs	£2,220,000 per QALY gained (pa)	Results of the sensitivity analysis conducted were not specifically relevant to the 2 strategies applicable to this review. See appendix I for details of the sensitivity analysis conducted.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; pa: per annum

(a) Only 2 of the interventions provide an appropriate comparison for this review question. The other interventions were too broad spanning treatment decisions and risk stratifications as well as monitoring intervals.

(b) 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 2 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 judge whether they believe someone is at a high risk of conversion to CAOG. 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.

Unit costs

The unit cost of monitoring visits to HES and monitoring visits conducted in the community were presented to the committee to aid consideration of cost effectiveness.

Table 33: UK costs of monitoring visits

Monitoring visit	Cost
Monitoring visit to hospital eye care services	£89
Monitoring visit to community optometrist	£51.20[(a)]

Source: NHS reference costs (2015-16)

(a) The cost of a community visit was assumed to be 80% of the 2016-17 Tariff for an ophthalmology follow-up visit by a single professional.

7.1.5 Recommendations and link to evidence

Recommendations

23. At each assessment, re-evaluate risk of conversion to COAG and risk of sight loss to set time to next assessment. [2017]

24. At each assessment, ask about general health and, if appropriate, factors affecting adherence to treatment, including cognitive impairment and any treatment side effects. [2017]

25. Discharge people back to primary eye care services if:

- **they were referred for OHT but do not need treatment**
- **they were referred for suspected COAG but this is no longer suspected.**

Advise people that they should continue with regular visits to their primary eye care professional, at clinically appropriate intervals.[2017]

Treated OHT (starting IOP≥24mmHg) with normal discs and visual fields

26. For people with treated OHT (baseline IOP of 24 mmHg or more) and a normal optic head and visual field at the most recent assessment:

- **use clinical judgement to assess control of IOP and risk of conversion to COAG, and**
- **reassess according to Table 34. [2017]**

Table 34: Time to next assessment for people being treated for OHT

Conversion from OHT to COAG	Control of IOP	Time to next assessment[1]
Not detected or uncertain conversion[2]	No	Review management plan and reassess between 1 and 4 months
Uncertain conversion[2]	Yes	Reassess between 6 and 12 months
No conversion detected	Yes	Reassess between 18 and 24 months
Conversion	No or yes	See recommendations on the diagnosis

		and reassessment of COAG (recommendations 9–22)

[1] Use clinical judgement to decide when the next appointment should take place within the recommended interval.
[2]Uncertain conversion includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).

Suspected COAG

27. For people with suspected COAG:

- **use clinical judgement to assess control of IOP and risk of conversion to COAG (optic nerve head damage and visual field defect), and**
- **reassess according to Table 35. [2017]**

Table 35: Time to next assessment for people with suspected COAG

Conversion to COAG	Control of IOP	Time to next assessment[1]
Not detected or uncertain conversion[2]	No	Review management plan and reassess between 1 and 4 months
Uncertain conversion[2]	Yes	Reassess between 6 and 12 months
No conversion detected	Yes	Reassess between 12 and 18 months
Conversion	No or yes	See recommendations on the diagnosis and reassessment of COAG (recommendations 9–22)

[1]Use clinical judgement to decide when the next appointment should take place within the recommended interval.
[2]Uncertain conversion includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).

Relative values of different outcomes	The committee agreed that the change from normal visual field to visual field defect, extent of glaucomatous visual field loss, development of glaucoma and health-related quality of life were critical outcomes. Optic nerve head damage, IOP level, and patient and carer satisfaction were agreed as important outcomes.
Quality of the clinical evidence	No evidence was identified.
Trade-off between benefits and harms	No evidence was identified. The committee identified potential benefits and harms of reassessment at different intervals based on its expertise and experience. A benefit of regular reassessment is the ability to identify any alteration in clinical diagnosis of people at risk of conversion from OHT or suspected glaucoma to glaucoma. This, in turn, may help to reduce the progression of glaucomatous damage to the eye as well as potential loss of vision. Regular reassessment for people having treatment for OHT also enables the maintenance of IOP control through effective treatment, which may also reduce the risk of conversion to COAG. A further benefit is that tolerance to treatment and adverse side effects can be monitored to ensure that optimal treatment is delivered and to maximise treatment adherence. The potential harms of regular reassessment include the personal inconvenience of

having to attend appointments and the clinical demand this places on secondary eye care services. The committee noted that the reassessment frequency for people with OHT or suspected COAG depends on their risk of conversion to COAG. A person's level of risk depends on the following factors: age, IOP, CDR and VF, appearance and size of optic nerve head, family history of glaucoma, family origin, and socioeconomic status. The committee agreed that the level of risk of conversion to COAG should be based on clinical judgement taking into consideration the aforementioned factors.

The committee agreed that the table in CG85 for deciding the reassessment intervals for people with OHT or suspected COAG was difficult to interpret and replacing this with a separate table for each condition would be clearer. Regarding IOP, the committee felt that there was a lack of evidence underpinning what constitutes a target IOP and that this would vary case-by-case. Furthermore, suggesting a 'target' IOP could lead to inappropriate treatment including surgery in some cases, which could cause unnecessary distress to the patient and an inappropriate use of resources. The committee agreed that a better term was 'clinically acceptable control of IOP', as a clinically acceptable IOP would vary between patients based on a number of factors.

In addition to this, the committee decided that the tests ordered at each reassessment should be at the discretion of the ophthalmologist to ensure the appropriate tests were conducted and to reduce the number of unnecessary tests.

The committee was concerned that all people within a category should not simply cycle through reassessment visits of the same intervals repeatedly. The committee stressed the importance of every monitoring visit being a 'reassessment' of a person's risk and the time that a person is next seen should reflect their perceived probability of conversion or progression, for which a number of factors should be taken into account. The committee felt that changing the language from 'monitoring' to 'reassessment' visits was appropriate. The committee stressed the importance in needing to reassess people who are not responding to treatment frequently and not needing to reassess people frequently who are responding to treatment and not considered at risk of conversion. Any time a person's status is reassessed, the diagnosing clinician should refer back to the table to determine which category the person is in and when would be appropriate to see them (within the recommended range).

The committee agreed that people with OHT who do not require treatment should be discharged to primary eye care services as the benefit of reassessing these patients in secondary care is limited and the perceived risk of loss of vision is low. When people with OHT who do not require treatment are discharged, the ocular status should be conveyed to both the referring optometrist (or an optometrist named by the person) and the patient to avoid unnecessary re-referral to ophthalmology services. Those who are discharged should be advised to visit their primary care optometrist annually so that any future changes in their condition are detected. To facilitate this, current IOP readings by GAT, re-referral IOP thresholds, a proposed review date and any other appropriate information should be communicated to a named optometrist or practice and copied to both the GP and patient. This will normally be to the optometry practice that initially referred the person, but the person might decide to change practices. In accordance with this, the committee noted the importance of having regular eye tests in primary care and agreed that this should be highlighted to people with OHT who are discharged so that any alterations in risk can be dealt with appropriately by the primary care optometrist.

Treated OHT (≥24mmHg) with normal discs and visual fields

The committee considered the previous categories of high and low risk of conversion in CG85 to be difficult to interpret and often to lead to unnecessary testing. Therefore, classification by conversion, conversion not detected, and uncertain conversion was adopted. The committee decided that patients with

	uncontrolled IOP who had no conversion or undetected conversion should have their treatment plan re-assessed at 1-4 months to ensure an optimal IOP is obtained and appropriate treatment is decided. Where IOP is clinically acceptable and controlled, the committee decided to recommend reassessment at 6-12 months where there is uncertain conversion and 18-24 months where conversion is undetected. The committee noted that the reassessment interval for people with uncertain conversion was longer than in CG85; this was partially due to published economic evidence suggesting that a more conservative reassessment interval is cost effective compared to reassessing people intensively. However, the committee expressed some concerns with the study (see the following section of this table for further details). Another reason the committee decided to lengthen the interval for this group was because of results of a sensitivity analysis of the OHT treatment model (see appendix N) where lengthening the reassessment intervals for people treated for ocular hypertension did not change the cost effectiveness of treatment. Please see Table 39 for reassessment of patients with COAG. The committee decided that people with OHT who are recommended to receive treatment but the treatment is not effective or tolerated should be monitored according to the COAG suspects table. The committee also noted the importance of treatment adherence and discussing any issues people have that may be affecting their ability or willingness to adhere to medications. The committee noted that health professionals should explore reasons for poor treatment adherence and make treatment adjustments accordingly. (See Chapter 12.) **Suspected COAG** The reassessment intervals for individuals with suspected COAG are the same as those for individuals with treated OHT with the exception of people who have controlled IOP and undetected conversion. The committee decided that the reassessment interval for these individuals should be shorter as suspects are at a higher risk of conversion than individuals with a normal optic disc and visual field. Please see Table 39 for reassessment of patients with COAG.
Trade-off between net clinical effects and costs	Reassessing people with OHT or COAG is associated with the cost of a visit (£89 for an outpatient visit at the Hospital Eye Service or £51 for a reassessment visit conducted in the community). It was the committee's opinion that reassessments could be conducted in the Hospital Eye Service in 90% of the cases, and in the community by optometrists in the remaining 10% of the cases. Unnecessary reassessment visits have a high opportunity cost; however, if reassessment is not performed at the right frequency, there is a risk of missing signs of COAG development or progression with the consequent quality of life detriment for people if they do not receive appropriate treatment in a timely manner in order to slow down progression. One economic evaluation was identified for this question; Burr et al.(2012)[20] reports the outcomes of a discrete event simulation model comparing the cost effectiveness of 5 different surveillance strategies for people with confirmed OHT. The strategies compared in the model spanned over the whole glaucoma pathway including risk stratification, surveillance and treatment decisions simultaneously; therefore, the model was not directly applicable to the review protocol for this question specifically on reassessment intervals for OCT and COAG suspects. Two of the strategies compared in the study that were most applicable to this review were the 'NICE intensive' and 'NICE conservative' pathways. These strategies were applicable as everything else (risk stratification and treatment decision) was the same apart from how often people were assessed. For this reason, a difference in outcomes could be solely attributed to the frequency of assessments. The NICE intensive pathway assessed people at the earliest time in the recommended ranges outlined in the previous guideline NICE guideline (CG85), and the conservative pathway

	assessed people at the latest time in the recommended ranges (for example, for people with a thick cornea and a low IOP, this was every 24 months in the conservative pathway but every 12 months in the intensive pathway). The results of the study suggest that it is not cost effective to reassess people too frequently, as the intensive pathway produced an incremental cost-effectiveness ratio (ICER) of £2,220,000 per QALY gained compared to the conservative pathway, which is greatly above an acceptable willingness to pay threshold for the NHS. This study was assessed as partially applicable because only some of the comparisons were felt to be relevant. It was also rated as having potentially serious limitations as the committee felt that a flaw with the study was how the previous guideline's reassessment intervals had been interpreted, which could be leading to an overestimation of the number of reassessment visits. An original cost–utility analysis was conducted for the treatment of OHT review question. Results of a sensitivity analysis of the OHT treatment model found that reassessing people less frequently did not change the cost effectiveness of the treatment. Using this information, as well as the results of the Burr (2012) study (interpreted with caution) and their own experiences and expert opinions, the committee decided to lengthen the recommended time to reassessment for people treated with ocular hypertension with normal fields and discs who have clinically acceptable control of IOP and conversion not identified from 12-24 months (original guideline CG85) to 18-24 months (updated recommendations). This could reduce costs to the NHS as some people might be reassessed less frequently although due to current capacity constraints, most people in this category are probably not likely to be being seen before 24 months. The time between reassessment visits should reflect individual situations and allow flexibility for clinical judgement. It was the committee's opinion that the ranges reflect the correct balance between effectiveness (in terms of risk and its reduction) and costs.
Other considerations	The committee agreed that the reassessment intervals, formulated by consensus for CG85, for people with OHT and suspected COAG were no longer appropriate due to the pressure they placed on secondary care eye services and the lack of any beneficial evidence. The changes to the recommendations in this update should be straightforward to implement, as they do not require any new resources, training or equipment. The restructuring of the recommendations is intended to make them easier to implement.

The committee thought it appropriate to retain some of the consensus supporting recommendations made in the original guideline that are relevant to reassessment. These are detailed in the following table.

Recommendation	**28. Discuss the benefits and risks of stopping treatment with people with OHT or suspected COAG who have both:** • **a low risk of ever developing visual impairment within their lifetime** • **an acceptable IOP** **If a person decides to stop treatment after this discussion, offer to assess their IOP in 1 to 4 months with further reassessment if clinically indicated. [2009]**
Relative values of different outcomes	The key outcome is knowledge that the IOP has not risen to a dangerous level following cessation of medication. Following a

2009

	clinical decision made in conjunction with a patient to discontinue treatment it is essential that the correctness of discontinuation is confirmed by an early assessment of IOP off treatment in order to avoid a possible unexpected high IOP going undetected over an extended period.
Trade off between clinical benefits and harms	Where the benefits of treatment for the patient are marginal, stopping treatment may be the best option. Early confirmation that IOP off treatment is acceptable is essential. If a high IOP rise occurs following withdrawal of treatment it may be necessary to re-start treatment and re-institute long term monitoring. During the period of treatment, information will have been gathered on the stability of the condition. Patients with progressive disease would not be eligible for stopping treatment. Following withdrawal of treatment, a further period of observation may be necessary to confirm stability off treatment prior to formal discharge.
Economic considerations	None
Quality of evidence	None
Other considerations	Following discharge patients should be advised to remain in regular (annual) contact with their primary care optometrist in the interest of COAG / OHT screening for possible future changes in their condition.

2009

7.2 Optimum intervals for chronic open-angle glaucoma

7.2.1 Review question: What are the optimum intervals for monitoring people with chronic open-angle glaucoma?

For full details, see review protocol in appendix C.

Table 36: PICO characteristics of review question

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
Comparison	Tests for monitoring IOP, optic nerve head, macular and retinal nerve fibre layer and visual field conducted at different intervals
Outcomes	Critical outcomes • 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) Important outcomes • 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

7.2.2 Clinical evidence

No relevant clinical studies comparing monitoring intervals for people with COAG were identified in this update. Similarly, no studies were identified for inclusion in the original guideline. See also the study selection flow chart in appendix E and excluded studies list in appendix L.

7.2.3 Economic evidence

Published literature

One health economic study was identified with the relevant comparison and has been included in this review. [32] The study is summarised in the health economic evidence profile below (Table 32) and the health economic evidence table in appendix I.

See also the health economic study selection flow chart in appendix F.

Table 37: Health economic evidence profile: six visual field tests in the first two years of COAG diagnosis (proposed practice) versus annual visual field testing (current practice)

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Crabb 2014 [32] (UK)	Directly Applicable[(a)]	Potentially serious limitations [(b)]	10,000 people simulated through a 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 6 VF tests in the first 2 years of clinical management following diagnosis (proposed practice) compared to annual VF tests (current practice).	£294 per patient per annum	0.1 QALYs per patient per annum	ICER = £21,679 per QALY gained per annum	Comprehensive deterministic and probabilistic sensitivity analysis 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

Abbreviations: DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years; PSA: probabilistic sensitivity analysis

(a) UK study with appropriate population and interventions.

(b) 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.

(c) 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.

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

Unit costs

The unit cost of a monitoring visit to the Hospital Eye Services was presented to the committee to aid consideration of cost effectiveness.

Table 38: UK costs of monitoring visits

	Cost
Monitoring visit (hospital eye care services)	£89

Source: NHS reference costs (2015-16)

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

7.2.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

One cost–utility analysis found that testing visual fields 6 times in the first 2 years after diagnosis of COAG was cost-effective compared to testing annually at a threshold of £30,000 per QALY gained (ICER: £21.679) but was not cost-effective at a threshold of £20,000 per QALY gained. This analysis was assessed as directly applicable with potentially serious limitations.

7.2.5 Recommendations and link to evidence

Recommendations

29. For people with COAG:

- **use clinical judgement to assess risk of COAG progression to sight loss, and**
- **reassess according to Table 39. [2017]**

Table 39: Time to next assessment for people with COAG

Progression of COAG	Control of IOP	Time to next assessment[1]
Not detected	No	Review treatment plan and reassess between 1 and 4 months
Uncertain progression[2] or progression	No	Review treatment plan and reassess between 1 and 2 months

	No progression detected and low clinical risk	Yes	Reassess between 12 and 18 months
	No progression detected and high clinical risk	Yes	Reassess between 6 and 12 months
	Uncertain progression[2] or progression	Yes	Review treatment plan and reassess between 2 and 6 months
	[1] Use clinical judgement to decide when the next appointment should take place within the recommended interval. [2]Uncertain progression includes having insufficient accurate information (perhaps because the person was unable to participate in the assessment).		
Relative values of different outcomes	The committee agreed that development of COAG, change from normal visual field to visual field defect, extent of glaucomatous field loss, and health-related quality of life were critical outcomes. Optic nerve head damage, IOP level and patient or carer satisfaction were agreed as important outcomes.		
Quality of the clinical evidence	No evidence was identified. The recommendations were made by consensus agreement of the committee.		
Trade-off between clinical benefits and harms	No evidence was identified. The committee identified potential benefits and harms of reassessment based on their own expertise and experience. The person's personal circumstances (including family history, family origin and socioeconomic status) and health status should be acknowledged when arranging when to reassess and when deciding on the tests to be used at reassessment visits. In terms of specific risk factors, the committee noted that it would consider age of particular importance, as younger people have a longer time available to progress to loss of vision, so they may need more frequent assessments than older people might. Based on feedback since the last version of the guideline, the committee agreed that the table in CG85 used to decide when to reassess for people with COAG was difficult to interpret and replacing this with a simplified table would aid interpretation. Regarding IOP, the committee felt that there was a lack of evidence underpinning what constitutes a target IOP and that this would vary case-by-case. Furthermore, suggesting a 'target' IOP could lead to inappropriate treatment, including surgery in some cases, causing unnecessary distress to the patient and an inappropriate use of resource. The committee agreed that a better term was 'control of IOP', as a clinically acceptable IOP would vary between people based on a number of factors. In addition to this, the committee decided that the tests ordered at each reassessment interval should be at the discretion of the ophthalmologist and will vary based on the rate and degree of progression. The committee agreed that all people with COAG should be reassessed regularly, as the benefits of regular reassessment outweigh the harms. A benefit of regular reassessment is the ability to identify any clinically significant changes, that is, progression of glaucomatous damage or progression visual field damage more quickly and therefore take timely therapeutic action in response to disease progression before		

	significant visual loss occurs. Any reduction in sight would lead to a reduced quality of life and vision loss would lead to significant loss of quality of life. A further benefit is that this enables the maintenance of IOP control through effective treatment, which reduces the risk of COAG progression to blindness and increases maintenance of a sighted lifetime. Treatments can be also monitored to ensure their tolerability, poor tolerance can be detected more quickly, and treatment can be changed accordingly. The committee also noted that regular reassessment intervals might increase adherence to treatment. The potential negatives of regular reassessment include the inconvenience of the person having to attend regular appointments and the increased demand for eye services. The committee noted that how often the person should be reassessed depends on whether treatment has been established as effective and tolerated their level of risk for COAG progression, which depends on whether optic nerve damage or visual field change were detected. When treatment has been initiated, an assessment will be required to check if the treatment is effective and tolerated with no adverse effects. After treatment is established, people need to be reassessed less frequently, depending on their risk of progression. The amount and the rate of progression are important considerations that will influence the decisions about reassessment intervals and interventions (as a substantially lower IOP may be required). The committee emphasised the importance of using clinical judgement to decide the time to the next reassessment visit within the recommended interval. The time between visits may increase or decrease depending on the clinical need. For people with a clinically acceptable IOP who have no signs of progression, the committee decided that the reassessment interval could be different based on clinical risk. For those at low risk, the reassessment interval could be increased from 6-12, as recommended in CG85, to every 12-18 months. People who are stable on treatment, who do not show progression and who are at low clinical risk, do not require as frequent reassessment. The committee considered that 6-12 months for these low-risk people was over-cautious and placed an unnecessary burden on patients whose condition had been demonstrated to be stable. It was agreed that extending this to 12-18 months would be safe and better reflect their care needs. The 6-12 month reassessment interval remains the same for those at high clinical risk. Factors that come into making this assessment of risk level may include patients with secondary open-angle glaucomas (such as pigmentary or exfoliative), patients with previous glaucoma surgery, patients with field loss affecting fixation, patients with advanced glaucoma on multiple medications, or patients with only one seeing eye.
Trade-off between net clinical effects and costs	Reassessing people with COAG is associated with the cost of a visit (£89 for an outpatient visit to the Hospital Eye Service). Unnecessary assessment visits have a high opportunity cost; however, if assessment is not performed at the right frequency, there is a risk of missing signs of COAG progression with the consequent quality of life detriment for the patient if they do not receive appropriate treatment in a timely manner in order to slow down progression. One economic evaluation was identified for this question; The study by Crabb et al. (2012)[32] assessed the cost effectiveness of increasing the number of visual field (VF) examinations done in people in the first 2 years after diagnosis of COAG compared to annual VF testing. The study reported that having 6 VF tests in the first 2 years would cost £21,679 per QALY gained compared to having 2 VF tests in 2 years. The committee highlighted that current practice is not annual VF testing after diagnosis and that the frequency of VF testing after diagnosis depends on a number of factors including the amount of damage identified at diagnosis and the perceived risk of the patient. People could have a number of VF tests in 1 year if they are considered high risk. The committee felt that the study was biased towards the increased VF testing intervention

	due to the misinterpretation of current practice and therefore the study was rated as directly applicable, with potentially serious limitations. The committee agreed that frequent VF testing is good to assess progression and due to the imperfect nature of the assessment of VF, more tests are better than less. However, the committee also agreed that costs needed to be factored in and that continuously measuring VF on people at very low risk of progression who are on stable treatment is not a good use of resources. The committee amended the recommendations made in CG85 to give the clinicians carrying out the assessments the autonomy to decide which tests they believe need to be undertaken at each reassessment visit. The committee felt that being too prescriptive can lead to an inefficient use of resources either when tests are performed too frequently when they are not necessary, or too infrequently when they would be beneficial. In reality, how frequently people are given different tests should depend on the status of the individual and what the clinician feels is appropriate given available resources and capacity. It was the committee's opinion that the recommended times to reassessment reflect the right balance between effectiveness (in terms of risk and its reduction) and costs.
Other considerations	The committee noted that the reassessment intervals for people with confirmed COAG needed to be adequately resourced due to the risk of visual loss. However, the committee noted that the previous presentations of the recommendations maybe subject to misinterpretation and therefore decided to clarify this, for example, by making it clear which reassessment intervals are appropriate for people where IOP has not been established at a clinically acceptable level. The previous table format was felt to be too prescriptive with respect to updating treatment plans and testing, and the updated table highlights that these decisions are at the discretion of the physician. As the intervals in the recommendations have not changed substantially, there should be no significant implementation challenges. However, the committee noted the variable implementation of the recommendations of the previous guideline (CG85) and that often there were delays in reassessment due to lack of capacity. The committee also noted that updates to the recommendations on reassessment for OHT involves releasing possible hospital capacity through community reassessment, which will help with capacity for COAG reassessment. The committee noted that it may be difficult for people living in rural areas to attend regular appointments due to difficulties accessing hospitals; therefore, the inconvenience of having to attend regular appointments and the personal burden this creates may be greater for people living in rural areas.

8 Overview of treatment

8.1 Introduction

Strategies for reduction of visual damage in COAG rely on reduction of intraocular pressure (IOP). When treating individual patients the short-term objective is to reduce IOP to a clinically acceptable level, at or below which it may be anticipated that clinically significant progression of damage will be avoided. A clinically acceptable pressure should not be viewed as absolute or rigid and should be interpreted in a context, which is relevant to the patient, including glaucoma severity, response to treatment, comorbidities and life expectancy. Adjustment of this level of pressure both up and down may be required. The longer-term strategy is then to maintain clinical observation looking for signs of progression of visual field defects and optic nerve head damage. Provided IOP reduction has been identified as an effective way to protect against visual and nerve damage then IOP can be regarded as a useful and conveniently measured 'surrogate outcome' for treatment success. This approach can also be extended to prevention of visual damage by treatment of elevated IOP prior to development of manifest visual damage. 2009

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

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

The mainstream treatments for COAG remain directed towards reduction of IOP. Other approaches to treatment have however been proposed and these are considered under Complementary and Alternative Treatments in Chapter 10. Neuroprotection is one such approach to COAG management.

The aim of this section is to identify whether treatment overall is clinically and cost effective, however, the cost effectiveness of treatment has been updated in the revised economic model (appendix N).

Provided IOP lowering by the various drug classes results in long-term protection of vision, then by pooling results to compare the effectiveness of 'any treatment' with 'no treatment' we can identify whether IOP lowering treatments have an effect on COAG damage. Once clinical efficacy has been established, then cost effectiveness and acceptability to patients must be considered.

8.2 Any treatment vs. no treatment

Evidence comparing treatment with no treatment and meeting the inclusion criteria is presented here. Included are the RCTs analysed in Chapter 9, and three additional RCTs: the Ocular Hypertension Study comparing any medication to no treatment[68]; the Early Manifest Glaucoma Trial comparing laser trabeculoplasty plus a beta-blocker to no treatment[54]; and the Collaborative Normal-Tension Study Group comparing any treatment (medication, laser or surgery) to no treatment[29]. 2009

8.2.1 Any treatment versus no treatment

See the study evidence tables in appendix H and the forest plots in appendix K.

8.2.1.1 Clinical evidence

Table 40: Any treatment vs. no treatment – Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Number of ocular hypertensive patients developing COAG (follow up 5 to 6 years)[64,92]	2	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	
Number of COAG patients showing progressive damage (follow up 4 to 5 years)[29,55]	2	RCT	Serious limitations (a,c)	Serious inconsistency (b)	No serious indirectness	
Visual field progression in patients with ocular hypertension (follow up 2 to 10 years)[40,54,64,68,72,92,132,134]	8	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Visual field progression in COAG patients (follow up 4 to 5 years)[29,55]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Mean change in IOP from baseline (follow up 1 to 6 years)[40,64,68,132,134]	5	RCT	Serious limitations (e)	Serious inconsistency (f)	No serious indirectness	

(a) One study was open label, the other study was placebo controlled
(b) The two studies produce different effect sizes and there is statistical heterogeneity in the results. The open label study shows a significant result and the placebo controlled study showed a non-significant result.
(c) The patients were not masked to treatment in either study
(d) Although no statistical heterogeneity in the results, the studies include different types of IOP lowering treatments, some shown to be better than others. This may have influenced the relative risk as the confidence intervals are quite wide and the upper confidence interval is close to the line of no effect.
(e) Only 2 of the 5 studies were masked to treatment.
(f) There is statistical heterogeneity within the results with IOP reduction varying from 1.70mmHg to 4.73mmHg. This does not appear to be due to the quality of the studies, type of intervention, follow-up period or condition (i.e. OHT or COAG).
(g) The method of randomisation is not stated for most the studies and there is no mention of allocation concealment.
(h) The patients were not masked to treatment in two of the studies.
(i) The wide confidence intervals make the estimate of effect imprecise.

Table 41: Any treatment versus no treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of ocular hypertensive patients developing COAG (follow up 5 to 6 years)	82/1353 (6.1%)	149/1360 (11%)	RR 0.55 (0.43 to 0.72)	49 fewer per 1000 (from 31 fewer to 63 fewer)	Low
Number of COAG patients showing	80/190 (42.1%)	109/205 (53.2%)	RR 0.78 (0.63 to 0.95)	117 fewer per 1000 (from 27 fewer to 197	Low

2009

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
progressive damage (follow up 4 to 5 years)				fewer)	
Visual field progression in patients with ocular hypertension (follow up 2 to 10 years)	81/1726 (4.7%)	124/1730 (7.2%)	RR 0.65 (0.5 to 0.86)	25 fewer per 1000 (from 10 fewer to 36 fewer)	Moderate
Visual field progression in COAG patients (follow up 4 to 5 years)	68/190 (35.8%)	102/205 (49.8%)	RR 0.69 (0.55 to 0.86)	154 fewer per 1000 (from 70 fewer to 224 fewer)	Moderate
Mean change in IOP from baseline (follow up 1 to 6 years)	1136	1137	Not applicable	MD -3.28 (-4.5 to -2.06)	Low

2009

8.2.1.2 Cost-effectiveness evidence

In the original guideline, 2 studies[75,145] were included as health economic evidence in the overview of treatment chapter comparing any treatment to no treatment. These studies were reassessed but due to changes in methodology and stricter inclusion criteria, they were excluded due to limited applicability. For economic conclusions, please see Chapter 9 on treatment and the updated economic model (appendix N) which assesses the cost effectiveness of no treatment compared to different pharmacological treatments in reducing IOP.

8.2.1.3 Patient views evidence

No studies were identified.

2009

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

Clinical	Treatment is more effective than no treatment in reducing the number of patients with ocular hypertension converting to COAG at 5-to-6 years' follow up. However, there is significant heterogeneity between the two studies. (LOW QUALITY) Treatment is more effective than no treatment in reducing the number of patients with COAG showing progressive damage at 4 to 5 years' follow up. (LOW QUALITY) Treatment is more effective than no treatment in reducing visual field progression in patients with ocular hypertension at 2 to 10 years follow up. (MODERATE QUALITY) Treatment is more effective than no treatment in reducing visual field progression in patients with COAG at 4 to 5 years follow up. (MODERATE QUALITY) Treatment is more effective than no treatment in reducing IOP from baseline at 1 to 6 years follow up. (LOW QUALITY)
Economic	Please see chapter 9 for updated economic evidence statements.

2009

8.3 Conclusions

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

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

2009

9 Treatment of ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

9.1 Pharmacological treatment for ocular hypertension, suspected chronic open-angle glaucoma and confirmed chronic open-angle glaucoma

9.1.1 Introduction

9.1.1.1 Treatment of ocular hypertension and suspected chronic open-angle glaucoma

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

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

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

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

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

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

Fixed combination eye drops contain 2 drugs dispensed in 1 bottle. Most currently marketed fixed combination products contain Timolol 0.5% and combinations are available with latanoprost, travoprost, tafluprost and bimatoprost for once daily use and with brimonidine, dorzolamide and brinzolamide for twice-daily use. A brimonidine and brimonidine fixed combination twice daily preparation is also available. When compared to prescribing the individual monotherapies, fixed combination therapies offer a simple and convenient dosing regimen, and may result in some cost saving for patients subject to prescription charges. However, fixed combinations may be more expensive than the cost of the 2 individual components separately and remove the possibility of titrating the individual components in terms of both concentration and timing of administration. Additionally, they might not always provide the same efficacy as proper use of the individual components. Unnecessary side effects may arise because of the higher concentration of Timolol in all currently available fixed combinations.

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

9.1.1.2 Treatment of chronic open-angle glaucoma

Pharmacological treatment

Eye drops are the most commonly used treatment for COAG. There are 5 main classes of drug available as eye drops to lower intraocular pressure (IOP): prostaglandin analogues, beta-blockers (beta receptor antagonists), carbonic anhydrase inhibitors, sympathomimetics (alpha receptor agonists), and miotics (cholinergic agonists).

Tablets of the oral carbonic anhydrase inhibitor acetazolamide are only rarely used to treat COAG (because of systemic side effects).

Laser treatment

The laser treatments under consideration in this guideline are argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT), both of which may be performed as outpatient procedures. Depending on the patient's ability to tolerate the procedure, both eyes may be treated at a single sitting.

ALT is thought to work by activating cells called trabeculocytes (which form part of the trabecular meshwork [TM]). It is believed that the TM function is improved by activation of these cells. A contact lens is placed on the eye to focus an 'aiming beam' accurately onto the TM. Only half (180 degrees) of the TM is treated during 1 sitting. It may take up to 6 weeks for treatment to have the full effect and after this, if further IOP lowering is needed, the second 180 degrees of the TM is treated. Re-treatments in the same area can cause scarring of the TM and raised IOP.

2009

Selective laser trabeculoplasty is similar to ALT but uses a different laser with a discharge of a very short duration. The spot size of the laser beam is much larger than that used for ALT, so accurate identification of the TM is not as critical and the procedure is technically simpler. The mechanism of action is thought to be the same as ALT, but re-treatments are said to be less likely to cause raised IOP because there is less photocoagulative damage to adjacent tissue.

Surgical treatment

The surgical treatments are classified as penetrating and non-penetrating surgery. In this guideline, the penetrating surgical procedure under consideration is trabeculectomy, and the non-penetrating surgical procedures are deep sclerectomy and viscocanalostomy.

During trabeculectomy, a flap of conjunctiva is dissected under the upper eyelid and a partial thickness flap of sclera is raised. A block of tissue is excised from the inner sclera exposing the iris beneath and a portion of iris is removed with the scleral flap and the conjunctiva then sutured back in place. Fluid from within the eye cavity filters around the edges of the scleral flap forming a fluid lake or 'bleb' under the conjunctiva below the upper eye lid from where it is absorbed by blood vessels of the sclera and conjunctiva into the bloodstream. Allowing some escape of fluid lowers the eye pressure.

Deep sclerectomy is a variant of trabeculectomy. Instead of removing a piece of the iris and inner sclera, only a thin strip of inner sclera overlying Schlemm's canal is removed. Fluid from the exposed canal filters slowly around the loosely applied scleral flap and a bleb is not formed. This method is advocated by some surgeons because it is regarded as being slightly less invasive than traditional trabeculectomy surgery, while still allowing fluid to escape from the eye and lowering the pressure.

Viscocanalostomy is a variant of deep sclerectomy. After Schlemm's canal is deroofed, it is cannulated and a viscoelastic solution injected to break open the inner wall to allow easier egress of fluid from the TM into Schlemm's canal over a larger circumference than just the area beneath the scleral flap.

2009

9.1.2 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?

For full details, see review protocol in appendix C.

Table 42: PICO characteristics of review question

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 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	• Topical solutions (eye drops)

	○ prostaglandin analogues (all doses): bimatoprost, tafluprost, travoprost 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 (all doses) - Pilocarpine ○ fixed-combination solutions (of different classes): prostaglandin analogue with beta-blockers; carbonic anhydrase inhibitors and sympathomimetics; carbonic anhydrase inhibitors with beta-blockers ○ topical solutions with any of the following preservatives: Benzalkonium chloride and SofZia • Systemic carbonic anhydrase inhibitors (all doses): Acetazolamide
Comparisons	• 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) ○ if study reported both allergic reaction or intolerance and hyperaemia – only allergic reaction or intolerance was extracted ○ 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 and RCTs

9.1.3 Clinical evidence

A search was conducted for randomised control trials and systematic reviews of randomised control trials comparing the effectiveness of various pharmacological treatments.

Eleven studies were added to the previous 34 studies included in the CG85 glaucoma guideline.[5,6,9,15,18,22,23,40-43,45,46,54,57,58,74,79,85-87,89,92,94,105,111,113,117,118,125,132-135,137,146,152,153,158-160,162] These are summarised in Table 26 below. Evidence from these studies is summarised in the clinical evidence summary below (appendix H). See also the study selection flow chart in appendix E, forest plots in appendix K, study evidence tables in appendix H, GRADE tables in appendix J and excluded studies list in appendix L.

The studies compared different classes of medicine including beta-blockers, prostaglandin analogues, sympathomimetics and carbonic anhydrase inhibitors with each other, no treatment or a placebo. Fixed combinations and separate combinations of these medicines were also compared with monotherapy. The update of this evidence review also looked at studies comparing solutions containing preservatives and preservative-free solutions.

Funnel plots were constructed to assess against potential publication bias for outcomes containing more than 5 studies (appendix K). This was taken into consideration as was assessing the quality of the evidence.

In order to input the clinical effectiveness data of multiple possible interventions into the economic model, it was proposed that a network meta-analysis be carried out on the outcome data for glaucomatous visual field loss. However, due to a paucity of evidence for this outcome, the NMA was instead undertaken on the surrogate outcome of change in IOP. Included papers had to report a change in IOP from baseline to follow-up or provide enough data that this could be calculated. For full details on the NMA methodology and results, please see appendix O.

Table 43: Summary of studies included in the review

Study	Intervention and comparison	Population	Outcomes	Comments
Alm 1995[5]	Intervention 1 (n=183): 0.005% latanoprost once per day Intervention 2 (n=84): 0.5% Timolol twice per day	n=267 People with primary open-angle glaucoma, pigmentary glaucoma, exfoliation glaucoma or ocular hypertension Age (mean): 67 (40-85) Intervention 1: Male/female: 82/101 Intervention 2: Male/female: 34/40 Family origin not reported	• Mean change in IOP from baseline (at 6 months) • Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Respiratory (at 6 months) • Adverse events: Cardiovascular (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Ang 2008[6]	Intervention 1 (n=54): 0.004% travoprost once per day Comparison (n=34): No treatment	n=88 People with normal tension glaucoma Intervention 1: Age (mean SD): 67.3 (13.1) Male/female: 30/24 Family origin: White: 53 Comparison (no treatment): Age (mean SD): 67.6 (9.6) Male/female: 15/19 Family origin: White: 33	• Mean change in IOP from baseline (at 6 months) • Adverse events: allergic reaction (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
Aung 2014[9]	Intervention 1 (n=193): Fixed combination 1% brinzolamide and 0.2% brimonidine twice per day Intervention 2 (n=191): 1% brinzolamide monotherapy Intervention 3 (n=175): 0.2% brimonidine monotherapy	n=559 People with primary open-angle glaucoma or ocular hypertension Intervention 1: Age (mean SD): 64.9 (12.2) Male/female: 87/106 Family origin: White: 133; Black or African-American: 20; Asian: 16; Multiracial: 4; Other: 20 Intervention 2: Age (mean SD): 64.1 (11.2) Male/female: 90/101 Family origin: White: 138; Black or African-American: 14; Asian: 16; Multiracial: 2; Other: 21 Intervention 3: Age (mean SD): 64.3 (11.6) Male/female: 73/102 Family origin: White: 123; Black or African-American: 14; Asian: 14; Multiracial: 3; Other: 21	• Mean change in IOP from baseline (%) at 09.00 (at 6 months) • Mean change in IOP from baseline (%) at 11.00 (at 6 months) • Mean change in IOP from baseline (%) at 16.00 (at 6 months) • Treatment discontinuation due to adverse events (at 6 months) • Adverse events: allergic reaction (at 6 months)	
Barnebey 2017[15]	Intervention 1 (n=41):	People 18 years or older diagnosed with open-angle	• Ocular hyperaemia • Cumulative % of days that people were	

Study	Intervention and comparison	Population	Outcomes	Comments
	Fixed combination travoprost 0.004% and Timolol 0.5% Intervention 2 (n=40): Separate combination travoprost 0.004% and Timolol 0.5%	glaucoma (including open-angle glaucoma with pigment dispersion and pseudoexfoliation) or ocular hypertension Age: FC: 58.7 (10.2) Separate: 61.5 (9.3) Gender (M/F): FC: 28/13 Separate: 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%) Separate: White: 37 (92.5%); Black or African-American: 3 (7.5%); Native Hawaiian or Pacific Islander: 0; Other: 0	adherent with dosing	
Bucci 1999[18]	Intervention 1 (49): 0.005% Latanoprost and 0.5% Timolol twice per day Intervention 2 (n=50): 0.005% Latanoprost once per day	n=99 People with primary open-angle glaucoma or pseudoexfoliation glaucoma Intervention 1: Age (mean SD): 63 (12)	• Mean change in IOP from baseline (at 6 months) • Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Respiratory (at 6 months) • Adverse events: Hyperaemia (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Male/female: 21/28 Family origin not reported Intervention 2: Age (mean SD): 59 (13) Male/female: 28/22 Family origin not reported		
Camras 1996[A22]	Intervention 1 (n=128): 0.005% Latanoprost once per day Intervention 2 (n=140): 0.5% Timolol twice per day	n=268 People with primary open-angle glaucoma, pigmentary glaucoma, exfoliation glaucoma or ocular hypertension Intervention 1: Age (mean SD): 61 (12) Male/female: 58/70 Family origin: Black: 27; Not black: 101 Intervention 2: Age (mean SD): 63 (11) Male/female: 56/84 Family origin: Black: 38; Not black: 102	• Mean change in IOP from baseline (at 6 months) • Adverse events: Cardiovascular (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Camras 2005[23]	Intervention 1 (n=151): 0.005% Latanoprost once per day Intervention 2 (n=150): 0.2% brimonidine twice per day	n=303 People with primary open-angle glaucoma or ocular hypertension	• Mean change in IOP from baseline (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Intervention 1: Age (mean± SEM): 62±1.0 Male/female: 70/81 Family origin: White: 104; African-American: 36; Other: 11 Intervention 2: Age (mean± SEM): 64±1.0 Male/female: 77/73 Family origin: White: 103; African-American: 39; Other: 8		
Epstein 1989[40]	Intervention 1: Timolol 0.5% twice per day Comparison: No treatment	n=107 People with ocular hypertension Age (mean): 60 Family origin: % African-Caribbean: 62 Gender not reported	• Visual field progression (at 5 years) • Mean change in IOP from baseline (at 5 years) • Number of people with an IOP >30mmHg (at 5 years) • Adverse events: Respiratory (at 5 years) • Adverse events: Cardiovascular (at 5 years)	
Fellman 2002[41]	Intervention 1 (n=197): 0.004% travoprost once per day Intervention 2 (n=199): 0.5% Timolol twice per day	n=396 People with primary open-angle glaucoma, pigmentary glaucoma, pseudoexfoliation glaucoma or ocular hypertension	• Mean change in IOP from baseline (at 6 months) • Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Hyperaemia (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Intervention 1: Age (mean SD): 64.4 (10.2) Male/female: 94/103 Family origin: Black: 17; Not black: 180 Intervention 2: Age (mean SD): 63.9 (11.2) Male/female: 64/105 Family origin: Black: 23; Not black: 176		
Frezzotti 2014[42]	Intervention 1 (n=20): 0.01% Benzalkonium chloride preserved 0.5% Timolol maleate (twice per day in both eyes) Intervention 2 (n=20): 0.1% preservative-free Timolol maleate gel (once per day in both eyes)	n=40 First primary open-angle glaucoma diagnosis requiring bilateral treatment to reduce intraocular pressure Intervention 1: Age (mean SD): 61.5 (13.2) Male/female: 9/11 Family origin not reported Intervention 2: Age (mean SD): 60.25 (8.9) Male/female: 10/10 Family origin not reported	• Mean intraocular pressure (at 12 months) • Major adverse events (at 12 months)	
Fuchsjager-Mayrl 2010[43]	Intervention 1 (n=57): Dorzolamide 3 times per day	n=140	• Mean change in IOP from baseline (% – 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention2 (n=83): Timolol twice per day	People with primary open-angle glaucoma or ocular hypertension POAG: Age (mean SD): 63 (13.0) Gender (M/F): 19/30 OHT: Age (mean SD): 61.2 (13.3) Gender (M/F): 48/43 Family origin not reported		
Garway-Heath 2015[45]	Intervention 1 (n=231): 0.005% Latanoprost once per day Comparison (n=230): Placebo (once per day in both eyes)	n=516 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 Intervention 1: Age (mean SD): 65 (11) Comparison: Age (mean SD): 66 (10) Overall male/female: 273/243	• Time to confirmed visual field deterioration (at 24 months) • Number of people reaching deterioration end point at 24 months (at 24 months) • Mean intraocular pressure reduction from baseline (at 24 months) • Adverse events: Cardiovascular (myocardial infarction; at 24 months)	Visual field deterioration is 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

Study	Intervention and comparison	Population	Outcomes	Comments
		Family origin not reported		
Goldberg 2001[46]	Intervention 1 (n=197): 0.004% travoprost once per day Intervention 2 (n=185): 0.5% Timolol twice per day	n=382 People with primary open-angle glaucoma, pigmentary glaucoma, pseudoexfoliation glaucoma or ocular hypertension Intervention 1: Age (mean SD): 63.0 (10.3) Male/female: 96/101 Family origin: Black: 2; Non-black: 195 Intervention 2: Age (mean SD): 62.5 (10.6) Male/female: 96/89 Family origin: Black: 2; Non-black: 183	• Mean change in IOP from baseline (at 9 months) • Number of people with a clinically acceptable IOP (at 9 months) • Adverse events: Hyperaemia (at 9 months)	
Heijl 2000[54]	Intervention 1: Timolol 0.5% twice per day Comparison: Placebo	n=90 People with ocular hypertension, pseudoexfoliation glaucoma or pigmentary glaucoma	• Visual field progression (at 10 years) • Number of people with an IOP >30mmHg (at 10 years)	
Higginbotham 2002[A57]	Intervention 1 (n=138): Fixed combination latanoprost 0.005% and Timolol 0.5% once per	n=418	• Mean change in IOP from baseline (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	day Intervention 2 (n=140): Latanoprost 0.005% once per day Intervention 3 (n=140): Timolol 0.5% twice per day	People with primary open-angle glaucoma, pigmentary glaucoma, pseudoexfoliative glaucoma or ocular hypertension Intervention 1: Age (mean SD): 61 (12) Male/female: 67/71 Family origin: White: 90; Black: 38; Hispanic: 7; Other: 3 Intervention 2: Age (mean SD): 63 (13) Male/female: 80/60 Family origin: White: 90; Black: 35; Hispanic: 14; Other: 1 Intervention 3: Age (mean SD): 63 (12) Male/female: 68/72 Family origin: White: 96; Black: 37; Hispanic: 6; Other: 1	• Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Hollo 2014[58]	Intervention 1 (n=201): Preservative-free fixed combination of tafluprost 0.0015% or Timolol 0.5% (once daily at 08.10) and preservative-	n=400 People aged 18 years and older with either ocular hypertension or open-angle glaucoma	• IOP reduction (at 6 months) • IOP reduction of ≥ 30% from baseline at (6 months) • IOP reduction of ≥ 35% from baseline at (6 months)	People in the Timolol-only arm received 0.5% Timolol twice per day compared to 0.5% Timolol once per day in

Study	Intervention and comparison	Population	Outcomes	Comments
	free placebo vehicle (twice daily at 08.00 and 20.00) Intervention 2 (n=199): Preservative-free, non-fixed combination of tafluprost 0.0015% (once daily at 08.10) and Timolol 0.5% at (twice daily at 08.00 and 20.00)	(primary open-angle, pseudoexfoliative or pigmentary glaucoma). People with glaucoma who constituted over 80% of the total population Intervention 1: Age (mean SD): 63.5 (10.6) Male/female: 75/126 Family origin: White: 100% Intervention 2: Age (mean SD): 64 (10.6) Male/female: 77/122 Family origin: White: 99%; Black: 0.5%; Hispanic: 0.5%	• Adverse events: Hyperaemia (at 6 months) • Mean IOP of ≤ 18mmHg at 6 months (at 6 months)	the fixed combination arm.
Kamal 2003[64]	Intervention 1: Betaxolol 0.5% twice per day Comparison: Placebo	n=356 People with ocular hypertension Age (mean): 66 Family origin not reported Gender not reported	• Visual field progression (at 5 years) • Mean change in IOP from baseline (at 5 years) • Number of people with an IOP >30mmHg (at 5 years)	
Kampik 2002[66]	Intervention 1 (n=187): Latanoprost 0.005% once per day	n=379 People with chronic open-angle glaucoma and ocular	• Mean change in IOP from baseline (at 6 months) • Adverse events: allergic reaction (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 2 (n=192): Brimonidine 0.2% twice per day	hypertension Intervention 1: Age (mean SD): 64 (11) Male/female: 77/110 Family origin not reported Intervention 2: Age (mean SD): 65 (12) Male/female: 77/115 Family origin not reported		
Kitazawa 1990[72]	Intervention: Timolol 0.5% twice per day Comparison: Placebo	n=20 People with ocular hypertension Age and family origin not reported	• Visual field progression (at 2 years)	
Krupin 2011[74]	Intervention 1: Brimonidine 0.2% twice per day Intervention 2: Timolol 0.5% twice per day	n=178 Mean age (SD): Brimonidine: 64.3 (10.9); Timolol: 65.7 (10.4) Male/female: Brimonidine: 44/55; Timolol: 31/48 Family origin: White: 137 (72.1%); Black: 26	• Visual field progression (at 48 months) • Discontinuation prior to year 1 • Discontinuation ≥ year 1 • Mean IOP (at 48 months) final value	

Study	Intervention and comparison	Population	Outcomes	Comments
		(13.7%); Hispanic: 14 (7.4%); Asian: 13 (6.8%)		
Leblanc 1998[79]	Intervention 1 (n=280): Brimonidine 0.2% twice per day Intervention 2 (n=183): Timolol 0.5% twice per day	n=463 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean range): 63 (28.5-86.4) Male/female: 138/142 Family origin: Black: 32; Non-black: 260 Intervention 2: Age (mean range): 61 (32.8-83) Male/female: 96/87 Family origin: Black: 15; Non-black: 168	• Visual field progression (at 12 months) • Mean change in IOP from baseline (at 12 months) • Treatment discontinuation due to allergic reaction (at 12 months)	
Manni 2004[85]	Intervention 1 (n=30): Latanoprost 0.005% and Timolol 0.5% once per day Intervention 2 (n=31): Bimatoprost 0.03% once per day	n=61 People with chronic open-angle glaucoma Intervention 1: Age (mean SD): 59.7 (13.5) Male/female: 16/14 Family origin not reported	• Mean change in IOP from baseline (at 6 months) • Adverse events: Hyperaemia (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Intervention 2: Age (mean SD): 59.2 (14.7) Male/female: 14/17 Family origin not reported		
March 2000[86]	Intervention 1 (n=150): Brinzolamide 1% twice per day Intervention 2 (n=153): Brinzolamide 1% 3 times per day Intervention 3 (n=75): Timolol 0.5% twice per day	n=378 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean SD): 63.0 (11.6) Male/female: 68/82 Black/non-black: 27/123 Intervention 2: Age (mean SD): 60.3 (12.9) Male/female: 76/77 Black/non-black: 33/120 Intervention 3: Age (mean SD): 59.9 (13.2) Male/female: 28/47 Black/non-black: 14/61	• Adverse events: Hyperaemia (at 18 months)	
Martin 2007[87]	Intervention 1 (n=30): Bimatoprost 0.03% once per day Intervention 2 (n=30): Timolol 0.5% twice per day	n=60 People with chronic open-angle glaucoma and ocular hypertension	• Mean change in IOP from baseline (at 6 months) • Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Hyperaemia (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Age, gender and family origin not reported		
Mastropasqua 1999[89]	Intervention 1 (n=18): Latanoprost 0.005% once per day Intervention 2 (n=18): Timolol 0.5% twice per day	n=36 People with pigmentary glaucoma Intervention 1: Age (mean SD): 46.1 (9.9) Male/female: 10/8 Family origin not reported Intervention 2: Age (mean SD): 45.8 (10.5) Male/female: 11/7 Family origin not reported	• Mean change in IOP from baseline (at 12 months) • Adverse events: Hyperaemia (at 12 months)	
Miglior 2005 (European Glaucoma Prevention study)[92]	Intervention (n= 536): Dorzolamide 2% 3 times per day Comparison(n=541): Placebo 3 times per day	n=1,077 People with ocular hypertension Intervention: Age (mean SD): 56.42 (10.32) Male/female: 232/304 Family origin not reported Comparison: Age (mean SD): 57.63 (10.3) Male/female: 259/282 Family origin not reported	• Conversion to COAG • Visual field progression • Number of people with an IOP >35mmHg (median follow-up 55.3 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
Mills 1983[94]	Intervention 1 (n=15): Timolol 0.25% twice per day Intervention 2 (n=15): Timolol 0.5% twice per day	n=30 People with chronic open-angle glaucoma Intervention 1: Age (mean): 71 Male/female: 9/6 Family origin not reported Intervention 2: Age (mean): 69 Male/female: 6/9 Family origin not reported	• Mean change in IOP from baseline (at 12 months)	
Netland 2001[105]	Intervention 1 (n= 197): Travoprost 0.004% once per day Intervention 2 (n=195): Timolol 0.5% twice per day Intervention 3 (n=193): Latanoprost 0.005% once per day	n=585 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean SD): 64 (13.3) Male/female: 100/97 Black/non-black: 49/148 Intervention 2: Age (mean SD):64.8 (11.6) Male/female: 107/88 Black/non-black: 40/155	• Mean change in IOP from baseline (at 12 months) • Number of people with a clinically acceptable IOP (at 12 months) • Adverse events: Cardiovascular (at 12 months) • Adverse events: Hyperaemia (at 12 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Intervention 3: Age (mean SD):64.5 (11.6) Male/female: 89/104 Black/non-black: 43/150		
Orengo-Nania 2001[111]	Intervention 1 (n=145): Separate combination travoprost 0.004% once per day and Timolol 0.5% twice per day Intervention 2 (n=139): Timolol 0.5% twice per day	n=271 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean SD): 63.9 (11.1) Male/female: 65/72 Black/non-black: 35/105 Intervention 2: Age (mean SD): 63.3 (1.3) Male/female: 56/78 Black/non-black: 32/102	• Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Ozturk 2007[113]	Intervention 1 (n=30): Fixed combination dorzolamide and Timolol twice per day Intervention 2 (n=35): Bimatoprost 0.03% once per day	n=65 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean; range): 64.9 (48-78) Male/female: 15/14 Family origin not reported	• Change in IOP from baseline (at 6 months) • Adverse events: Respiratory (at 6 months) • Adverse events: Hyperaemia (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Intervention 2: Age (mean range): 61.9 (48-75) Male/female: 13/21 Family origin not reported		
Pfeiffer 2002[117]	Intervention 1 (n=140): Fixed combination latanoprost 0.005% and Timolol 0.5% once per day Intervention 2 (n=147): Latanoprost 0.005% once per day Intervention 3 (n=149): Timolol 0.5% twice per day	n=436 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean SD): 64 (13) Male/female: 67/73 Family origin not reported Intervention 2: Age (mean SD): 63 (12) Male/female: 77/70 Family origin not reported Intervention 3: Age (mean SD): 64 (10) Male/female: 52/97 Family origin not reported	• Mean change in IOP from baseline (at 6 months) • Number of people with a clinically acceptable IOP (at 6 months) • Adverse events: Respiratory (at 6 months) • Adverse events: Cardiovascular (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Polo 2005[118]	Intervention 1 (n=30): Separate combination dorzolamide 2% and Timolol 0.5% twice per day Intervention 2 (n=31):	n=61 People with chronic open-angle glaucoma Intervention 1:	• Mean change in IOP from baseline (at 24 months) • Number of people with a clinically acceptable IOP (at 24 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Latanoprost 0.005% once per day	Age (mean SD): 67.9 (11.2) Male/female: 60%/40% Family origin not reported Intervention 2: Age (mean SD): 64.6 (19.1) Male/female: 64%/36% Family origin not reported		
Rismanchian 2008[125]	Intervention 1 (n=60): 0.005% latanoprost (1 drop daily in affected eye) Intervention 2 (n=60): 2% Dorzolamide (1 drop 3 times per day in affected eye) and 0.5% Timolol (1 drop twice per day in affected eye; not fixed combination)	n=120 People with primary open-angle glaucoma defined as either visual field defect or glaucomatous changes of the optic nerve head in association with elevated intraocular pressure of at least 22mmHg preceding the commencement of the study Intervention 1: Age (mean SD): 52.7 (10.84) Male/female: 32/28 Family origin not reported Intervention 2: Age (mean SD): 54.8 (15.49) Male/female: 28/32 Family origin not reported	• Mean change in IOP from baseline (at 6 months)	
Schulzer 1991[132]	Intervention: Timolol	n=137	• Visual field progression (at 6 years) • Mean change in IOP from baseline (at 6	

Study	Intervention and comparison	Population	Outcomes	Comments
	0.25% - 0.5% twice per day Comparison: Placebo	People with ocular hypertension Age (mean): 60 Gender and family origin not reported	years) • Number of people with an IOP >30mmHg (at 6 years)	
Schuman 1997[133]	Intervention 1 (n=186): Brimonidine 0.2% twice per day Intervention 2 (n=188): Timolol 0.5% twice per day	n=374 People with chronic open-angle glaucoma and ocular hypertension Age, gender and family origin not reported	• Visual field progression (at 12 months) • Mean change in IOP from baseline (at 12 months) • Adverse events: allergic reaction (at 12 months)	
Schwartz 1995[134]	Intervention: Timolol 0.5% twice per day Comparison: Placebo	n=37 People with ocular hypertension Age (mean): 60 Gender and family origin not reported	• Visual field progression (at 1-2 years) • Mean change in IOP from baseline (at 1-2 years)	
Sherwood 2006[135]	Intervention 1 (n=385): Fixed combination brimonidine 0.2% and Timolol 0.5% twice per day Intervention 2 (n=382): Brimonidine 0.2% 3 times per day	n=1,159 People with bilateral chronic open-angle glaucoma and ocular hypertension Intervention 1:	• Number of people with a clinically acceptable IOP (at 12 months) • Adverse events: allergic reaction (at 12 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 3 (n=392): Timolol 0.5% twice per day	Age (mean SD): 62.0 (12.2) Male/female: 181/204 Family origin not reported Intervention 2: Age (mean SD): 63.8 (11.8) Male/female: 151/231 Family origin not reported Intervention 3: Age (mean SD): 62.0 (12.3) Male/female: 186/206 Family origin not reported		
Siesky 2010[137]	Intervention 1 (n=12): 0.5% Timolol maleate (twice daily) Intervention 2 (n=12): Dorzolamide or Timolol (twice daily)	n=24 People with primary open-angle glaucoma POAG: Age (mean SD): 64 (10.3) Control: Age (mean SD): 49 (6.4) Overall family origin: White: 16; Black: 5; Asian: 1	• Mean change in IOP (% – right eye; at 8 months) • Mean change in IOP (% – left eye; at 8 months)	Study does not mention adjusting for inter-eye correlation
Strahlman 1995[146]	Intervention 1 (n=313): Dorzolamide 2% 3 times per day Intervention2 (n=103): Timolol 0.5% twice per day	n=523 People with chronic open-angle glaucoma and ocular hypertension	• Mean change in IOP from baseline (at 12 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
	Intervention 3 (n=107): Betaxolol 0.5% twice per day	Intervention 1: Age (mean SD): 62.1 (11.6) Male/female: 136/177 Black/non-black: 4/309 Intervention 2: Age (mean SD): 63.8 (11.4) Male/female: 53/50 Black/non-black: 2/101 Intervention 3: Age (mean SD): 60.7 (12.0) Male/female: 54/53 Black/non-black: 3/104		
Tomita 2004[152]	Intervention 1 (n=31): Latanoprost 0.005% once per day Intervention 2 (n=31): Timolol 0.5% twice per day	n=62 People with normal tension glaucoma Intervention 1: Age (mean SD): 56 (10) Male/female: 14/17 Family origin not reported Intervention 2: Age (mean SD): 54.3 (8.5) Male/female: 15/16 Family origin not reported	• Mean change in IOP from baseline (at 3 years)	
Tsai 2005[153]	Intervention 1 (n=22):	n=44	• Mean change in IOP from baseline (at 12	

Study	Intervention and comparison	Population	Outcomes	Comments
	Brimonidine 0.2% twice per day Intervention 2 (n=22): Timolol 0.5% gel once per day	People with primary open-angle glaucoma Intervention 1: Age (mean SD): 61.9 (8.6) Intervention 2: Age (mean SD): 60.0 (9.4) Gender and family origin not reported	months)	
Varma 2010[158]	Intervention 1 (n=278): Fixed combination latanoprost and Timolol once per day Intervention 2 (n=287): Latanoprost once per day Intervention 3 (n=289): Timolol twice per day	n=854 People with primary open-angle glaucoma, pigmentary or pseudoexfoliative glaucoma or ocular hypertension Intervention 1: Age (mean SD): 62.3 (12.8) Male: 134 Family origin: White: 229; African-American: 38; Other: 11 Intervention 2: Age (mean SD): 63.2 (12.2) Male: 145 Family origin: White: 242; African-American:	• Change in diurnal IOP fluctuation at 26 weeks	Diurnal IOP fluctuation was defined as the highest IOP minus the lowest IOP of 3 measurements

Study	Intervention and comparison	Population	Outcomes	Comments
		37; Other: 8 Intervention 3: Age (mean SD): 63.8 (11.6) Male: 132 Family origin: White: 239; African-American: 35; Other: 15		
Vetrugno 2004[159]	Intervention 1 (n=19): Bimatoprost 0.3% once per day Intervention 2 (n=19): Timolol 0.5% twice per day	n=38 People with primary open-angle glaucoma Intervention 1: Age (mean SD): 52.1 (5.01) Male/female: 12/7 Intervention 2: Age (mean SD): 51.2 (4.12) Male/female: 10/9 Family origin not reported	• Mean change in IOP from baseline (at 6 months) • Adverse events: Hyperaemia (at 6 months)	
Watson 1996[160]	Intervention 1 (n=149): Latanoprost 0.005% once per day Intervention 2: Timolol 0.5% twice per day	n=294 People with chronic open-angle glaucoma and ocular hypertension Intervention 1: Age (mean SD): 64.7 (9.5)	• Mean change in IOP from baseline (at 6 months) • Adverse events: Cardiovascular (at 6 months) • Adverse events: allergic reaction (at 6 months)	

Study	Intervention and comparison	Population	Outcomes	Comments
		Male/female: 98/51 White/Black: 143/6 Intervention 2: Age (mean SD): 65.3 (10.5) Male/female: 93/52 White/Black: 142/3		
Whitson 2013[162]	Intervention 1 (n=218): Fixed combination 1% brinzolamide and 0.2% brimonidine Intervention 2 (n=232): 0.2% brimonidine monotherapy Intervention 3 (n=229): 1% brinzolamide monotherapy 3 times per day	n=679 People with open-angle glaucoma or ocular hypertension Overall Age (mean SD): 64.9 (10.4) White: 529 (77.9%); Black: 130 (19.1%); Asian: 9 (1.3%); Multiracial: 3 (0.4%); Other: 8 (1.2%) Gender not reported	• Adverse events: allergic reaction (at 6 months)	

Table 44: Clinical evidence summary: preservative versus preservative-free solutions

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with preservative-free solutions	Risk difference with Preservative versus preservative-free solutions (95% CI)
Change in IOP from baseline	40 (1 study) 12 month	LOW[a,b] due to risk of bias, imprecision	-	The mean change in IOP from baseline in the control groups was 16.2 mmHg	The mean change in IOP from baseline in the intervention groups was 0.4 higher (0.63 lower to 1.43 higher)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with preservative-free solutions	Risk difference with Preservative versus preservative-free solutions (95% CI)
Major adverse events (no definition)	40 (1 study) 12 months	LOW[a] due to risk of bias	[c]	[c]	The risk difference in the intervention group was 0 (0.09 lower to 0.09 higher)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Unable to calculate relative effect due to zero events in each arm.

Table 45: Clinical evidence summary: prostaglandin analogues versus placebo or no treatment

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Prostaglandin analogues versus placebo (95% CI)
Number of people reaching deterioration endpoint at 24 months	461 (1 study) 24 months	MODERATE[a] due to imprecision	RR 0.59 (0.41 to 0.86)	257 per 1,000	105 fewer per 1,000 (from 36 fewer to 151 fewer)
Adverse events: myocardial infarction	461 (1 study) 24 months	LOW[a] due to imprecision	RR 0.5 (0.05 to 5.45)	9 per 1,000	4 fewer per 1,000 (from 8 fewer to 39 more)
Change in IOP from baseline	461 (1 study) 24 months	HIGH	-	The mean change in IOP from baseline in the control groups was 1.3 mmHg	The mean change in IOP from baseline in the intervention groups was 2.7 higher (2.06 to 3.34 higher)
Time to confirmed visual field deterioration	461 (1 study) 24 months	HIGH	HR 0.44 (0.28 to 0.69)	[c]	
Final IOP	76 (1 study)	VERY LOW[a,b] due to risk of		The mean final IOP in the control group was 14.5mmHg	The mean final IOP in the intervention group was 2.00 lower

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Prostaglandin analogues versus placebo (95% CI)
	6 months	bias, imprecision			(3.11 to 0.89 lower)
Adverse events: allergic reaction	81 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 5.73 (0.34 to 96.66)	353 per 1,000	1,000 more per 1,000 (from 233 fewer to 1,000 more)

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

b 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

c Unable to calculate as study reported summary statistic only

Table 46: Clinical evidence summary: beta-blockers versus no treatment

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with Beta-blocker (95% CI)
Visual field progression	743 (6 studies) 2-6 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.77 (0.52 to 1.14)	235 per 1,000	54 fewer per 1,000 (from 113 fewer to 33 more)
Mean change in IOP from baseline	637 (4 studies) 2-6 years	VERY LOW[a,b,d] due to risk of bias, inconsistency	-	The mean change in IOP from baseline in the control group was -1.32mmHg	The mean change in IOP from baseline in the intervention groups was 2.88 lower (4.14 to 1.61 lower)
Number of people with an IOP >30mmHg	690 (4 studies) 2-10 years	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.56 (0.22 to 1.46)	32 per 1,000	14 fewer per 1,000 (from 25 fewer to 15 more)
Adverse events: Respiratory	107 (1 study) 5 years	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.53 (0.15 to 379.54)	[c]	

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with Beta-blocker (95% CI)
Adverse events: Cardiovascular	107 (1 study) 5 years	LOW[a,b] due to risk of bias, imprecision	Peto OR 7.99 (1.09 to 58.33)	[c]	

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Unable to calculate as zero events in 1 arm of the trial
d Heterogeneity, I^2=75%

Table 47: Clinical evidence summary: carbonic anhydrase inhibitors versus no treatment

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No treatment	Risk difference with Carbonic anhydrase inhibitors (95% CI)
Conversion to COAG	1,077 (1 study) 5 years	MODERATE[a] due to imprecision	RR 0.77 (0.54 to 1.11)	111 per 1,000	26 fewer per 1,000 (from 51 fewer to 12 more)
Visual field progression	1,077 (1 study) 5 years	MODERATE[a] due to imprecision	RR 0.69 (0.43 to 1.12)	70 per 1,000	22 fewer per 1,000 (from 40 fewer to 8 more)
Number of people with an IOP >35mmHg	1,077 (1 study) 5 years	HIGH	RR 0.08 (0.01 to 0.64)	22 per 1,000	20 fewer per 1,000 (from 8 fewer to 22 fewer)

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

Table 48: Clinical evidence summary: fixed combination versus separate combination (prostaglandin analogue and beta-blocker)

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow-up	evidence (GRADE)	effect (95% CI)	Risk with Separate combination	Risk difference with Fixed combination (95% CI)
Change in IOP from baseline	400 (1 study) 6 months	HIGH[a]	-	The mean change in IOP from baseline in the control group was 8.3 mmHg	The mean change in IOP from baseline in the intervention group was 0.3 lower (0.86 lower to 0.26 higher)
IOP reduction of ≥ 30% from baseline	400 (1 study) 6 months	MODERATE[a] due to imprecision	RR 0.87 (0.75 to 1.01)	668 per 1,000	87 fewer per 1,000 (from 167 fewer to 7 more)
IOP reduction of ≥ 35% from baseline	400 (1 study) 6 months	MODERATE[a] due to imprecision	RR 0.85 (0.67 to 1.08)	427 per 1,000	64 fewer per 1,000 (from 141 fewer to 34 more)
Adverse events: Hyperaemia	481 (2 studies) 6-12 months	LOW[a] due to imprecision	RR 1.58 (0.73 to 3.41)	42 per 1,000	24 more per 1,000 (from 11 fewer to 101 more)
Mean IOP of ≤ 18mmHg at 6 months	400 (1 study) 6 months	HIGH	RR 1.01 (0.89 to 1.16)	678 per 1,000	7 more per 1,000 (from 75 fewer to 109 more)
Cumulative % of days that participants were adherent with dosing	81 (1 study) 12 months	MODERATE[a] due to imprecision	-	The mean cumulative % of days that people were adherent with dosing in the control group was 43%	The mean cumulative % of days that people were adherent with dosing in the intervention group was 17 higher (5.02 to 28.98 higher)
a Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 49: Clinical evidence summary: beta-blocker dosage (Timolol 0.5% versus Timolol 0.25%)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Timolol 0.25%	Risk difference with Timolol 0.5% (95% CI)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Timolol 0.25%	Risk difference with Timolol 0.5% (95% CI)
Mean IOP change from baseline (right and left eye)	30 (1 study) 12 months	LOW[a,b] due to risk of bias, imprecision	-	The mean change in IOP from baseline in the control group was -4.95mmHg	The mean change in IOP from baseline in the intervention groups was 1.62 lower (2.95 to 0.38 lower)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 50: Clinical evidence summary: prostaglandin analogues versus beta-blockers

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Prostaglandins (95% CI)
Change in diurnal IOP fluctuation	576 (1 study) 26 weeks	VERY LOW[a,c] due to risk of bias, indirectness		The mean change in diurnal IOP fluctuation in the control group was 0.36	The mean change in diurnal IOP fluctuation from baseline in the intervention groups was 0.25 lower (0.86 lower to 0.36 higher)
Change in IOP from baseline	2,675 (12 studies) 6 to 36 months	MODERATE[d] due to inconsistency	-	The mean change in IOP from baseline in the control group was -4.61mmHg	The mean change in IOP from baseline in the intervention groups was 1.32 lower (1.79 to 0.84 lower)
Number of people with a clinically acceptable IOP	1,924 (7 studies)	VERY LOW[b,e] due to	RR 1.54 (1.21 to	395 per 1,000	213 more per 1,000 (from 83 more to 379 more)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Prostaglandins (95% CI)
	6 to 12 months	imprecision, inconsistency	1.96)		
Adverse events: Respiratory	563 (2 studies) 6 months	MODERATE[b] due to imprecision	RR 0.59 (0.35 to 1)	103 per 1,000	42 fewer per 1,000 (from 67 fewer to 0 more)
Adverse events: Cardiovascular	1,710 (5 studies) 6 to 12 months	MODERATE[b] due to imprecision	RR 0.87 (0.67 to 1.13)	126 per 1,000	16 fewer per 1,000 (from 42 fewer to 16 more)
Adverse events: Allergic reaction	294 (1 studies) 6 months	MODERATE[b] due to imprecision	RR 0.19 (0.01 to 4.02)	14 per 1,000	11 fewer per 1,000 (from 14 fewer to 42 more)
Adverse events: Hyperaemia	2,791 (9 studies) 6 to 12 months	HIGH	RR 3.56 (2.92 to 4.33)	87 per 1,000	222 more per 1,000 (from 166 more to 289 more)

a 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

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

c The majority of evidence had indirect outcomes

d Heterogeneity, I^2=55%

e Heterogeneity, I^2=85%

Table 51: Clinical evidence summary: prostaglandin analogues versus sympathomimetics

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sympathomimetics	Risk difference with Prostaglandins (95% CI)
Change in IOP from baseline	680 (2 studies) 6 to 12	LOW[a,b,] due to risk of bias,	-	The mean change in IOP from baseline in the control groups was -4.15 mmHg	The mean change in IOP from baseline in the intervention groups was 2.02 lower (2.72 to 1.69 lower)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sympathomimetics	Risk difference with Prostaglandins (95% CI)
	months	imprecision			
Adverse events: Allergic reaction	375 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 0.14 (0.05 to 0.36)	85 per 1,000	73 fewer per 1,000 (from 54 fewer to 81 fewer)
Adverse events: Hyperaemia	375 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.45 to 2.26)	59 per 1,000	1 more per 1,000 (from 32 fewer to 74 more)

a 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

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

Table 52: Clinical evidence summary: carbonic anhydrase inhibitors versus sympathomimetics

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sympathomimetics	Risk difference with Carbonic anhydrase inhibitors (95% CI)
% change in IOP from baseline (09.00)	323 (1 study) 6 months	HIGH		The mean % change in IOP from baseline (%) in the control group was -23.6%	The mean change in IOP from baseline (%) in the intervention groups was 2.00 lower (4.84 lower to 0.84 higher)
% change in IOP from baseline (11.00)	323 (1 study) 6 months	HIGH		The mean % change in IOP from baseline (%) in the control group was -30.0%	The mean change in IOP from baseline (%) in the intervention groups was 2.1 higher (0.44 lower to 4.64 higher)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Sympathomimetics	Risk difference with Carbonic anhydrase inhibitors (95% CI)
% change in IOP from baseline (16.00)	322 (1 study) 6 months	HIGH		The mean % change in IOP from baseline (%) in the control group was -23.6%	The mean change in IOP from baseline (%) in the intervention groups was 2.2 lower (5.23 lower to 0.83 higher)
Adverse events: Allergic reaction	827 (2 studies) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.22 (0.05 to 0.87)	17 per 1,000	13 fewer per 1,000 (from 2 fewer to 16 fewer)
Treatment discontinuation due to adverse events	366 (1 study) 6 months	HIGH	RR 0.07 (0.01 to 0.53)	74 per 1,000	69 fewer per 1,000 (from 35 fewer to 74 fewer)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 53: Clinical evidence summary: carbonic anhydrase inhibitors versus beta-blockers

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Carbonic anhydrase inhibitors (95% CI)
Adverse events: Hyperaemia – Brinzolamide (2 and 3 times per day)	453 (1 study) 18 months	LOW[a,b] due to risk of bias, imprecision	Peto OR 4.58 (1.21 to 17.33)	[c]	[c]
Change in IOP from baseline (%)	140 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean change in IOP from baseline in the control group was -22.5%	The mean change in IOP from baseline in the intervention groups was 2.74 higher

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Carbonic anhydrase inhibitors (95% CI)
					(1.49 lower to 6.97 higher)
Change in IOP from baseline (mmHg)	416 (1 study) 12 months	VERY LOW[a,b] due to risk of bias, imprecision		The mean change in IOP from baseline (mmHg) in the control groups was 4.7mmHg	The mean change in IOP from baseline (mmHg) in the intervention groups was 1.3 higher (0.37 to 2.23 higher)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Unable to calculate as 0 events in 1 arm of the trial

Table 54: Clinical evidence summary: sympathomimetics versus beta-blockers

Outcome	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Sympathomimetics (95% CI)
Visual field progression	829 (3 studies) 12-48 months	VERY LOW[a,b,d] due to risk of bias, inconsistency, imprecision	RR 0.52 (0.18 to 1.50)	161 per 1,000	77 fewer per 1,000 (from 132 fewer to 80 more)
Change in IOP from baseline – Trough effect (before morning medication)	837 (2 studies) 12 months	MODERATE[a] due to risk of bias	-	The mean change in IOP from baseline – trough effect (before morning medication) in the control group was -5.99mmHg	The mean change in IOP from baseline - trough effect (before morning medication) in the intervention groups was 2.27 higher (1.8 to 2.74 higher)

Outcome	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Sympathomimetics (95% CI)
Change in IOP from baseline –Peak effect (2 hours after morning medication)	837 (2 studies) 12 months	LOW[a,e] due to risk of bias, inconsistency	-	The mean change in IOP from baseline – peak effect (2 hours after morning medication) in the control group was -5.90mmHg	The mean change in IOP from baseline – peak effect (2 hours after morning medication) in the intervention groups was 0.27 lower (0.98 lower to 0.45 higher)
Change in IOP from baseline – Mean diurnal IOP	222 (2 study) 12 months	LOW[a] due to risk of bias	-	The mean change in diurnal IOP from baseline in the control group was 9.75mmHg	The mean change in diurnal IOP from baseline in the intervention groups was 0.24 lower (0.58 lower to 0.09 higher)
Adverse events: Allergic reaction	1,217 (2 study) 12 months	VERY LOW[a,b,f] due to risk of bias, imprecision, inconsistency	RR 8.15 (0.68 to 98.32)	77 per 1,000	547 more per 1,000 (from 24 fewer to 1000 more)
Treatment discontinuation due to allergic reaction	483 (1 study) 12 months	MODERATE[a] due to risk of bias	Peto Odds ratio 6.12 (3.23 to 11.61)	[c]	
Treatment discontinuation prior to 1 year	178 (1 study) 48 months	HIGH	RR 3.59 (1.77 to 7.28)	101 per 1,000	262 more per 1,000 (from 78 more to 636 more)
Treatment discontinuation > 1 year	178 (1 study) 48 months	LOW[b] due to imprecision	RR 0.96 (0.52 to 1.78)	190 per 1,000	8 fewer per 1,000 (from 91 fewer to 148 more)

a 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

Outcome	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	Risk difference with Sympathomimetics (95% CI)
risk of bias b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs c Unable to calculate as 0 events in 1 arm of the trial d Heterogeneity, I^2=83% e Heterogeniety, I^2=55% f Heterogeneity, I^2=71%					

Table 55: Clinical evidence summary: fixed combination prostaglandin analogue and beta-blocker versus prostaglandin analogue

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	
Change in diurnal IOP fluctuation	565 (1 study) 26 weeks	VERY LOW[a,d] due to risk of bias, indirectness		The mean change in diurnal IOP fluctuation from baseline was 0.11	The mean change in diurnal IOP fluctuation in the intervention group was 0.79 lower (1.4 lower to 0.18 lower)
Change in IOP from baseline	565 (2 studies) 6 months	VERY LOW[a,c] due to risk of bias, inconsistency	-	The mean change in IOP from baseline in the control group -2.1mmHg	The mean change in IOP from baseline in the intervention groups was 0.34 lower (1.81 lower to 1.13 higher)
Number of people with a clinically acceptable IOP	565	LOW[a,b]	RR 1.07	314 per	22 more per 1,000

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Beta-blockers	
(<18mmHg)	(2 studies) 6 months	due to risk of bias, imprecision	(0.84 to 1.36)	1,000	(from 50 fewer to 113 more)
Adverse events: Respiratory	287 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.53 (0.13 to 2.06)	41 per 1,000	19 fewer per 1,000 (from 36 fewer to 43 more)
Adverse events: Cardiovascular	287 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 5.25 (0.62 to 44.83)	7 per 1,000	29 more per 1,000 (from 3 fewer to 295 more)
Adverse events: Hyperaemia	287 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.1 (0.39 to 11.28)	14 per 1,000	15 more per 1,000 (from 8 fewer to 140 more)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Heterogeneity, I^2=84%
d The majority of evidence had indirect outcomes

Table 56: Clinical evidence summary: fixed combination prostaglandin analogue and beta-blocker versus beta-blocker

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
Change in diurnal IOP fluctuation	567 (1 study) 26 weeks	VERY LOW[a,d] due to risk of bias, indirectness		The mean change in diurnal IOP	The mean change in diurnal IOP fluctuation in the intervention group was 1.04 lower (1.65 lower to 0.43 lower)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
				fluctuation in the control group was 0.36	
Change in IOP from baseline	567 (2 studies) 6 months	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	-	The mean change in IOP from baseline in the control group was -0.7mmHg	The mean change in IOP from baseline in the intervention groups was 1.75 lower (4.00 lower to 0.51 higher)
Number of people with a clinically acceptable IOP (<18mmHg)	567 (2 studies) 6 months	VERY LOW[a,b,e] due to risk of bias, inconsistency, imprecision	RR 2.27 (0.99 to 5.23)	166 per 1,000	211 more per 1,000 (from 2 fewer to 703 more)
Adverse events: Respiratory	289 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.46 (0.12 to 1.73)	47 per 1,000	25 fewer per 1,000 (from 41 fewer to 34 more)
Adverse events: Cardiovascular	289 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision	RR 2.66 (0.52 to 13.49)	13 per 1,000	22 more per 1,000 (from 6 fewer to 168 more)
Adverse events: Hyperaemia	289 (1 study) 6 months	VERY LOW[a,c] due to risk of bias, imprecision	RR 4.26 (0.48 to 37.63)	7 per 1,000	22 more per 1,000 (from 3 fewer to 246 more)

a 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
b Heterogeneity, I^2=93%

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
c Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs d The majority of evidence had indirect outcomes e Heterogeneity, I^2=82%					

Table 57: Clinical evidence summary: fixed combination carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
Change in IOP from baseline	65 (1 study) 6 months	LOW[a,b] due to risk of bias, imprecision	-	The mean change in IOP from baseline in the control group was -6.2mmHg	The mean change in IOP from baseline in the intervention groups was 0.3 lower (1.32 lower to 0.72 higher)
Adverse events: Respiratory	65 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 3.48 (0.15 to 82.48)	[c]	
Adverse events: Hyperaemia	65 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 0.26 (0.1 to 0.68)	514 per 1,000	381 fewer per 1,000 (from 165 fewer to 463 fewer)
a 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					

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
risk of bias b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs c Unable to calculate due to 0 events in 1 arm					

Table 58: Clinical evidence summary: fixed combination sympathomimetic and beta-blocker versus beta-blocker

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
Number of people with a clinically acceptable IOP (<17.5mmHg)	777 (1 study) 12 months	HIGH	RR 1.62 (1.36 to 1.92)	324 per 1,000	201 more per 1,000 (from 117 more to 298 more)
Adverse events: Allergic reaction	777 (1 study) 12 months	HIGH	RR 2.17 (1.58 to 2.97)	120 per 1,000	140 more per 1,000 (from 70 more to 236 more)

Table 59: Clinical evidence summary: fixed combination carbonic anhydrase inhibitor and beta-blocker versus beta-blocker

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
% change in IOP from baseline (right and left eye)	22 (1 study) 8 months	LOW[a,b] due to risk of bias, imprecision	-	The mean % change in IOP from baseline	The mean % change in IOP from baseline (right and left eye) in the intervention groups was 13.75 lower (23.06 to 4.43 lower)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
				(right and left eye) in the control group was -0.14%	

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 60: Clinical evidence summary: fixed combination carbonic anhydrase inhibitors and sympathomimetics versus sympathomimetics

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
% change in IOP from baseline (11am)	305 (1 study) 6 months	MODERATE[b] due to imprecision		The mean % change in IOP from baseline in the control group was -30%	The mean % change in IOP from baseline in the intervention groups was 5 lower (7.62 to 2.38 lower)
% change in IOP from baseline (4pm)	305 (1 study) 6 months	MODERATE[b] due to imprecision		The mean % change in IOP from baseline in the control group was -23.6%	The mean % change in IOP from baseline in the intervention groups was 5.2 lower (8.28 to 2.12 lower)
% change in IOP from baseline (9am)	305 (1 study) 6 months	MODERATE[b] due to imprecision		The mean % change in IOP from baseline in the control group was -23.6%	The mean % change in IOP from baseline in the intervention groups was 4.1 lower (6.92 to 1.28 lower)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
Treatment discontinuation due to adverse events	368 (1 study) 6 months	LOW[b] due to imprecision	RR 1.39 (0.72 to 2.72)	74 per 1,000	29 more per 1,000 (from 21 fewer to 128 more)
Adverse events: Allergic reaction	818 (2 studies) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.49 (1.05 to 5.9)	17 per 1,000	26 more per 1,000 (from 1 more to 84 more)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 61: Clinical evidence summary: fixed combination carbonic anhydrase inhibitors and sympathomimetics versus carbonic anhydrase inhibitors

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
% change in IOP from baseline (11am)	338 (1 study) 6 months	MODERATE[b] due to imprecision	-	The mean % change in IOP from baseline in the control groups was -27.9 %	The mean % change in IOP from baseline in the intervention groups was 7.1 lower (9.71 to 4.49 lower)

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single medications	Risk difference with Fixed combination (95% CI)
% change in IOP from baseline (4pm)	338 (1 study) 6 months	HIGH	-	The mean % change in IOP from baseline in the control groups was -25.8 %	The mean % change in IOP from baseline in the intervention groups was 3.0 lower (5.92 to 0.08 lower)
% change in IOP from baseline (9am)	338 (1 study) 6 months	HIGH	-	The mean % change in IOP from baseline in the control groups was -25.6 %	The mean % change in IOP from baseline in the intervention groups was 2.1 lower (4.78 to 0.58 lower)
Treatment discontinuation due to adverse events	384 (1 study) 6 months	HIGH	RR 19.79 (2.68 to 146.01)	5 per 1,000	98 more per 1,000 (from 9 more to 759 more)
Adverse events: Allergic reaction	831 (2 studies) 6 months	LOW[a] due to risk of bias	RR 12.06 (2.3 to 63.29)	2 per 1,000	26 more per 1,000 (from 3 more to 148 more)
a 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 b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 62: Clinical evidence summary: separate combination prostaglandin analogue and beta-blocker versus prostaglandin analogue

Outcomes	Number of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow-up	evidence (GRADE)	effect (95% CI)	Risk with single medication	Risk difference with separate combination (95% CI)
Change in IOP from baseline	160 (2 studies) 6 months	LOW[a] due to risk of bias	-	The mean change in IOP from baseline in the control groups was -6mmHg	The mean change in IOP from baseline in the intervention groups was 0.66 lower (1.44 lower to 0.13 higher)
Number of people with a clinically acceptable IOP (<18mmHg)	91 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.96 (0.72 to 1.27)	696 per 1,000	28 fewer per 1,000 (from 195 fewer to 188 more)
Adverse events: Respiratory	99 (1 study) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	Peto OR 7.54 (0.15 to 380.14)	[c]	
Adverse events: Hyperaemia	160 (2 studies) 6 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.54 (0.98 to 2.44)	222 per 1,000	120 more per 1,000 (from 4 fewer to 320 more)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Unable to calculate due to 0 events in 1 arm

Table 63: Clinical evidence summary: separate combination carbonic anhydrase inhibitor and beta-blocker versus prostaglandin analogue

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with single medication	Risk difference with separate combination (95% CI)
Number of people with a clinically acceptable IOP (<21mmHg)	75 (1 study) 24 months	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.49 to 0.97)	822 per 1,000	255 fewer per 1,000 (from 25 fewer to 419 fewer)
Change in IOP from baseline	181 (2 studies)	VERY LOW[a,b,c]	-	The mean change in IOP from	The mean change in IOP from baseline in the intervention groups was 0.41 higher

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with single medication	Risk difference with separate combination (95% CI)
	6 months	due to risk of bias, imprecision, inconsistency		baseline in the control groups was -6.95mmHg	(1.06 lower to 1.88 higher)

a 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
b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
c Heterogeneity, I^2=76%

Table 64: Clinical evidence summary: separate combination prostaglandin analogue and beta-blocker versus beta-blocker

Outcomes	Number of Participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with single medication	Risk difference with separate combination (95% CI)
Number of people with a clinically acceptable IOP (<17mmHg)	226 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 4.91 (2.72 to 8.88)	98 per 1,000	384 more per 1,000 (from 169 more to 774 more)
Adverse events: Hyperaemia	290 (1 study) 6 months	MODERATE[a] due to risk of bias	RR 4 (2.28 to 7.02)	90 per 1,000	269 more per 1,000 (from 115 more to 540 more)

a 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

9.1.4 Economic evidence

Published literature

CG85

The original guideline also included 4 studies as health economic evidence in the chapter on the treatment for ocular hypertension and suspected chronic open-angle glaucoma,[31,130,131,143] and 1 study in the treatment for chronic open-angle glaucoma chapter.[78] These studies were reassessed; however, due to changes in methodology and stricter inclusion criteria, they were excluded due to limited applicability or methodological issues. All of these are listed in appendix I, with their reasons for exclusion provided.

Update search

Nine economic studies relating to this review question were identified but were excluded due to limited applicability.[35,60,76,77,99,115,149,154,155] One study was also identified but excluded due to methodological limitation.[144] All of these are listed in appendix M, with their reasons for exclusion provided.

See also the health economic study selection flow chart in appendix F.

Unit costs

The unit costs of a month of each class of pharmacological treatment for ocular hypertension were estimated to aid consideration of cost effectiveness. The weighted average costs of each drug class were estimated using September 2016 drug tariff costs and prescribing data for England.

Table 65: Unit costs of drugs by class

Drug Class		% of their class	Cost per month (£)	weighed cost (£)	Cost per month (£) (class)
Beta blocker	Betaxolol	6	2.28	0.14	2.39
Beta blocker	Carteolol Hydrochloride	5	8.00	0.43	
Beta blocker	Levobunolol Hydrochloride	8	1.85	0.15	
Beta blocker	Timolol	80	2.08	1.67	
Carbonic anhydrase inhibitor	Acetazolamide (oral)	7	32.36	2.17	4.48
Carbonic anhydrase	Brinzolamide	73	2.56	1.87	

Drug Class		% of their class	Cost per month (£)	weighed cost (£)	Cost per month (£) (class)
inhibitor					
Carbonic anhydrase inhibitor	Dorzolamide	20	2.17	0.44	
Combination	Brinzolamide & Timolol	12	11.05	1.27	8.32
Combination	Brinzolamide/Brimonidine	2	9.23	0.18	
Combination	Dorzolamide & Timolol	28	1.92	0.54	
Combination	Latanoprost & Timolol	14	2.22	0.32	
Combination	Tafluprost & Timolol	0			
Combination	Timolol & Bimatoprost	31	13.95	4.27	
Combination	Timolol & Brimonidine	4	10.00	0.39	
Combination	Timolol & Travoprost	10	13.95	1.35	
Miotics	Pilocarpine Hydrochloride	100	8.47	8.47	8.47
Prostaglandin analogues	Bimatoprost	27	11.71	3.14	5.52
Prostaglandin analogues	Latanoprost	57	1.54	0.88	
Prostaglandin analogues	Tafluprost	3			
Prostaglandin analogues	Travoprost	14	10.95	1.50	
Sympathomimetics	Apraclonidine	10	10.88	1.12	2.64
Sympathomimetics	Brimonidine Tartrate	90	1.70	1.53	

New cost-effectiveness analysis

Approach to analysis:

This area was prioritised for original economic analysis. A de novo cost-effectiveness analysis was conducted. The analysis was based on a model built for the original guideline. In the original guideline 2 treatment models were conducted, 1 on a population with OHT and 1 on a population with COAG. The surveillance report that prompted this update highlighted the need for updating these models to take into account decreases in the cost of prostaglandin analogues (PGA), which were identified as the most effective pharmacological treatment in the original guideline but not cost effective in OHT subgroups at lower risk of developing COAG. The OHT treatment model was updated to incorporate the changes in costs as well as new evidence on the effectiveness of the pharmacological treatments being compared. The COAG model was not updated because PGAs were found to be the most cost-effective treatment for a COAG population in the original guideline, and therefore PGA's will be even more cost effective if they have reduced in price. The results of the OHT treatment model (base-case and sensitivity analyses) could also be extrapolated to a COAG population.

The population of people diagnosed with OHT was split into people with an IOP between 21 and 25 and >25 and these groups were analysed separately. Each IOP group was further divided into people with different levels of central corneal thickness (low:<555 micrometre, intermediate: 555-590 micrometre and high: > 590 micrometre). The model was a decision analytic Markov model comparing PGA, Beta-blockers (βB) and no treatment and their effect on prolonging the time to conversion to COAG, and then progression through different stages of COAG (early, moderate and advanced) to severe visual impairment, for each of the different subgroups of people with OHT.

To mitigate uncertainty and assess the robustness of the results, the model was built probabilistically and a number of sensitivity analyses were also conducted.

To inform the model, a Network Meta-Analysis was conducted to analyse the existing evidence on the effectiveness of beta-blockers and PGAs at reducing IOP for people with OCT or COAG. Please see appendix O for full details on the methods and results of the NMA.

Results of the cost-effectiveness analysis:

The base-case results of the model estimated that beta-blockers (βB) were the most cost-effective treatment for all of the different subgroups of people with OHT (please see Table 66 for a summary of the base-case model results).

For the base-case model, the cost of PGA medication per month was calculated using a weighted average of all PGA drugs prescribed within the PGA drug class (£5.52 per month). In a sensitivity analysis, this cost was replaced with the monthly cost of generic PGA (£1.54 for 1 month of Latanoprost). Changing the cost of PGA to the cost of the generic drug changed the results of the cost effectiveness analysis; generic PGA became the most cost effective treatment for all subgroups of people with OHT. Please see Table 67 for a summary of the results of this sensitivity analysis. This is reported separately because it played a key part in informing the recommendations made by the committee.

Please see appendix N for full details on the methods and results of the cost-effectiveness analysis.

Table 66: Health economic evidence profile: PGA versus βB versus no treatment (Base-case model results)

Study	Applicability	Limitations	Other comments	Total cost per strategy	Total QALYs per strategy	Cost-effectiveness: NMB at £20,000 threshold (highest NMB = most cost effective treatment option)	Uncertainty
Original cost-utility analysis conducted for the guideline	Directly Applicable[(a)]	Potentially serious limitations [(b)]	An original cost-utility analysis was conducted to determine the most cost-effective treatment option for people with OHT. The population was split into people with an IOP between 21 and 25 and >25 and these groups were analysed separately. Each IOP group was further divided into people with different levels of central corneal thickness (low:<555µm, intermediate: 555-590 µm and high: > 590µm). The model was a decision analytic Markov model with a lifetime horizon, comparing PGA, βB and no treatment at	**IOP ≥21 and <25** ***CCT low*** No treatment=£3,857 βB=£3,659 PGA=£4,033 ***CCT intermediate*** No treatment=£2,828 βB=£2,820 PGA=£3,250 ***CCT high*** No treatment=£1,666 βB=£1,903 PGA=£2,397 **IOP >25** ***CCT low*** No treatment=£5,704 βB=£5,233 PGA=£5,512 ***CCT intermediate*** No treatment=£3,307	**IOP ≥21 and <25** ***CCT low*** No treatment=12.55 βB=12.62 PGA=12.62 ***CCT intermediate*** No treatment=12.67 βB=12.72 PGA=12.73 ***CCT high*** No treatment=12.82 βB=12.84 PGA=12.84 **IOP >25** ***CCT low*** No treatment=12.32 βB=12.42 PGA=12.43 ***CCT intermediate*** No treatment=12.61	**IOP ≥21 and <25** ***CCT low*** No treatment=£247,102 βB=£248,663 PGA=£248,432 ***CCT intermediate*** No treatment=£250,622 βB=£251,603 PGA=£251,275 ***CCT high*** No treatment=£254,647 βB=£254,860 PGA=£254,414 **IOP >25** ***CCT low*** No treatment=£240,697 βB=£243,072 PGA=£242,998 ***CCT intermediate*** No treatment=£248,978	The model was built probabilistically with 10,000 simulations in the base-case. Several sensitivity analyses (SA) were conducted changing key parameters in the model (for example, the criteria for inclusion of studies in the NMA on treatment effect, the frequency of monitoring, mean defect at diagnosis of early COAG and utilities). 2,500 simulations were run for each SA and the majority of the sensitivity analysis conducted did not change the cost-effectiveness results. A sensitivity analysis replacing the cost of PGA (a weighted average of all drugs prescribed within the PGA drug

Study	Applicability	Limitations	Other comments	Total cost per strategy	Total QALYs per strategy	Cost-effectiveness: NMB at £20,000 threshold (highest NMB = most cost effective treatment option)	Uncertainty
			prolonging the time to conversion to COAG and then progression through different stages of COAG (early, moderate and advanced) to severe visual impairment, for people with OHT.	βB=£3,208 PGA=£3,611 ***CCT high*** No treatment=£2,250 βB=£2,361 PGA=£2,822	βB=12.67 PGA=12.68 ***CCT high*** No treatment=12.74 βB=12.78 PGA=12.78	βB=£250,242 PGA=£249,960 ***CCT high*** No treatment=£252,593 βB=£253,211 PGA=£252,826	class) with the cost of generic PGA (Latanoprost) changed the cost-effectiveness results of the model. Please see Table 67 for the results of this sensitivity analysis. Several threshold analyses were also conducted (for example, on age at diagnosis, baseline rate of progression and treatment effects)

Abbreviations: ßB: beta-blockers; CCT: Central Corneal Thickness; COAG: Chronic Open-Angle Glaucoma; OHT: Ocular Hypertension; PGA: prostaglandin analogues; QALY: quality-adjusted life years; µm: micro-meters

(a) The population, comparators and outcomes were directly applicable to the review question.

(b) Limitations: The highest weighted study in the NMA conducted on the treatment effect feeding into the model came from a high-risk population. The study used to estimate the baseline risk of progression had an inclusion criteria of people having an IOP≥24 mmHg; however, the model population was technically all people diagnosed with OHT, which in practice, is anyone with an IOP consistently above 21mmHg.The model assumed that people would be correctly diagnosed with OHT prior to being given treatment. In reality, due to the dynamic nature of IOP and the inaccuracy in measuring IOP (even with the reference standard GAT) many people would require monitoring prior to either being discharged or given treatment. Some people will end up having false positive or false negative diagnoses; however, these scenarios were not incorporated into the model as the clinical review used GAT as the reference standard and assumed 100% diagnostic accuracy. The model assumes a linear relationship between IOP reduction from treatment and reduction in probability of progression with a 1-unit reduction of mmHg leading to a 10% reduction in probability of progression. The committee did not believe that this relationship was linear. The committee believed that for people with an IOP < 24mmHg, reducing IOP through treatment would have no effect on probability of progression to COAG. The committee also believed that for people with very high IOP, a reduction in 1 unit of mmHg would not lead to a 10% reduction in their probability of progression.

Table 67: Health economic evidence profile: PGA versus βB versus no treatment (Results of sensitivity analysis using the cost of generic PGA only for cost of PGA)

Study	Applicability	Limitations	Other comments	Total cost per strategy	Total QALYs per strategy	Cost-effectiveness: NMB at £20,000 threshold (highest NMB= most cost effective treatment option)	Uncertainty
Sensitivity analysis of the original cost-utility analysis conducted for the guideline	Directly Applicable[a]	Minor limitations[b]	In the base-case model, the cost of PGA was calculated by taking a weighted average of the different PGA medications prescribed within the PGA drug class. The weighted average estimated that one month of PGA medication would cost £5.52. For this sensitivity analysis, the cost of generic PGA (Latanoprost), £1.54 per month was used for the cost per month of PGA mediation.	**IOP ≥21 and <25** ***CCT low*** No treatment=£3,809 βB=£3,619 PGA=£3,435 ***CCT intermediate*** No treatment=£2,802 βB=£2,799 PGA=£2,620 ***CCT high*** No treatment=£1,665 βB=£1,902 PGA=£1,731 **IOP >25** ***CCT low*** No treatment=£5,644 βB=£5,181 PGA=£4,995 ***CCT intermediate***	**IOP ≥21 and <25** ***CCT low*** No treatment=12.55 βB=12.61 PGA=12.61 ***CCT intermediate*** No treatment=12.66 βB=12.71 PGA=12.71 ***CCT high*** No treatment=12.79 βB=12.81 PGA=12.81 **IOP >25** ***CCT low*** No treatment=12.33 βB=12.42 PGA=12.43 ***CCT intermediate***	**IOP ≥21 and <25** ***CCT low*** No treatment=£247,096 βB=£248,537 PGA=£248,850 ***CCT intermediate*** No treatment=£250,489 βB=£251,371 PGA=£251,639 ***CCT high*** No treatment=£254,170 βB=£254,350 PGA=£254,565 **IOP >25** ***CCT low*** No treatment=£241,029 βB=£243,253 PGA=£243,619 ***CCT intermediate***	The sensitivity analysis was probabilistic and 2,500 simulations were run to estimate the results of this sensitivity analysis.

Study	Applicability	Limitations	Other comments	Total cost per strategy	Total QALYs per strategy	Cost-effectiveness: NMB at £20,000 threshold (highest NMB= most cost effective treatment option)	Uncertainty
				No treatment=£3,295 βB=£3,198 PGA=£3,016 ***CCT high*** No treatment=£2,250 βB=£2,359 PGA=£2,184	No treatment=12.61 βB=12.66 PGA=12.67 ***CCT high*** No treatment=12.72 βB=12.76 PGA=12.76	No treatment=£248,856 βB=£250,021 PGA=£250,309 ***CCT high*** No treatment=£252,204 βB=£252,770 PGA=£25,3018	

Abbreviations: ϐB: beta-blockers; CCT: Central Corneal Thickness; COAG: Chronic Open-Angle Glaucoma; OHT: Ocular Hypertension; PGA: prostaglandin analogues; QALY: quality-adjusted life years; µm: micro-meters

(a) The population, comparators and outcomes were directly applicable to the review question.

(b) The highest weighted study in the NMA conducted on the treatment effect feeding into the model came from a high-risk population. The study used to estimate the baseline risk of progression had an inclusion criteria of people having an IOP≥24 mmHg; however, the model population was technically all people diagnosed with OHT, which in practice, is anyone with an IOP consistently above 21mmHg.The model assumed that people would be correctly diagnosed with OHT prior to being given treatment. In reality, due to the dynamic nature of IOP and the inaccuracy in measuring IOP (even with the reference standard GAT), many people would require monitoring prior to either being discharged or given treatment. Some people will end up having false positive or false negative diagnoses; however, these scenarios were not incorporated into the model as the clinical review used GAT as the reference standard and assumed 100% diagnostic accuracy.

9.1.5 Evidence statements

Clinical

Eleven studies were added to the previous 34 studies included in the original glaucoma guideline. The studies included comparisons of different classes of medicine including beta-blockers, prostaglandin analogues, sympathomimetics and carbonic anhydrase inhibitors with each other, no treatment or a placebo. Fixed combinations and separate combinations of these medicines were also compared with monotherapy. Evidence was also found comparing preservative free medicines with medicines containing preservatives.

The evidence from these studies ranged from very low to high quality. This was based on a number of contributory factors including risk of bias, imprecision due to wide confidence intervals, indirectness of the outcomes or population and inconsistency in the point estimate of meta-analysed outcomes. The majority of the high quality evidence was found for outcomes reporting change in IOP from baseline or the number of people achieving a specific level of IOP reduction in a number of comparisons. High quality evidence was also found for treatment discontinuation. A clinical benefit was found between prostaglandin analogues versus no treatment; carbonic anhydrase inhibitors versus no treatment and sympathomimetics versus beta-blockers for the outcomes visual field progression and conversion to COAG but this evidence was rated as moderate to very low quality.

The committee discussed the potential influence of publication bias on the direction and magnitude of the study results. Funnel plots that were constructed to assess against potential publication bias for outcomes containing more than 5 studies, showed no significant effect being observed (appendix K). No evidence was found for the outcomes: optic nerve head damage, progression of optic nerve head damage, normal or suspicious to abnormal optic nerve head, health related quality of life, vision loss, normal visual field to visual field defect and glaucoma visual field loss. Where studies reported both allergic reaction and hyperaemia, we only extracted allergic reaction to avoid over-reporting of these outcomes. The results of the NMA showed that prostaglandin analogues were the most clinically effective treatment for lowering IOP.

Economic

One original cost–utility analysis found that for treating OHT:

- Base-case results
    - 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/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/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/QALY gained. PGA was not cost effective compared to BB producing an ICER of £118,620.08/QALY gained.
    - In people with an IOP≥25 mmHg and central corneal thickness low: <555µm, BB dominated no treatment. PGA was cost effective compared to beta-blockers producing an ICER of £18,899.01/QALY gained.
    - In people with an IOP≥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 £46,531.63/QALY gained.

- In people with an IOP≥25 mmHg and central corneal thickness high: >590µm, beta-blockers dominated no treatment. PGA was not cost effective compared to BB producing an ICER of £80,924.14/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/QALY gained.

- The results of a sensitivity analysis on the cost of PGA (SA7) found that the generic prostaglandin analogue (Latanoprost) dominated beta-blockers and no treatment for all central corneal thickness subgroups for both IOP groups, people with IOP between >21 and <25 mmHg and people with IOP≥25 mmHg.

9.2 Laser treatment for COAG

9.2.1 Selective laser trabeculoplasty versus argon laser trabeculoplasty

See the study evidence tables in appendix H and the forest plots in appendix K.

9.2.1.1 Clinical evidence

Table 68: Selective laser trabeculoplasty vs. argon laser trabeculoplasty - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 12 months)30	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Number of patients with an unacceptable IOP (follow up 12 months)30	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: PAS formation 30	1	RCT (a)	Serious limitations (b)	No Serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)

(a) Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007. [128]
(b) Randomisation and allocation concealment are adequate but masking of outcome assessment is not reported.
(c) Wide confidence interval making estimate of effect uncertain.
(d) All patients were maintained on current IOP lowering medications throughout study and some patients previously received ALT treatment.

2009

Table 69: Selective laser trabeculoplasty vs. argon laser trabeculoplasty - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	89	87	not applicable	MD 0.18 (-1.45 to 1.81)	Moderate
Number of patients with an unacceptable IOP	35/89 (39.3%)	27/87 (31%)	1.27 (0.84 to 1.90)	84 more per 1000 (from 50 fewer to 249 more)	Low
Complications: PAS formation	1/89 (1.1%)	1/87 (1.1%)	0.98 (0.06 to 15.38	0 fewer per 1000 (from 10 fewer to 158 more)	Low

9.2.1.2 Economic evidence

No studies were identified.

9.2.1.3 Patient views evidence

No studies were identified.

9.2.1.4 Evidence statements - Selective laser trabeculoplasty vs. argon laser trabeculoplasty

Clinical	There were no studies that reported number of patients with visual field progression. There is no statistically significant difference between SLT and ALT in reducing IOP from baseline at 12 months follow up. (MODERATE QUALITY) There is no statistically significant difference between SLT and ALT in number of patients with an unacceptable IOP at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between SLT and ALT in PAS formation at 12 months follow up. (LOW QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared argon laser trabeculoplasty to selective laser trabeculoplasty.

9.2.2 Laser trabeculoplasty versus pharmacological treatment

See the study evidence tables in appendix H and the forest plots in appendix K.

9.2.2.1 Clinical evidence

Table 70: Laser trabeculoplasty vs. pharmacological treatment - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up	3	RCT (a)	Serious limitations (b)	No serious inconsistency	Serious indirectness (c)	Serious imprecision (d) Additional notes (e)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
2 to 48 months)45,98,104						
Complications	0					

(a) Studies are supplemented by data from the Cochrane systematic review Rolim 2007[128].
(b) Allocation concealment and randomisation methods are not reported in one study[44] and masking of outcome assessment is not reported in any of the studies.
(c) One study[97] included 51% OHT patients.
(d) Wide confidence interval making estimate of effect uncertain.
(e) Although there was no statistical heterogeneity observed other differences between studies were noted in length of follow up, IOP failure criteria, laser modality, laser degrees of treatment, class of medications, mean baseline IOP and COAG population (previously untreated or treated). One study[97] tested different in laser degrees of treatment against prostaglandin analogues. For the purposes of comparison, the 360 degree was selected.

Table 71: Laser trabeculoplasty vs. pharmacological treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	32/115 (27.8%)	22/111 (19.8%)	1.37 (0.86 to 2.17)	73 more per 1000 (from 28 fewer to 232 more)	Very Low

2009

9.2.2.2 Economic evidence

No studies were identified.

9.2.2.3 Patient views evidence

No studies were identified.

9.2.2.4 Evidence statements - Laser trabeculoplasty vs. pharmacological treatment

Clinical	There were no studies that reported number of patients with visual field progression. There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation. There is no statistically significant difference between laser trabeculoplasty and pharmacological treatment in terms of number of patients with an unacceptable IOP at 2 to 48 months follow up. (VERY LOW QUALITY) There were no studies that reported complications lasting longer than 1 week.
Economic	No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty to pharmacological treatment.

9.2.3 Laser trabeculoplasty plus pharmacological treatment versus pharmacological treatment

See the study evidence tables in appendix H and the forest plots in appendix K.

9.2.3.1 Clinical evidence

Table 72: Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment- Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months)[96,136]	2	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Complications	0					

(a) *Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007.*[128]
(b) *Allocation concealment, randomisation methods and masking of outcome assessment are not reported in one study.*[96]
(c) *I-squared value of 81% indicates high statistical heterogeneity, which may have been due to the studies being from very different populations. One study*[96] *is exclusively in Afro-Caribbean patients. Variations between studies are also noted in laser degrees of treatment and mean baseline IOP.*
(d) *Wide confidence interval making estimate of effect uncertain.*

2009

Table 73: Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	10/49 (20.4%)	41/46 (89.1%)	0.22 (0.05 to 1.00)	695 fewer per 1000 (from 846 fewer to 0 more)	Very Low

9.2.3.2 Economic evidence

No studies were identified.

9.2.3.3 Patient views evidence

No studies were identified.

9.2.3.4 Evidence statements - Laser trabeculoplasty + pharmacological treatment vs. pharmacological treatment

Clinical	There were no studies that reported number of patients with visual field progression. There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation. There is no statistically significant difference between laser trabeculoplasty + pharmacological treatment and pharmacological treatment alone in terms of

	number of patients with an unacceptable IOP at 12 months follow up. (VERY LOW QUALITY) There were no studies that reported complications lasting longer than 1 week.
Economic	No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty + pharmacological treatment to pharmacological treatment.

9.2.4 Laser trabeculoplasty versus trabeculectomy

See the study evidence tables in appendix H and the forest plots in appendix K.

9.2.4.1 Clinical evidence

Table 74: Laser trabeculoplasty vs. trabeculectomy - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 0 - 6 months) [2,91]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Number of patients with an unacceptable IOP (follow up 3 - 24 months)[2,91]	2	RCT (a)	No serious limitations (b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision Additional notes (d)
Complications	0					

(a) Studies are supplemented by data from the Cochrane systematic reviews Rolim 2007.[128]
(b) One study[91] *does not report masking of outcome assessment.*
(c) Although there is no statistical heterogeneity observed at 0 – 6 months follow up, the I-squared value is high (51%) for 3 – 24 months follow up.
(d) Differences between studies are noted in IOP failure criteria, laser degrees of treatment and mean baseline IOP.

Table 75: Laser trabeculoplasty vs. trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP (follow up 0 - 6 months)	34/419 (8.1%)	10/400 (2.5%)	3.14 (1.60 to 6.18)	54 more per 1000 (from 15 more to 130 more)	Moderate
Number of patients with an	72/459 (15.7%)	34/442 (7.7%)	2.03 (1.38 to 2.98)	79 more per 1000 (from 29 more to	Low

2009

Outcome	Interventio n	Control	Relative risk	Absolute effect	Quality
unacceptable IOP (follow up 3 - 24 months)				152 more)	

9.2.4.2 Economic evidence

No studies were identified.

9.2.4.3 Patient views evidence

No studies were identified.

9.2.4.4 Evidence statements - Laser trabeculoplasty vs. trabeculectomy

Clinical	There were no studies that reported number of patients with visual field progression. There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation. Laser trabeculoplasty is less effective than trabeculectomy in reducing the number of patients with an unacceptable IOP at 0 to 6 months follow up. (MODERATE QUALITY) Laser trabeculoplasty is less effective than trabeculectomy in reducing the number of patients with an unacceptable IOP at 3 to 24 months follow up. However, there is significant unexplained statistical heterogeneity within the results. (LOW QUALITY) There were no studies that reported complications lasting longer than 1 week.
Economic	No studies meeting the inclusion criteria were identified which compared laser trabeculoplasty to trabeculectomy.

9.3 Surgical Treatment for COAG

9.3.1 Trabeculectomy versus pharmacological treatment

See the study evidence tables in appendix H, forest plots in appendix K and the economic model in appendix N.

9.3.1.1 Clinical evidence

Table 76: Trabeculectomy vs. pharmacological treatment- Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression (follow up 1 to 5 years)[61,91]	2	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	Serious imprecision (d) Additional notes (e)
Mean change in IOP from baseline (follow	3	RCT (a)	Serious limitations (b)	Serious inconsistency (c)	No serious indirectness	No serious imprecision Additional notes (e)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
up 12 months) [61,83 , 91]						
Mean change in IOP from baseline (follow up 1 to 5 years) [83, 91]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d) Additional notes (e)
Mean change in IOP from baseline (follow up >5 years) [83, 91]	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d) Additional notes (e)
Number of patients with an unacceptable IOP (follow up 12 months) [61]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Complications: Cataract formation [61,83,91]	3	RCT (a)	Serious limitations (b)	Not estimable as individual study data not reported	No serious indirectness	No serious imprecision Additional notes (e)

(a) Studies are supplemented by data from the Cochrane systematic review Burr 2004[19].
(b) Randomisation and allocation concealment are adequate for all studies but masking of outcome assessment is not attempted. Attrition bias is noted for 2 studies[83, 91] where treatment failures are excluded from the analysis.
(c) Statistically significant heterogeneity possibly due to differences in types of medications, classification methods for visual field changes and length of follow up.
(d) For visual field progression in the medium term and IOP failure at 12 months, wide confidence intervals make estimate of effect uncertain. For mean change in IOP from baseline in the medium and long term, the lower confidence interval is clinically insignificant.
(e) Other differences in study populations are noted in baseline IOP, severity of COAG and race.

Table 77: Trabeculectomy vs. pharmacological treatment - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Visual field progression	47/98 (48%)	52/97 (53.6%)	0.81 (0.38 to 1.73)	102 fewer per 1000 (from 332 fewer to 391 more)	Very Low
Mean change in IOP from baseline (follow up 12 months)	397	388	not applicable	MD -4.92 (-6.93 to -2.91)	Low
Mean change in IOP from baseline (follow up 1 to 5 years)	326	285	not applicable	MD -2.04 (-2.85 to -1.23)	Low
Mean change in IOP from baseline (follow up >5 years)	257	229	not applicable	MD -2.15 (-3.10 to -1.19)	Low
Number of patients with an unacceptable IOP	7/46 (15.2%)	17/53 (32.1%)	0.47 (0.22 to 1.04)	170 fewer per 1000 (from 250 fewer to 13 more)	Low

2009

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Complications: Cataract formation	57/403 (14.1%)	24/406 (5.8%)	2.45 (1.55 to 3.87	82 more per 1000 (from 32 more to 166 more)	Not estimable (a)

(a) Figures taken from the systematic review[19]. Data not provided for individual studies consequently no forest plot is provided in this guideline's appendices.

2009

9.3.1.2 Economic evidence

We found a cost analysis comparing early trabeculectomy (within 4 weeks of diagnosis) to medical management. See economic evidence table in appendix I for details.

In CG85, an original model was constructed to compare various strategies for the first-choice treatment of COAG patients, including trabeculectomy and pharmacological treatment with beta-blockers and prostaglandin analogues. Surgical treatments have not been updated in this guideline update; therefore, the cost-effectiveness of surgery versus pharmacological treatments has not been evaluated in this update. Please see appendix P for the CG85 COAG model.

We also constructed an original model to compare various strategies for the first-choice treatment of COAG patients, including trabeculectomy and pharmacological treatment with beta-blockers and prostaglandin analogues. This was based on clinical evidence comparing trabeculectomy to beta-blockers (see 9.3.1.1).

Table 78: Trabeculectomy vs. pharmacological treatment - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Ainsworth 1991[3] (a)	Serious limitations (b)	Partially applicable (c)	Early trabeculectomy was compared to conventional management: up to a maximum of three different topical or systemic drugs and late trabeculectomy if medical therapy has failed.
NCC-AC model	Minor limitations	Directly applicable	

2009

a) Based on the RCT Jay1988[61] – see clinical evidence in 9.3.1.1
b) Not a full economic evaluation.
c) Average length of stay after surgery was 7.6 days and therefore longer than the current average.

Table 79: Trabeculectomy vs. pharmacological treatment - Economic summary of findings

Study	Incremental cost (£)	Incremental effects	ICER (£/QALY)	Uncertainty
Ainsworth 1991[3]	cost saving (a)	NR	NA	Incremental cost per unilateral COAG patient is £219.
Early COAG				
NCC-AC model Trabeculectomy vs BB	1,230	0.135 QALY	9,113	95% CI (£/QALY): cost saving – 85,631 Results sensitive to probability of progression: if <6% per year (~0.18 dB/year) treatment with

Study	Incremental cost (£)	Incremental effects	ICER (£/QALY)	Uncertainty
				BB is more cost effective. Results also sensitive to cost of surgery and age.
NCC-AC model Trabeculectomy vs PGA	1,134	0.104 QALY	10,906	95% CI (£/QALY): cost saving – 122,050 Results sensitive to probability of progression: if <6% per year (~0.18 dB/year) treatment with PGA is more cost effective. Results also sensitive to cost of surgery and age.
Moderate COAG				
NCC-AC model Trabeculectomy vs BB	397	0.218	1,822	If progression is <2% per year (~0.08dB/year) treatment with BB is more cost-effective. Results are sensitive to age.
NCC-AC model Trabeculectomy vs PGA	363	0.165 QALY	2,194	If progression is <2% per year (0.08dB/year) treatment with PGA is more cost-effective. Results are sensitive to age.
Advanced COAG				
NCC-AC model Trabeculectomy vs BB	cost saving	0.307 QALY	cost saving	Results are not sensitive to progression rate or age.
NCC-AC model Trabeculectomy vs PGA	cost saving	0.233 QALY	cost saving	Results are not sensitive to progression rate or age.

a) In bilateral COAG patients.

2009

9.3.1.3 Patient views evidence

No studies were identified.

9.3.1.4 Evidence statements - Trabeculectomy vs. pharmacological treatment

Clinical	There is no statistically significant difference between visual field progression for the comparison of trabeculectomy and pharmacological treatment. (VERY LOW QUALITY) Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at 12 months follow up. (LOW QUALITY) Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at 1 to 5 years follow up but the effect size may be too small to be clinically significant. (LOW QUALITY) Trabeculectomy is more effective than pharmacological treatment in reducing IOP from baseline at >5 years follow up but the effect size may be too small to be clinically significant. (LOW QUALITY)

	There is no statistically significant difference in number of patients with an unacceptable IOP for the comparison of trabeculectomy and pharmacological treatment at 12 months follow up. (LOW QUALITY) Trabeculectomy causes more cataracts than pharmacological treatment (QUALITY NOT ESTIMABLE)
Economic	In COAG patients, trabeculectomy is more cost-effective than pharmacological treatment. However, this result is sensitive to the progression rate for patients in the early stages of COAG. This evidence has minor limitations and direct applicability.

9.3.2 Trabeculectomy plus pharmacological augmentation versus trabeculectomy

See the study evidence tables in appendix H and the forest plots in appendix K.

9.3.2.1 Clinical evidence

Table 80: Trabeculectomy + pharmacological augmentation vs. trabeculectomy - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months) [30,37 ,47,88 ,110,120,127,147]	8	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Cataract Formation (follow up 9-18 months) [30,37 ,47,81,88,120,127,147]	8	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Persistent hypotony (follow up 9-18 months) [30,37 ,47,81,88,120,147]	7	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Wound leak (follow up 9-18 months) [30,37 ,47,81,120,147]	6	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)
Complications: Corneal epithelial defects (follow	5	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
up 9-18 months) [37,47,81,110,147]						Additional notes (d)

(a) Studies are supplemented by data from the Cochrane systematic reviews Wilkins 2005[163] and Wormald 2001[165].

(b) For the antimetabolite MMC: 3 studies do not report details of randomisation method.[30,127,147] 3 studies do not report details of allocation concealment.[88,120,147] 3 studies do not report masking of outcome assessment[30,120,147]. Only 2 studies were placebo controlled[30,147]. For the antimetabolite 5-FU: 2 studies do not report details of randomisation method[37, 110]*. 3 studies do not report details of allocation concealment, masking of outcome assessment and are not placebo controlled[37,47, 110]. One study[81] is a placebo controlled double blind design.*

(c) Wide confidence intervals making estimate of effect uncertain.

(d) Although there is no statistical heterogeneity observed other differences between studies are noted in type of antimetabolite (MMC or 5-FU) used and dosage, delivery method of 5-FU (intraoperative or postoperative injections), IOP failure criteria, length of follow up, reporting of complications, proportion of patients with closed-angle glaucoma of <50%, mean baseline IOP and whether patients received previous laser treatment. One study[37] is exclusively in Afro-Caribbean patients and one study[127] is exclusively in patients from the Indian sub-continent.

Table 81: Trabeculectomy + pharmacological augmentation vs. trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	35/337 (10.4%)	82/218 (37.6%)	0.33 (0.23 to 0.47)	252 fewer per 1000 (from 199 fewer to 290 fewer)	Moderate
Complications: Cataract Formation	56/335 (16.7%)	19/210 (9.0%)	1.61 (0.96 to 2.70)	55 more per 1000 (from 4 fewer to 153 more)	Low
Complications: Persistent hypotony	12/169 (7.1%)	3/155 (1.9%)	2.60 (0.97 to 6.97)	30 more per 1000 (from 1 fewer to 113 more)	Low
Complications: Wound leak	26/139 (18.7%)	11/125 (8.8%)	2.02 (1.06 to 3.84)	90 more per 1000 (from 5 more to 250 more)	Low
Complications: Corneal epithelial defects	32/125 (25.6%)	6/111 (5.4%)	3.75 (1.76 to 7.99	149 more per 1000 (from 41 more to 337 more)	Low

2009

9.3.2.2 Economic evidence

No studies were identified.

9.3.2.3 Patient views evidence

No studies were identified.

9.3.2.4 Evidence statements - Trabeculectomy + pharmacological augmentation vs. trabeculectomy

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

	There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation. Trabeculectomy + pharmacological augmentation is more effective than trabeculectomy alone in reducing the number of eyes with an unacceptable IOP at 12 month follow up. (MODERATE QUALITY). There is no statistically significant difference between trabeculectomy + pharmacological augmentation and trabeculectomy alone in causing cataract formation at 9 to 18 months follow up. (LOW QUALITY). There is no statistically significant difference between trabeculectomy + pharmacological augmentation and trabeculectomy alone in causing persistent hypotony at 9 to 18 months follow up. (LOW QUALITY) Trabeculectomy + pharmacological augmentation is more likely to cause wound leaks than trabeculectomy alone at 9 to 18 months follow up. (LOW QUALITY) Trabeculectomy + pharmacological augmentation is more likely to cause corneal epithelial defects than trabeculectomy alone at 9 to 18 months follow up. (LOW QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared trabeculectomy + pharmacological augmentation to trabeculectomy alone.

9.3.3 Trabeculectomy plus antimetabolite drug MMC versus antimetabolite drug 5-FU

See the study evidence tables in appendix H and the forest plots in appendix K.

9.3.3.1 Clinical evidence

Table 82: Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline	0					
Number of patients with an unacceptable IOP (follow up 12 months)[139,169]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Cataract Formation IOP (follow up 12 months) [139]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Persistent hypotony IOP (follow up 12 months) [139,169]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)
Complications: Wound leak IOP	2	RCT	Serious limitation	No serious inconsistency	No serious indirectness	Serious imprecision (b)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
(follow up 12 months) [139,169]			s (a)			Additional notes (c)
Complications: Corneal epithelial defects IOP (follow up 12 months)[169]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b) Additional notes (c)

(a) One study[139] reports adequate randomisation methods but neither study reports allocation concealment. Masking of outcome assessment is only performed in one study[169].

(b) Wide confidence intervals make estimate of effect uncertain.

(c) Although there no statistical heterogeneity is observed, other differences between studies are noted in antimetabolite dosage, delivery method of 5-FU (intraoperative or postoperative injections), IOP failure criteria, length of follow up, reporting of complications and mean baseline IOP. One study[139] was exclusively in Afro-Caribbean patients.

Table 83: Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP	5/54 (9.3%)	13/47 (27.7%)	0.34 (0.13 to 0.88)	183 fewer per 1000 (from 33 fewer to 241 fewer)	Low
Complications: Cataract Formation	3/44 (6.8%)	3/37 (8.1%)	0.84 (0.18 to 3.92)	13 fewer per 1000 (from 66 fewer to 237 more)	Low
Complications: Persistent hypotony	2/54 (3.7%)	3/47 (6.4%)	0.63 (0.13 to 3.11)	24 fewer per 1000 (from 56 fewer to 135 more)	Low
Complications: Wound leak	2/54 (3.7%)	2/47 (4.3%)	1.00 (0.17 to 5.77)	0 fewer per 1000 (from 36 fewer to 205 more)	Low
Complications: Corneal epithelial defects	0/10 (0%)	3/10 (30%)	0.14 (0.01 to 2.45)	258 fewer per 1000 (from 297 fewer to 435 more)	Low

2009

9.3.3.2 Economic evidence

No studies were identified.

9.3.3.3 Patient views evidence

No studies were identified.

9.3.3.4 Evidence statements - Trabeculectomy + antimetabolite drug MMC versus antimetabolite drug 5-FU

Clinical	There were no studies that reported number of patients with visual field progression. There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation.

	Trabeculectomy + antimetabolite drug MMC is more effective than antimetabolite drug 5-FU in reducing the number of patients with an unacceptable IOP at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in cataract formation at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing persistent hypotony at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing wound leaks at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between trabeculectomy + antimetabolite drug MMC and antimetabolite drug 5-FU in causing corneal epithelial defects at 12 months follow up. (LOW QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared trabeculectomy + antimetabolite drug MMC to antimetabolite drug 5-FU.

9.3.4 Viscocanalostomy versus deep sclerectomy

See the study evidence tables in appendix H and the forest plots in appendix K.

9.3.4.1 Clinical evidence

Table 84: Viscocanalostomy versus deep sclerectomy - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months)[38]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Number of patients with an unacceptable IOP	0					
Complications	0					

(a) Randomisation method, allocation concealment and masking of outcome assessment are not reported.
(b) Confidence intervals are wide making estimate of effect uncertain.

Table 85: Viscocanalostomy versus deep sclerectomy - Clinical summary of findings

Table Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline	12	10	not applicable	MD 2.79 (-2.95 to 8.53)	Low

2009

9.3.4.2 Economic evidence

No studies were identified.

9.3.4.3 Patient views evidence

No studies were identified.

9.3.4.4 Evidence statements - Viscocanalostomy versus deep sclerectomy

Clinical	There were no studies that reported number of patients with visual field progression. There is no statistically significant difference between viscocanalostomy and deep sclerectomy in reducing IOP from baseline at 6 months follow up. (LOW QUALITY) There were no studies that reported number of patients with an unacceptable IOP. There were no studies that reported complications.
Economic	No studies meeting the inclusion criteria were identified which compared viscocanalostomy to deep sclerectomy.

9.3.5 Non-penetrating surgery versus trabeculectomy

See the study evidence tables in appendix H and the forest plots in appendix K.

9.3.5.1 Clinical evidence

Table 86: Non-penetrating surgery versus trabeculectomy - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field progression	0					
Mean change in IOP from baseline (follow up 6 months) [24,25 ,26 , 38,39,63 ,73,84,167, 168]	10	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c) Additional notes (d)
Mean change in IOP from baseline (follow up 12 months) [24,25 ,26 , 39,73,84,167, 168]	8	RCT	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	Serious imprecision (c) Additional notes (d)
Number of eyes with an unacceptable IOP (follow up 6 or 12 months) [24,25 ,26 , 39,63 ,73,84,167, 168]	9	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Cataract Formation (follow up 12 – 36	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
months) [25,26, 39,73,84,167,168]						
Complications: Persistent hypotony (follow up 12 – 36 months) [24,26, 39,73,84,167, 168]	7	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision Additional notes (d)
Complications: Wound leak (follow up 6 - 12 months) [39,63]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c) Additional notes (d)

(a) Only 3 studies report adequate randomisation methods[26, 73,168] and only 2 studies report allocation concealment[24,168]. Only 2 studies report masking of outcome assessment[25,26], but all studies report low or zero dropout rates.

(b) Some statistical heterogeneity is noted in mean change in IOP from baseline at 6 and 12 months, which is not satisfactorily explained by subgroup analysis for type of non-penetrating surgery, use of augmentation or presence of PXF in population.

(c) For mean change in IOP from baseline at 6 and 12 months, the lower confidence interval is clinically insignificant. For complications: wound leak wide confidence intervals make estimate of effect uncertain.

(d) Other differences between studies are noted in non-penetrating surgery type (viscocanalostomy or deep sclerectomy with or without implant); use of augmentation; study design where 3 studies[25,73,168] randomised fellow eyes to treatment; IOP failure criteria; length of follow up from 6 months to 2 years; reporting of complications and mean baseline IOP. 5 studies[24,26,38,84,168] included a proportion of patients diagnosed with PXF and one study[168] included some CACG patients but <50%.

2009

Table 87: Non-penetrating surgery versus trabeculectomy - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Mean change in IOP from baseline (follow up 6 months)	222	226	not applicable	MD 2.57 (1.35 to 3.80) (e)	VERY LOW
Mean change in IOP from baseline (follow up 12 months)	202	204	not applicable	MD 2.45 (1.46 to 3.44)	VERY LOW
Number of eyes with an unacceptable IOP	88/208 (42.3%)	52/210 (24.8%)	1.70 (1.30 to 2.23)	174 more per 1000 (from 74 more to 305 more)	MODERATE
Complications: Cataract Formation	4/177 (2.3%)	31/179 (17.3%)	0.20 (0.09 to 0.44)	138 fewer per 1000 (from 97 fewer to 157 fewer)	MODERATE
Complications: Persistent hypotony	8/184 (4.3%)	39/187 (20.9%)	0.25 (0.13 to 0.48)	157 fewer per 1000 (from 109 fewer to 182 fewer)	MODERATE
Complications: Wound leak	1/49 (2%)	4/49 (8.2%)	0.33 (0.05 to 2.02)	55 fewer per 1000 (from 78 fewer to 84 more)	LOW

(e) One study[38] included 3 arms, viscocanalostomy, deep sclerectomy and trabeculectomy. The data for trabeculectomy is added twice meaning there is some double counting. The overall effect to the weighted mean difference is around 0.1mmHg.

9.3.5.2 Economic evidence

No studies were identified.

9.3.5.3 Patient views evidence

No studies were identified.

9.3.5.4 Evidence statements - Non-penetrating surgery versus trabeculectomy

Clinical	There were no studies that reported number of patients with visual field progression. Trabeculectomy is more effective than non-penetrating surgery in reducing IOP from baseline at 6 months follow up but the effect size may be too small to be clinically significant. (VERY LOW QUALITY) Trabeculectomy is more effective than non-penetrating surgery in reducing IOP from baseline at 12 months follow up but the effect size may be too small to be clinically significant. (VERY LOW QUALITY) Trabeculectomy is more effective than non-penetrating surgery in reducing the number of eyes with an unacceptable IOP at either 6 or 12 months' follow up. (MODERATE QUALITY) Trabeculectomy is more likely to cause cataract formation than non-penetrating surgery at 12 to 36 months follow up. (MODERATE QUALITY) Trabeculectomy is more likely to cause persistent hypotony than non-penetrating surgery at 12 to 36 months follow up. (MODERATE QUALITY) There is no statistically significant difference between trabeculectomy and non-penetrating surgery in causing wound leaks at 6 to 12 months follow up. (LOW QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared non-penetrating surgery to trabeculectomy.

9.3.6 Non-penetrating surgery plus pharmacological augmentation versus non-penetrating surgery

See the study evidence tables in appendix H and the forest plots in appendix K.

9.3.6.1 Clinical evidence

Table 88: Non-penetrating surgery + pharmacological augmentation vs. non-penetrating surgery - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Visual field Progression	0					
Mean change in IOP from baseline	0					
Number of patients with	1	RCT	Serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
an unacceptable IOP (follow up 12 months)[106]			(a)			
Number of patients with an unacceptable IOP (follow up 24 months) [106]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Complications: Persistent hypotony (follow up 24 months) [106]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Complications: Wound leak (follow up 24 months) [106]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (b)

(a) Randomisation method, allocation concealment and masking of outcome assessment are not reported and the study is not placebo controlled. Despite randomisation baseline, IOP was 5 mmHg higher in the MMC group.

(b) Wide confidence intervals make estimate of effect uncertain.

Table 89: Non-penetrating surgery + pharmacological augmentation vs. non-penetrating surgery - Clinical summary of findings

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Number of patients with an unacceptable IOP (follow up 12 months)	0/13 (0%)	2/13 (15.4%)	0.2 (0.01 to 3.80)	123 fewer per 1000 (from 152 fewer to 431 more)	Low
Number of patients with an unacceptable IOP (follow up 24 months)	1/13 (7.7%)	1/13 (7.7%)	1.00 (0.07 to 14.34)	0 fewer per 1000 (from 72 fewer to 1000 more)	Low
Complications: Persistent hypotony	0/13 (0%)	0/13 (0%)	Not estimable	Not estimable	Low
Complications: Wound leak	0/13 (0%)	0/13 (0%)	Not estimable	Not estimable	Low

2009

9.3.6.2 Economic evidence

No studies were identified.

Patient views evidence

No studies were identified.

9.3.6.3 Evidence statements - Non-penetrating surgery plus pharmacological augmentation vs. non-penetrating surgery

Clinical	There were no studies that reported number of patients with visual field progression. There were no studies that reported mean change in IOP from baseline expressed as an absolute value with standard deviation. There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in reducing the number of patients with unacceptable IOP at 12 months follow up. (LOW QUALITY) There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in reducing the number of patients with an unacceptable IOP at 24 months follow up. (LOW QUALITY) There were no studies that reported number of patients with cataract progression. There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in causing persistent hypotony at 24 months follow up. (LOW QUALITY) There is no statistically significant difference between non-penetrating surgery + pharmacological augmentation and non-penetrating surgery alone in causing wound leaks at 24 months follow up. (LOW QUALITY) There were no studies that reported corneal epithelial defects.
Economic	No studies meeting the inclusion criteria were identified which compared non-penetrating surgery + pharmacological augmentation to non-penetrating surgery alone.

2009

9.4 Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion

Patients with COAG or OHT associated with pseudoexfoliation or pigment dispersion were included in the scope for this guideline. We searched for evidence of effectiveness of treatments but no studies were found either in these groups alone or as part of subgroup analysis within the comparisons listed above. Therefore, the GDG decided not to make a specific recommendation regarding these patients. Patients should be treated according to the recommendations used for COAG patients.

9.5 Recommendations and link to evidence

Recommendations	**30. Take into account any cognitive and physical impairments when making decisions about management and treatment. [2017]**

	Treatment for people with OHT **31. Offer a generic prostaglandin analogue (PGA)[17] to people with IOP of 24 mmHg or more (OHT) if they are at risk of visual impairment within their lifetime (see recommendation 12). [2017]** **32. Do not offer treatment to people with OHT who are not at risk of visual impairment in their lifetime. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]** **33. Offer another pharmacological treatment to people with an IOP of 24 mmHg or more who cannot tolerate their current treatment. The first choice should be an alternative generic PGA, if available, and if this is not tolerated, offer a beta-blocker. If none of these options is tolerated, offer non-generic PGA, carbonic anhydrase inhibitors, sympathomimetics, miotics or a combination of treatments. [2017]** **Treatment for people with suspected COAG** **34. Do not offer treatment to people with suspected COAG and IOP less than 24mmHg. Advise people to continue regular visits to their primary eye care professional, at clinically appropriate intervals. [2017]** **35. Offer a generic PGA[18] to people with suspected COAG and IOP of 24 mmHg or more, in line with the recommendations on treatment for people with OHT. [2017]** **Treatment for people with COAG** **36. Offer a generic PGA[19] to people with COAG. [2017]**
Research recommendations	**4. What is the clinical and cost effectiveness of treating an intraocular pressure (IOP) of 22 or 23 mmHg?** **5. What instrument should be used to measure health-related quality of life in people with glaucoma?**
Relative values of different	The committee agreed that the critical outcomes for decision-making were glaucomatous visual field loss, deterioration of normal visual field to visual field defect, progression of

[17] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[18] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[19] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

outcomes	glaucomatous visual field defect, vision loss, health-related quality of life and adverse events including allergic reaction or intolerance (including hyperaemia), breathing difficulties and cardiovascular events. The committee agreed that the important outcomes for decision-making were optic nerve head damage, progression of optic nerve head damage, normal or suspicious-to-abnormal optic nerve head, IOP level, treatment adherence and treatment discontinuation. Adverse events relating to allergic reaction or intolerance and hyperaemia were often defined in a similar way depending on the study. To avoid double counting, allergic reaction or intolerance outcomes were extracted primarily, and then hyperaemia outcomes were extracted if no allergic reaction or intolerance outcomes were reported by the same study. Glaucomatous visual field loss was considered to be of the greatest value for decision-making regarding treatment and was therefore designated as the outcome of choice for inclusion within the network meta-analysis (NMA). However, due to a paucity of evidence regarding this outcome, the committee agreed that IOP was an appropriate proxy outcome for inclusion within the NMA if there was insufficient evidence for the outcome of glaucomatous visual field loss. This is based on the assumption that pharmacological treatments will lower IOP, which in turn will reduce glaucomatous visual field loss (see chapter 8).
Quality of the clinical evidence	Forty-four studies were included in the pharmacological treatment review. The quality of the evidence ranged between very low and high. Studies were predominantly downgraded because of a risk of bias or imprecision due to wide confidence intervals. The committee noted that visual field loss was often not reported by studies. The committee noted that pharmaceutical companies sponsored a proportion of the studies included in the review. Publication bias was therefore assessed through the construction of funnel plots for outcomes of comparisons including 5 or more studies (appendix K). These showed no indication of publication bias. Four studies were included in the NMA conducted to estimate the treatment effect of beta-blockers (BBs) and prostaglandin analogues (PGAs) that fed into the cost-effectiveness analysis. The inclusion criteria for the NMA were that the studies reported a change in IOP from baseline to follow-up appointment, or that this change in IOP could be estimated. The people in the studies were either newly diagnosed or had a washout period of any previous treatment of at least 4 weeks. The largest of the studies was a UK study where people had a mean baseline IOP of at least 30. This study would have been weighted more highly in the NMA than the other smaller studies with lower IOP populations. Therefore, the committee noted that the treatment effect feeding into the model is mostly based on a high IOP population. Please see appendix O for full details of the NMA.
Trade-off between clinical benefits and harms	<u>Treatment for people with OHT and suspected COAG</u> The results of the base-case second analysis (section 1.7 in appendix O), a network meta-analysis on the treatment effect, showed that prostaglandin analogues were the most effective treatment for lowering IOP in people with OHT. PGA produced a mean effect of 3.6 mmHg compared to a mean effect of 3.3 mmHg from beta-blockers. The committee noted that prostaglandin analogue treatment is associated with less adverse effects compared with other treatments. The committee discussed the relative harm associated with BB, in particular respiratory and cardiovascular side effects, and noted that these side effects posed a significant risk and were likely to have an effect on treatment continuation and adherence. Considering this, the committee agreed that based on the updated clinical evidence, prostaglandin analogues are the most clinically effective first-line treatment for people with OHT and suspected COAG. Further rationale for the final recommendation took into consideration the sensitivity analysis in the health economic model regarding the cost effectiveness of the treatments for different IOP and CCT subgroups and consensus on revising the IOP threshold of when to begin treating people for ocular hypertension.

	The previous version of this guideline (CG85) recommended treatment with beta-blockers for people with an untreated IOP of >25 to 32mmHg and a CCT of 555-590 micrometres until the age of 60. For people with a CCT of less than 555 micrometres, PGA was recommended until the age of 65 for people with an untreated IOP of >21 to 25mmHg and until the age of 80 years for an untreated IOP of >25 to 32mmHg. For individuals with an untreated IOP of >32mmHg, it was recommended to treat with prostaglandin analogues regardless of CCT or age. The updated health economic model showed that the generic PGA is cost-effective treatment for all levels of CCT; therefore, treatment decisions do not need to be based on CCT measurements. The committee agreed that it is no longer meaningful to base treatment decisions on CCT and therefore decided to make a treatment recommendation based on IOP independent of CCT. With respect to the previous guideline's age thresholds, please see the next section on net clinical effects and cost for details on the updated cost effectiveness analysis (see appendix N for details) and discussion on the committee's decision to base the recommendation on the risk of visual impairment within a person's lifetime, rather than specify an age threshold. Side effects of topical glaucoma medications may cause significant morbidity for patients. Intolerance to medication is likely to lead to poor adherence. Therefore, an alternative may be required. Both sympathomimetics and carbonic anhydrase inhibitors are only licenced for use if beta-blockers are contraindicated or not tolerated. The clinical evidence showed no clinical difference between the two treatments but that carbonic anhydrase inhibitors are better tolerated than sympathomimetics. A hierarchy was not adopted between the two treatments that should both only be offered if prostaglandin analogues and beta-blockers have both either been contraindicated or not been tolerated. Treatment for people with newly diagnosed COAG and at risk of significant visual loss in their lifetime As there is a scarcity of evidence on glaucomatous visual field loss, the committee believed it was acceptable to extrapolate the results of the OHT treatment model to the COAG population. There is a higher risk of progression to blindness if acceptable control of IOP is not achieved; therefore, it is even more important that people are offered the most effective treatment. The previous guideline recommended treatment with prostaglandin analogues for people with newly diagnosed early or moderate COAG, who are at risk of significant visual loss in their lifetime. Based on the updated clinical and cost-effectiveness evidence, the committee decided to edit the existing recommendation to specify generic prostaglandin analogues, as these were shown to be the most cost-effective treatment for lowering IOP.
Trade-off between net clinical effects and costs	In the original guideline, 2 studies[75,145] were included as health economic evidence in the overview of treatment chapter comparing any treatment to no treatment. These studies were reassessed but due to updates in methodology and stricter inclusion criteria, they were excluded due to limited applicability. The original guideline also included four studies as health economic evidence in the chapter on the treatment for ocular hypertension and suspected chronic open-angle glaucoma,[31,130,131,143] and 1 study in the treatment for chronic open-angle glaucoma chapter.[78] These studies were reassessed but due to updates in methodology and stricter inclusion criteria, they were excluded due to limited applicability or methodological issues. **OHT** ***What treatment to offer:*** Due to reductions in the cost of medications since the previous guideline was published, specifically prostaglandin analogues (PGA) coming off patent, and in light of new clinical evidence on the effectiveness of the medications in lowering IOP, a cost–utility analysis was conducted (based on the OHT treatment model conducted for CG85) to estimate the most cost-effective first line pharmacological treatment strategy (beta-blockers, prostaglandin analogues or no treatment) for people with OHT to help prevent conversion to COAG through the reduction of IOP. BB and PGA are the only pharmacological

treatments licenced as first line treatment options for OHT. The analysis was completed separately for the following OHT subgroups: people with IOP of <25mmHg (referred to as the IOP low group) and people with IOP ≥ 25mmHg (referred to as the IOP high group) as the committee thought the cost effectiveness results might be different for the different subgroups as they have different baseline risks of developing COAG. The committee specifically wanted to see if it was cost effective to treat people with an IOP below 25 mmHg. For each subgroup, the populations were split further into people with CCT <555, 555 – 590, or >590 micrometres. Please see appendix N for full details of the cost-effectiveness analysis methods and results.

The base-case results of the cost–utility analysis estimated that offering everyone (in both the IOP low and high populations) beta-blockers was the most cost-effective treatment strategy compared to offering everyone PGA, not treating anyone or measuring central corneal thickness and giving people the most cost effective treatment according to their specific subgroup (BB for all CCT categories in the IOP low population and BB for CCT less than 555 micrometres and PGA for CCT greater than or equal to 555 micrometres in the IOP high population) at a £20,000 per QALY gained willingness to pay threshold.

In the base-case analysis, the cost of PGA medication per month was calculated as a weighted average of the costs of all drugs prescribed in the UK within the PGA drug class. Currently, 41% of PGAs prescribed are more expensive than the price of generic PGAs. A sensitivity analysis was conducted to see if replacing the weighted average monthly cost of PGAs (£5.52) to the cost of generic PGAs (£1.54) had an effect on the cost-effectiveness results. Using the cost of generic PGAs, offering everyone generic PGAs (and not measuring CCT) became the most cost-effective strategy for both IOP subgroups.

The committee considered the results of this sensitivity analysis alongside the results of the treatment review, taking into account adverse effects from treatments. The committee decided that as generic PGAs are cost effective, associated with fewer adverse effects, and more people are able to tolerate them as a first line treatment option, it would be in the interest of patients and an efficient use of resources to recommend the use of generic PGAs as the primary treatment medication for ocular hypertension.

Both sympathomimetics and carbonic anhydrase inhibitors are only licenced for use if beta-blockers are contraindicated or not tolerated. The cost of sympathomimetics is lower than carbonic anhydrase inhibitors; however, the clinical evidence showed no clinical difference between the two in percentage change in IOP from baseline but that carbonic anhydrase inhibitors have 69 fewer per 1,000 people discontinuing the treatment. Discontinuation of treatment can lead to more frequent hospital visits therefore would increase the cost of treatment. It was not possible to determine which is the most cost effective. For this reason, a hierarchy was not adopted between these two treatment classes.

At what IOP threshold to begin offering treatment:

The cost-effectiveness analysis results aided the committee in deciding what treatment to offer to people with OHT; however, the committee expressed significant concerns with treating all people with OHT, which in current practice is people identified as having IOP>21 mmHg. The committee was not convinced that there is sufficient evidence to suggest that people with a baseline IOP of less than 24 mmHg (who have never had a reading greater than 24 mmHg, as those in OHTS had) are at a significant risk of ever converting to COAG to justify treating. Within the IOP range considered OHT, the lower IOP levels (22 and 23mmHg) make up the largest proportion of the population, and there is no good quality evidence that people with IOP <24mmHg are at an increased risk developing COAG. The committee did not want to make recommendations that have considerable cost impact based on insufficient evidence of risk and treatment benefit. They felt confident that patients would not be placed at risk of visual impairment if a threshold for referral was set and subsequently the treatment threshold was updated; and that this would lead to better care for people who are confirmed as being at increased risk of visual impairment.

For both the IOP low and high subgroups, the model assessed what treatment was cost effective. Due to the limited data available, the model could not determine what IOP

threshold treatment should begin as the subgroups were treated as 2 distinct groups. If the model results had concluded that it was not cost effective to treat the low IOP subgroup, we could have inferred that a natural IOP treatment threshold had occurred. The outcome of the model estimated that it is cost effective to treat individuals in both subgroups with generic PGAs, because the downstream health impact and costs of developing glaucoma outweigh the relatively low cost of treatment. Despite these results, the committee was concerned with the applicability of the model results to people with lower IOPs in the low IOP subgroup due to the lack of evidence regarding the baseline risk for these people

The Ocular Hypertension Treatment Study (OHTS)[68] was used to determine the baseline risk of progression according to IOP and CCT levels that fed into the cost–utility analysis. Theoretically, the model population was people with OHT, which in current practice is considered to be anyone with an IOP>21 mmHg. 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 included people with IOP between 25 and 32 mmHg. Although this was the theoretical classification, the baseline risk probabilities for the subgroups were calculated from people (in OHTS) where the inclusion criteria for the study was that people had to have a baseline IOP of >24. The IOP categories in the study came from later readings where some people's IOP had decreased. The committee did not feel that this data sufficiently captured people who have never had an IOP reported to be 24 mmHg or over.

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 0.37% for no treatment to be cost effective.

The committee also considered there to be an ethical argument. They discussed the notion that placing a large number of people on treatment when the threshold of 21 mmHg comes from historical practice that is not sufficiently backed up by any strong evidence of risk was not in the interest of patients.

The threshold of 21 mmHg – embedded in the management of OHT – comes from a study conducted in the 1960s.[59] The population in this study had a higher proportion of females and was significantly younger than the present population; therefore, the committee felt that this threshold followed in practice is not relevant to the current UK population and includes people who they do not believe are at risk of ever developing COAG.

The committee felt confident that the treatment threshold could be increased, which would reduce costs without this leading to increased clinical harm. The committee made a consensus decision to change the threshold of when to initiate treatment for OHT from an IOP > 21 mmHg to an IOP≥24 mmHg. The committee recommended that people with IOP between 21-23 who will not be referred or treated, should be advised to book and attend regular eye tests, and therefore if their IOP level increases to ≥24mmHg, it would be picked up at a future appointment, and they would then be referred and put on an appropriate treatment plan. The committee decided that as there are approximately 1.8 million people in the UK with IOP 22 or 23 (Chan, Foster 2017 – Unpublished, personal communication) and there is still uncertainty about treatment for these people with IOP above 21 but below 24, that they would prioritise a research recommendation in this area.

The committee agreed with the results of the model in that generic prostaglandins are cost effective to offer people being treated for OHT and that treatment does not need to differ according to central corneal thickness. Therefore, the model informed the recommendations. Despite this, due to issues with the baseline risk data informing the model (outlined above) the committee felt the results of the model were not applicable to people with IOP<24mmHg and therefore the model was rated as having potentially serious limitations. The committee did not perceive people with IOP<24mmHg to be at an increased risk of conversion to COAG. Additional service considerations, the low probability of conversion, slow progression of the condition and the likelihood that people who do progress will be picked up at future eye appointments were also factors that influenced the final consensus recommendation to set the IOP threshold of who should be

	treated to IOP≥24mmHg. **When people should not be offered treatment:** In the OHT treatment model, a threshold analysis was performed on the age of people at diagnosis to see at what age treatment is no longer cost effective (see appendix N for details). CG85 recommendations specified ages where treatment was not considered necessary; however, the committee decided against putting specific ages into the updated recommendations. The committee felt it was more appropriate to allow flexibility and leave the decision down to the diagnosing optometrist or ophthalmologist along with the individual, to determine whether the person being assessed is likely to experience visual loss within their lifetime. **COAG suspects** The committee agreed that COAG suspects should be treated with generic PGAs if they have IOP of 24 mmHg or above. COAG suspects with IOP less than 24 should be reassessed regularly (see chapter 7) but not treated. **COAG** It was not considered necessary to update the COAG treatment model. As the results of the OHT treatment model found that it is cost effective to treat people with OHT with generic PGAs, the results could be extrapolated to assume that it will be also be cost effective to treat people with COAG with generic PGAs, as the COAG population have a higher risk of progression.
Other considerations	Generic PGA The committee took the view that in the absence of firm evidence that generic prescribing was less effective than branded prescribing, the less expensive generic option should be recommended. The committee considered that branded prescribing was most frequently done 'out of habit' rather than with a belief that branded drugs were more effective. It would be expected however that manufacturers of generic drops would adhere to usability standards for drop bottle design and compatibility with suitable dispensing aids where required. Capacity issues In light of new population data (committee personal communication), it is estimated that people with an IOP>21mmHg make up about 4% of the population in the UK (roughly 2 million people), whereas people with an IOP≥24mmHg make up about 0.4% (roughly 230,000). Hospital Eye Care Services are currently struggling to find the capacity to see the large numbers of people who are referred. Due to the inaccuracy of instruments used to measure IOP (as even the reference standard GAT is not 100% accurate) and the issue with dynamic nature of IOP, as well as other parameters, when there is no referral filtering in place, the committee estimated that roughly 30%-40% of people referred are discharged at the first visit as they are not perceived to be at risk. The committee said that in practice they would usually discharge people with an IOP< 24 mmHg who had normal fields and disc. Another 30%-40% of those who return due to uncertain visual fields will then be discharged on their second or third visit. Establishing a referral threshold and revising the treatment threshold would have a significant impact on the numbers of people referred on to have a diagnosis of OHT confirmed and the number of people put on treatment and requiring ongoing reassessment. This would likely reduce costs to the NHS and divert capacity to people who are at higher risk. Patient choice Pharmacists and GPs can discuss with patients the different types of droppers available as this may help patient choice decisions. Health professionals can refer to the NICE Medicines Optimisation guideline (NG5; https://www.nice.org.uk/guidance/ng5) and the Medicines Adherence guideline (CG76; https://www.nice.org.uk/guidance/cg76) to help address these options in discussion with patients. Cognitive impairment When discussing treatment and management decisions, with patients and carers, the

potential for cognitive and physical impairment should be taken into account. Health care practitioners should ensure that the style and form of communication is appropriate for the patient and that adequate assistance can be provided to ensure treatment adherence.

Research recommendations

4. Treatment for people with an IOP of 22 or 23 mmHg:

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. 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. The costs associated with management in these people are sufficient to make this question of national importance. There was no evidence on cost effectiveness. More information can be found in appendix Q.

5. An instrument to measure health-related quality of life in people with glaucoma:

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. More information can be found in appendix Q.

Recommendation	**37. Check that there are no relevant comorbidities or potential drug interactions before offering pharmacological treatment. [2009]**
Trade off between clinical benefits and harms	Some pharmacological treatments that are effective at lowering IOP may have serious systemic side effects, particularly worsening of chronic obstructive pulmonary disease and asthma by beta-blocker eye drops. There are many potential drug interactions with beta-blockers and alpha-receptor agonists. The patient's general health should not be compromised by any pharmacological treatment, as alternative treatments for COAG are available.
Economic considerations	None
Other considerations	Older people are more likely to experience adverse reactions to medications

2009

Recommendation	**38. Refer people whose IOP cannot be reduced sufficiently with pharmacological treatment to prevent the risk of progression to sight loss to a consultant ophthalmologist to discuss other options. [2009]**	
Trade off between clinical benefits and harms	The trade off between the benefits and harms of having surgery in these patients is unclear. Therefore, the next step in the clinical pathway should be discussed between the ophthalmologist and the patient to determine on a case-by-case basis.	2009
Economic considerations	None	
Other considerations	None	

Recommendation	**39. Offer people with advanced COAG, surgery with pharmacological augmentation (MMC[20]) as indicated. Offer them information on the risks and benefits associated with surgery. [2009, amended 2017]**	
Relative values of different outcomes	Surgery is the most potent treatment for lowering IOP and can save remaining sight. If there are complications of surgery sight could be lost more quickly than if there had been persistence with pharmacological treatment. If surgery is successful, the risk of losing further sight and progressing to complete blindness is reduced.	2009
Trade off between clinical benefits and harms	There is a risk of progression to complete blindness if COAG is not adequately treated. Although surgery has a higher risk than pharmacological treatment in the short term of causing blindness, it reduces this risk in the long term. If pharmacological treatment causes a satisfactory fall in IOP, surgery may be deferred.	
Economic considerations	Trabeculectomy is cost-effective for this group of patients even if the progression rate is very low (see appendix P).	
	Blindness has a large personal and social cost (see calculation of cost of blindness in appendix N).	
Quality of evidence	Clinical evidence was generally of low quality. The economic evidence has minor limitations but direct applicability.	2009
Other considerations	There were no trials due to the ethical implications of not treating patients with severe COAG.	
	The committee involved in the guideline update believed that 5FU was no longer used as part of standard practice during surgical treatment and postoperative care. Therefore, they decided that it was no longer clinically necessary to mention it specifically in the recommendation.	

[20] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Recommendation	**40. Offer people who present with advanced COAG and who are listed for surgery, interim treatment with a generic PGA.[21] [2009, amended 2017]**	2009
Trade off between clinical benefits and harms	If COAG is severe when first diagnosed, treatment to lower IOP should be started immediately as any amount of progression could cause additional severe visual disability. There is a risk of progression to complete blindness if COAG is not adequately treated.	
Economic considerations	Blindness has a large personal and social cost (see NICE's social value judgements document)	
Other considerations	None	
	Generic PGAs are now recommended in the guideline for first-line treatment. Since CG85 published, there have been reductions in the cost of medications, specifically prostaglandin analogues (PGA) coming off patent. These new costs were included in the updated cost–utility analysis. Please see appendix N for full details of the cost-effectiveness analysis methods and results.	

Recommendation	**41. Encourage people to continue with the same pharmacological treatment unless:** • **their IOP cannot be reduced sufficiently to prevent the risk of progression to sight loss** • **there is progression of optic nerve head damage** • **there is progression of visual field defect** • **they cannot tolerate the drug. [2009]**	2009
Trade off between clinical benefits and harms	Persisting with medication will reduce the risk of progression to blindness. If the medication is causing harm because of allergy or intolerance, a different medication can be offered.	
Economic considerations	Changes in therapy are associated with additional costs of visits. If a change is unnecessary then these costs should be avoided.	
Other considerations	None	

[21] At the time of publication (November 2017), not all generic PGAs had a UK marketing authorisation for first-line treatment. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Recommendation	**42. Offer surgery with pharmacological augmentation (MMC[22]) 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. [2009, amended 2017]**	
Relative values of different outcomes	Progression is the most important outcome.	
Trade off between clinical benefits and harms	There is a balance to be found. On the one hand, there is a higher risk of progression to blindness if a clinically acceptable level of pressure is not achieved. On the other hand, there is a higher risk of side effects with more aggressive interventions. For example, the risks of surgery are greater than the risks from medical treatment.	
Economic considerations	Trabeculectomy is cost-effective in cases of a detectable progression despite topical treatment.	2009
Quality of evidence	Clinical evidence was generally of low quality. The economic evidence has minor limitations but direct applicability.	
Other considerations	Patients may not be fit for surgery or may not wish to proceed to surgery because of anxiety or other issues. Where this situation arises, alternative attempts at IOP lowering may be necessary. Options that may need to be considered include laser treatments, or multiple topical pharmacological treatments.	
	The guideline update committee believed that 5FU was no longer used as part of standard practice during surgical treatment and postoperative care. Therefore, the committee decided that it was no longer clinically necessary to mention it specifically in the recommendation.	

Recommendation	**43. Offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor[23] 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. [2009, amended 2017]**	
Trade off between clinical	When a first choice medication is not effective at reducing the IOP	2009

[22] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[23] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

benefits and harms	the risk of progression to COAG remains.	2009
Economic considerations	Progression to COAG is related to IOP (see Chapter 6). Therefore, it is cost-effective to offer a treatment that effectively reduces IOP.	
Other considerations	Whenever there appears to be no reduction in IOP with a glaucoma medication, adherence and drop instillation technique should be checked with the patient.	
	The update committee amended the original recommendation for 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).	

Recommendation	**44. 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. [2009, amended 2017]**	
Relative values of different outcomes	The surrogate outcome is IOP reduction, which in turn, reduces the risk for future conversion to COAG in people with elevated IOP. Intolerance to preservative requires the use of a preservative-free preparation, which alters cost effectiveness.	2009
Trade off between clinical benefits and harms	Side effects of topical glaucoma medications may cause significant morbidity for patients. Intolerance to medications is likely to lead to poor persistence.	
Economic considerations	Preservative free Latanoprost (Monopost) drops are currently £6.95 more costly per month than standard preserved generic prostaglandins. Due to the higher monthly cost, any benefits of preservative agents in reducing irritation, etc. would have to be equivalent to an average gain of 0.05 (for people with an IOP < 25 mmHg) and 0.1 (for people with an IOP ≥ 25 mmHg) quality adjusted life years (QALYs) before the use of these drops as a first line treatment for all would represent good value for money. This amounts to an additional 18.25 and 36.5 days in full health. The committee did not think this amount of gain was plausible; therefore, preservative-free drops have only been recommended as first line to people who have an allergy to preservatives or as second line if a person is intolerant to the persevered drops.	
Quality of evidence	There is no direct clinical evidence. The economic evidence has minor limitations and direct applicability.	

Other considerations	None	2009
	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.	

Recommendation	**45. 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[24] 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[25]) as indicated.** **If the drug treatment option is chosen, after trying drugs from 2 therapeutic classes, consider offering surgery with pharmacological augmentation (MMC[26]) as indicated or laser trabeculoplasty. [2009, amended 2017]**	
Trade off between clinical benefits and harms	Complications of surgery may cause harm but if alternative treatments fail then surgery offers the least risk of progression to blindness.	2009
Economic considerations	None.	
Other considerations	Patients may not be fit for surgery or may prefer not to proceed to surgery because of anxiety or other issues.	
	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. Therefore, the	

[24] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[25] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[26] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

committee decided that it was no longer clinically necessary to mention it specifically in the recommendation.

Recommendation	**46. Consider offering people with COAG who cannot tolerate a treatment:** • **a drug from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor[27] 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[28]) as indicated or laser trabeculoplasty. [2009, amended 2017]**
Trade off between clinical benefits and harms	Prescribing an alternative medication should reduce the risk of progression to blindness. If there is intolerance, allergy or an inadequate IOP lowering effect surgery should be offered as an alternative treatment.
Economic considerations	Offering a more costly BB (preservative-free preparation) is still more cost-effective than no treatment in patients with COAG.
Quality of evidence	There was no clinical evidence. The economic evidence has minor limitations but direct applicability.
Other considerations	Patients may not be fit for surgery or may not wish to proceed to surgery because of anxiety or other issues. In such instances laser treatment may be helpful in improving IOP control.
	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. Therefore, the committee decided that it was no longer clinically necessary to mention it specifically in the recommendation.

2009

[27] At the time of publication (November 2017), some carbonic anhydrase inhibitors were licensed for use only when beta-blockers were not tolerated or were contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

[28] At the time of publication (November 2017), MMC did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

Recommendation	**47. 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. [2009, amended 2017]**	
Trade off between clinical benefits and harms	If surgery fails to control IOP topical medical treatment should be restarted. Repeat surgery may be required and if so should be offered. Cyclodiode laser treatment may need to be considered.	2009
Economic considerations	None.	
Other considerations	Patients may prefer certain options ahead of others.	
	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug.	

Recommendation	**48. 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. [2009, amended 2017]**	
Trade off between clinical benefits and harms	Alternative treatments to surgery are less effective but have a lower risk of immediate loss of sight. Some patients may choose a higher long term risk of sight loss to a low risk of immediate sight loss.	2009
Economic considerations	None.	
Other considerations	Patients may prefer certain options ahead of others.	
	Clarification that the drug should be from another therapeutic class when switching to another monotherapy and when adding another drug.	

10 Complementary and alternative interventions

10.1 Introduction

This chapter addresses approaches other than the mainstream interventions that are directed towards the lowering of IOP. The GDG decided to investigate the effectiveness of neuroprotective agents as a possible alternative to IOP lowering treatments. These agents attempt to preserve those cells which have been adversely affected by a glaucoma 'insult' and remain vulnerable to damage[69]. A variety of pharmacological agents, growth factors, and other compounds have been reported to be neuroprotective in vitro, and in a number of neurologic and neurodegenerative disorders.

An initial search was also undertaken to identify other candidate complementary and alternative treatments for OHT and COAG. Two reviews[124,126] suggested that a range of treatments may be of value for glaucoma patients.

We conducted a subsequent search for evidence on the following interventions and approaches in patients with OHT and COAG:

- neuroprotective agents (i.e. memantine)
- acupuncture
- megavitamins
- special diets
- herbal remedies (including cannabis and cannabinoids)
- ginkgo biloba
- exercise
- spinal manipulation
- homeopathy
- meditation (including relaxation techniques)
- therapeutic touch

2009

10.2 Complementary and alternative treatments

We searched for RCT evidence investigating the effectiveness of these interventions using the same criteria, which were applied for evidence supporting the medical, laser and surgical interventions.

10.2.1 Comparison of complementary and alternative treatments used alone or as an adjuvant

10.2.1.1 Clinical evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified

10.2.1.2 Economic evidence

No studies meeting the inclusion criteria for any of the treatments mentioned above were identified

10.2.1.3 Patient views evidence

No studies were identified

10.3 Conclusions

In the absence of objective scientific evidence supporting the use of these approaches, the consensus view of the GDG was sought. It was decided that without either supportive evidence or accepted practice it was not possible to form an opinion either in support of or against the use of the identified candidate complementary and alternative treatments for glaucoma. As such, no recommendations on these interventions have been made.

2009

11 Organisation of care

11.1 Service models for case finding, referral filtering and diagnosis

11.1.1 Introduction

False-positive referrals are inconvenient for the individuals referred and create unnecessary anxiety. In addition, these referrals put unnecessary strain on Health Services in terms of wasted cost and high demands on a limited outpatient resource. For these reasons, some regions have adopted 'Referral Filtering' models to improve the accuracy of referrals to secondary eye services. These include:

- Repeat measures schemes – Repeating the intraocular pressure measurement on the same visit or on another occasion (by use of the reference standard Goldmann Applanation tonometer or Perkins hand-held tonometer), and sometimes also repeating a suspect visual field assessment
- Enhanced case finding – A more in-depth assessment is carried out specifically for the detection of glaucoma. This process may include history taking, repeating measurements as above and the addition of further examination techniques or investigations
- Referral refinement – The assessment includes all the necessary examination techniques and tests sufficient to make a diagnosis of OHT and suspected COAG and formulation of a clinical management plan.

11.1.2 Review question: 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?

For full details, see review protocol in appendix C.

Table 90: PICO characteristics of review question

Population	Adults (18 and over)
Intervention(s)	Single or combinations of the following tests, including repeat measures, enhanced case finding, referral refinement, and triage stations in primary and secondary care: **For measuring intraocular pressure** • Goldmann applanation tonometry (GAT) by a 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 reassessment 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)
Comparison(s)	• 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

11.1.3 Clinical evidence

No relevant randomised controlled trials or cohort studies were identified that compared service models for identifying people who require onward referral from first contact primary care to confirming diagnosis. See also the study selection flow chart in appendix E, forest plots in appendix K, study evidence tables in appendix H, GRADE tables in appendix J and excluded studies list in appendix L.

11.1.4 Economic evidence

Published literature

Three health economic studies were identified with the relevant comparison and have been included in this review. [10,114,116] These are summarised in the health economic evidence profile below (Table 32) and the health economic evidence tables in appendix I.

One economic study relating to this review question was identified but was excluded due to limited applicability.[33] This is listed in appendix M, with the exclusion reason provided.

See also the health economic study selection flow chart in appendix F.

Table 91: Health economic evidence profile: triaging or refinement services versus each other, no refinement, or current practice

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Azuara-Blanco 2016[10] (UK)	Directly Applicable[(a)]	Potentially serious limitations [(b)]	Markov model of glaucoma diagnosis and progression comparing 4 hospital triage strategies (using different imaging technologies) to current practice where no initial triaging takes place. Population was people referred from community optometrists or general practitioners to hospital eye services with any possible glaucoma-related findings. Time horizon was 50 years.	**Incremental cost:** (combination test triage using OCT – combination test triage using GDx): £126 **Incremental cost:** (combination test triage using HRT-MRA – combination test triage using OCT): £35 **Incremental cost:** (combination test triage using HRT-GPS – combination test triage using HRT-MRA): £9 **Incremental cost:** (current practice – combination test triage using HRT-GPS): £123	**Incremental QALYs:** (combination test triage using OCT – combination test triage using GDx): 0.0045 **Incremental QALYs:** (combination test triage using HRT-MRA – combination test triage using OCT): 0.0025 **Incremental QALYs:** (combination test triage using HRT-GPS – combination test triage using HRT-MRA): 0 **Incremental QALYs:** (current practice – combination test triage using HRT-GPS): 0.0009	**ICER:** (combination test triage using OCT versus combination test triage using GDx): Extendedly dominated **ICER:** (combination test triage using HRT-MRA versus combination test triage using GDx): £22,904 per QALY **ICER:** (combination test triage using HRT-GPS versus combination test triage using HRT-MRA): Dominated **ICER:** (current practice versus combination test triage using HRT-MRA): £156,985 per QALY gained	Current practice becomes cost-effective when the total cost 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. Relaxing the assumption that clinicians are 100% accurate in their diagnosis further increases the ICER favouring triage strategies.
Parkins 2011 (UK) [114]	Partially applicable[(c)]	Potentially serious limitations	Total costs of 2 different referral filtering schemes to commissioners	**Incremental cost:** (Enhanced glaucoma repeat measurement – Regular hospital	**Incremental effect:** (Enhanced glaucoma repeat measurement – Regular hospital eye	Both schemes reduce costs compared to having no scheme in place. If it is assumed that the people	NA

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
		(d)	were estimated (a 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 where there was no referral filtering; everyone referred straight to HES from initial case-finding appointment.	eye service pathway): saves £81.79 **Incremental cost:** (Refinement by the community team after clinical assessment − Regular hospital eye service pathway): saves £4.69	service pathway): 86% fewer referrals to HES **Incremental effect:** (Refinement by the community team after clinical assessment − Regular hospital eye service pathway): 41% fewer referrals to HES	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.	
Peeters 2008 (The Netherlands) [116]	Partially applicable (e)	Potentially serious limitations (f)	Three case-finding strategies are analysed and compared. The simulated cohort consists of all initial patients aged at least 40 years visiting an ophthalmic practice. All patients undergo ophthalmoscopy, but tonometry is	**Incremental cost:** (tonometry is routinely performed to high-risk patients only – tonometry is not performed on anyone): £27 **Incremental cost:** (tonometry is performed on everyone -	**Proportion of people not becoming blind:** Incremental: (tonometry is routinely performed to high-risk patients only – tonometry is not performed on anyone): 0.002 Incremental: (tonometry is performed on everyone - tonometry	**Extra cost to prevent 1 person becoming blind:** (tonometry is routinely performed to high-risk patients only versus tonometry is not performed on anyone): £13,500 (tonometry is performed on everyone versus tonometry is routinely performed to high-risk patients only):	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

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
			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. Transition probabilities are taken from the literature. The (direct) costs of diagnosis and treatment represent those for the Netherlands.	tonometry is routinely performed to high-risk patients only): £21	is routinely performed to high-risk patients only): 0.007 **Years of blindness:** Incremental: (tonometry is routinely performed to high-risk patients only – tonometry is not performed on anyone): 0.009 Incremental: (tonometry is performed on everyone - tonometry is routinely performed to high-risk patients only): 0.032	£3,000 **Extra cost per year of vision saved**: (tonometry is routinely performed to high-risk patients only versus tonometry is not performed on anyone): £3,000 (tonometry is performed on everyone versus tonometry is routinely performed to high-risk patients only): £656.25	(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.

Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life years

(a) The economic analysis conducted in the report was assessed as being directly applicable as the population and interventions matched the protocol for the question.

(b) Due to a lack of data in 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 such as a misdiagnosis of those at risk of glaucoma as having glaucoma (initiation of unnecessary treatment) or a failure to diagnose some glaucoma cases (no initiation of treatment).

(c) The study was assessed as being partially applicable as the population and interventions met the protocol, but the current practice element of the evaluation was hypothetical.

(d) A major limitation of the study was its inability 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 would free up capacity; however, we cannot determine how this would affect clinical outcomes for people with or without glaucoma. If referral refinement through either type of scheme were to increase the number of false negatives and therefore miss people who require treatment, it could cost the NHS more money in the end, as people could progress to glaucoma faster than if such people were initially picked up. People go for an eye test on average every 3 years (reference); however, if the rates of false negatives through the schemes are high (we cannot know), it would not be guaranteed that a FN diagnoses would be corrected at the next appointment. Another limitation is that the study compares 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. Without taking into account the lifetime health outcomes for participants or modelling average lifetime costs and QALYs produced by the different schemes and current practice (referring all to

HES), the cost effectiveness of the referral schemes cannot be determined. The schemes might just shift costs by reducing short-term costs of fewer people referred and monitored in HES to increasing long-term costs of more people requiring treatment later.

(e) 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 it might not reflect a present UK population visiting UK practices.

(f) 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.

Supporting evidence

An additional study was identified in the review of health economic evidence,[56] but as the study did not include any comparators – it only analysed 1 service model – it could not be included as evidence for this review. The study results were presented as supporting evidence for the implementation of referral refinement prior to referral to Hospital Eye Services (HES).

Henson (2003)[56] analysed the implementation of a Manchester-based referral refinement scheme designed to reduce the number of false-positive referrals to the HES. "Patients with suspected glaucoma, instead of being referred to their GP and then on to the hospital eye service, were referred to a group of specially trained community optometrists working to an agreed set of referral criteria. Those patients who did not meet the referral criteria were returned to the referring optometrist, while those who met the referral criteria were referred directly to Manchester Royal Eye Hospital. The patient's GP was informed in all cases. The number of suspect glaucoma cases referred to the Manchester Royal Eye Hospital was reduced by 40%. This figure is close to the percentage of false-positive referrals measured at Manchester Royal Eye Hospital prior to the onset of this study. The information accompanying referral has been improved and the scheme produces a small financial cost saving to the NHS of approximately £17 per patient." [56]

New cost-effectiveness analysis

This area was not prioritised for new cost-effectiveness analysis.

11.1.5 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

- One cost-utility analysis found that setting up a hospital triage process prior to people having a clinical examination by a clinician was cost effective compared to having no triage process in place. The most cost effective triage process was to use GDx in the triage tests however this type of imaging test was not a test included in the review protocol. This study was assessed as directly applicable with potentially serious limitations.
- One comparative cost analysis found that setting up referral filtering schemes in the community (repeat measures or enhanced case finding) could decrease costs per patient compared to having no referral filtering in place and could significantly decrease the number of referrals to hospital eye services(HES). This study was assessed as directly applicable with potentially serious limitations.
- One cost-effectiveness analysis found that giving everyone tonometry testing in the community versus doing tonometry to high-risk individuals only cost £656.25 per extra year

of vision saved and £3,000 per extra person prevented from going blind. This study was assessed as partially applicable with potentially serious limitations.

11.1.6 Recommendations and link to evidence

Recommendations	**49. Before deciding to refer, consider repeating visual field assessment and IOP measurement on another occasion to confirm a visual field defect or IOP of 24 mmHg or more, unless clinical circumstances indicate urgent or emergency referral is needed. [2017]** **50. People planning and providing eye care services should use a service model that includes Goldmann-type applanation tonometry before referral for diagnosis of COAG and related conditions. [2017]** **51. People planning eye care services should consider commissioning referral-filtering services (for example, repeat measures, enhanced case finding, or referral refinement) for COAG and related conditions. [2017]** **52. Provide results of all examinations and tests with the referral. [2017]** **53. Give a discharge summary to people who have been assessed and discharged to primary care. Send a copy to their GP and, with patient consent, copy the relevant information to the primary eye care professional nominated by the patient. Advise people to take their discharge summary with them when attending future sight tests. [2017]**
Relative values of different outcomes	The committee agreed that the critical outcomes were the effects of the accuracy of various service models such as appropriate referral or non-referral, missed OHT, suspect COAG or COAG, and vision loss as a result of incorrect non-referral. Other outcomes that were considered important were long-term visual field loss (measured as a continuous outcome) or the dichotomous outcome of change from normal visual field to visual field defect, long-term optic nerve head damage (measured as a continuous outcome) or the dichotomous outcome of change from normal or suspicious to abnormal optic nerve head, health-related quality of life and participant satisfaction reported on validation scores.
Quality of the evidence	No clinical evidence was identified for inclusion in this review.
Trade-off between clinical benefits and harms	Hospital Eye Care Services (HES) are currently struggling to find the capacity to see the large numbers of people referred from primary and community services; these people are referred largely based on single readings of IOP (above the CG85 recommended treatment threshold of 21 mmHg). When there is no referral filtering system in place, roughly 30%-40% of people referred are discharged after the first visit. Another 30%-40% of those who return due to uncertain visual fields will then be discharged on the second or third visit. Similar to other physiological measurements, IOP fluctuates both throughout the day (short-term) and from day-

to-day (long-term) and, as such, there can be considerable measurement noise surrounding IOP measurement. [140,142] Due to the dynamic nature of IOP, as well as other ocular parameters that can cause erroneous IOP measurements (for example, CCT), single IOP measurement techniques only provide an estimate at a given moment in time and may lead to over- or under-estimations of IOP.

Repeat measures

Recommending repeat measures prior to referral would have a significant impact on the numbers of people referred into secondary eye care services for confirmation of diagnosis and treatment implementation. This would reduce costs to the NHS and free up capacity in the HES. In the context of primary care optometry a simple repeat measures scheme may involve repeating IOP measurement when prior non-contact tonometry readings indicate an IOP of 24 mmHg or above. Other repeat measures schemes may also involve repeating visual field measurements. [27,70]

The committee decided to make a consider recommendation, as no strong evidence was found. The committee did specify 'on another occasion' to highlight that the repeated measures should not be conducted all in the same visit with respect to the dynamic nature of IOP and the associated measurement noise. If clinical circumstances indicate urgent or emergency referral is required then repeating tests may not be needed if it would slow down the referral.

Goldmann-type applanation tonometry

The committee recommended that Goldmann-type applanation tonometry should be included in any service model before referral. This was because the results of GAT are more reliable than non-contact tonometry. Please see the chapter on case finding for further discussion on this.

Referral filtering

There was no clinical evidence identified comparing different models for organising case-finding and diagnosis services and the impact different referral pathways may have on the health benefits for patients. However, some applicable cost effectiveness evidence was identified and is discussed in the next section. The committee highlighted the 2016 NICE accredited Commissioning Guide for Glaucoma [27,70] that offers definitions for some of the ways in which glaucoma services could be arranged at the local level in order to provide referral filtering with the aim of relieving capacity issues in the Hospital Eye Care Service (HES). These include repeat measures (discussed above), enhanced case finding and referral refinement. Enhanced case finding refers to the use of specific tests such as slit-lamp mounted Goldmann applanation tonometry and dilated slit-lamp indirect biomicroscopy performed prior to referral to confirm abnormal results identified at case finding. Referral refinement describes a two-tiered assessment pathway where any initially concerning result picked up at the case-finding stage (tier 1) is validated by a subsequent enhanced assessment (tier 2). This second tier is a step up from a simple repeat measures scheme in that the clinician providing the referral refinement service must be qualified to make a diagnosis of OHT and suspected glaucoma and to carry out gonioscopy to exclude angle-closure glaucoma. The 3 referral filtering systems [27,70] each involve different arrangements of repeat testing, different levels of clinical skill and qualification required for using some of the specific tests, and can occur in different contexts along the patient pathway (community or primary eye care services, or in-hospital triage). The committee believed that in many locations

	around the UK some form of these referral-filtering systems was already in place. In light of the economic evidence and the committee's experience and knowledge of existing local arrangements, the committee decided to recommend that those who organise and commission glaucoma services consider providing some form of referral-filtering service to improve the accuracy of referrals and address current HES capacity issues. Further discussion on the possible cost-saving implications of such arrangements is in the following section. Providing results with the referral The committee made a strong recommendation that services should be set up to ensure that the results of all examinations and tests should be provided with the referral. This is to ensure that the healthcare professional receiving the patient is aware of previous results and the reasons for referral. Discharge summary The committee recommended that a discharge summary is given to people who have been assessed and discharged to primary care. A copy should be sent to their GP and, with patient consent, a copy of the relevant information to the primary eye care professional nominated by the patient. People should be advised to take their discharge summary with them when attending future sight tests. The committee considered that this may help to prevent patients being re-referred unnecessarily.
Trade-off between net clinical effects and costs	Three economic evaluations were identified for this review plus 1 study that was presented as supporting evidence. The cost–utility analysis[10] estimated that having a hospital triage process in place where optic nerve head imaging, IOP and visual tests are performed by nurses and technicians prior to people either being seen for a full examination by a clinician or discharged, would be cost saving compared to not having a hospital triage process in place. All 4 triage strategies compared in the study reduced costs; however, they all also reduced health outcomes due to the imperfect accuracy of the tests used to triage. The most cost-effective strategy was to use GDx and then HRT-MRT and then OCT to image the optic nerve head however, GDx was not included in the review protocol and the committee discussed the issue that HRT technology was becoming less widely used due to manufacturing and maintenance issues and was likely to be disestablished in the near future. The same study reported that 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. The committee therefore decided not to recommend triaging using imaging in a diagnosis setting. The comparative cost analysis[114] suggests that implementing enhanced glaucoma referral schemes (repeat measures or referral refinement) could reduce mean costs per patient and could significantly reduce the number of people referred to hospital eye services (HES), compared to the numbers likely to be referred without any referral filtering scheme in place. The study was unable to analyse the diagnostic accuracy and whether they would increase the number of false negative diagnoses, as fewer people would be referred onwards for a full examination by a consultant ophthalmologist. The study also assumed that without a scheme in place, community optometrists would refer everyone suspected of having a COAG related condition directly to HES and costed this scenario. For these reasons, this study was rated as having potentially serious limitations as any interpretation would need to have these caveats in mind. They did not base the 'no scheme' cost on data as everyone

	referred in the area over the study period were all referred via 1 of the 2 schemes. The committee mentioned that in areas where there is no referral filtering in place, roughly 30%-40% of people are discharged at their first HES appointment as false positive referrals. The committee felt that as people referred through a scheme would have had a more thorough investigation, it would not be likely that the schemes would increase the number of false negatives (even if fewer people are examined by a HES clinician), but it would be likely that referral-filtering schemes would decrease the number of false positives referred to HES. As HES is currently experiencing significant issues regarding capacity constraints, the committee felt that it was important that people planning eye care services consider providing referral filtering schemes such as repeat measures by optometrists to reduce the number of false positive referrals. Although having referral filtering in place would increase costs, these would most likely be offset by reductions of costs due to less referrals to HES. This would be likely to reduce costs to the NHS and unlikely to increase the risks to patients. In order for referral filtering schemes to work and ensure wide participation from community optometrists, the committee noted that there must be reimbursement mechanisms in place for tests performed in addition to what is required in NHS sight tests, as well as any repeat measure tests or additional assessments performed prior to onward referral. How areas model the service delivery of the new recommendations will depend on what type of referral filtering models they decide to implement in accordance with what model they believe will work best in that particular area. Recommending that all people receive an IOP measurement using Goldmann-type applanation tonometry does not mean that all community optometrists need to invest in the equipment needed to perform Goldmann-type applanation (a large proportion will already have the equipment). However, it does require that optometrists that do not use Goldmann-type applanation (for example, if they use a non-contact test) will need to refer people suspected of OHT on to an enhanced case finding or referral refinement service, where they will receive GAT prior to an onward referral to HES. The cost-effectiveness analysis study from the Netherlands[116] estimated that routinely performing GAT for all people aged at least 40 years visiting an ophthalmic practice cost an additional £3,500 per person avoided becoming blind, and an additional £656.25 per year of vision saved (over a 20 year time horizon), compared to only performing GAT on people considered to be high risk. This study was rated as partially applicable with potentially serious limitations, as it is not a UK study and the outcomes are difficult to interpret because it is not a cost-utility analysis. The committee did not recommend that everyone who goes for an eye test should receive a GAT test, as this would have a significant cost impact to community optometrists who do not already have the equipment and to the NHS who would need to reimburse optometrist for all the GAT tests performed. However, the evidence does support the recommendation that Goldmann-type applanation should be performed on everyone being considered for an onward referral to diagnosis. The committee also highlighted some additional research by Ratnarajan et al. (2013) [121] that supports implementing referral filtering models prior to referral to HES.
Other considerations	Various forms of referral filtering schemes are currently in place throughout the country, for example, Manchester and Bexley.

11.2 Skills required by healthcare professionals

11.2.1 Introduction

The majority of patients in the UK who develop COAG are initially identified when they present to their own optometrist for routine eye examination. Optometrists employ a case-finding approach to identifying individual patients who either exhibit signs consistent with COAG, or appear to be at risk of COAG development. Traditionally, individuals identified in this manner are then referred, via their General Practitioner, for comprehensive specialist examination by Ophthalmologists within the Hospital Eye Service (HES). Within the HES setting, patients receive a formal diagnosis and ongoing management, if required, by ophthalmology staff. Patients with no evidence of COAG are typically discharged, whilst those diagnosed with COAG receive appropriate treatment and ongoing monitoring. Individuals with ocular hypertension or COAG suspect status that are considered at sufficient risk of COAG development receive either treatment and HES monitoring, HES monitoring alone or discharge, dependent upon the specific clinical scenario of risk of COAG development.

Over the past decade, increasing demand for care of patients with COAG, ocular hypertension and COAG suspect status has led to involvement of non-medical and non-ophthalmologist medical healthcare professionals in COAG care beyond traditional roles. NHS service developments have also supported and encouraged changes to provision of COAG care. This has resulted in deviations from the traditional patient pathway in which non-ophthalmologist healthcare professionals participate in roles previously undertaken by ophthalmologists. In some locations, revised pathways now provide for parts of COAG-related patient care in non-HES locations. In the future it is possible that an increasing proportion of these patients will need to be managed by non-medical and non-ophthalmologist healthcare professionals to meet the burgeoning demands on COAG service provision.

In this section, we examine evidence on effectiveness of care delivered by different healthcare professionals. For the purposes of this guideline the term ‘healthcare professional’ refers to a trained individual involved in glaucoma related care including: ophthalmologists, optometrists, orthoptists, pharmacists, nurses and general practitioners. We have reviewed the evidence for diagnosis, monitoring and treatment

11.2.2 Matrices of healthcare professionals considered in our clinical questions

Below are the matrices showing where evidence was identified which compared agreement between different groups of healthcare professionals in the management of ocular hypertension and COAG. A box filled with **Yes** represents where evidence was found and is reviewed in this chapter. A box filled with **No** represents where no evidence was found or where the resulting statistical measure for agreement between comparisons was less than moderate. In this case no section on this comparison is included in the chapter. A box crossed out represents where the comparison was not considered for review.

Matrix 1: Effectiveness of diagnosis by different healthcare professionals

General	

2009

ophthalmologist						
Specialist ophthalmologist	Yes p. 258 Appendix U					
Certified optometrist with specialist interest	Yes p. 259 Appendix U	No				
Non specialist optometrist	Yes p. 255 Appendix U	Yes p. 256 Appendix U	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with specialist interest + training	No	No	No	No	No	
	General ophthalmologist	Specialist ophthalmologist	Certified optometrist with specialist interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

2009

Matrix 2: Effectiveness of monitoring by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	No					
Certified optometrist with specialist interest	No	No				
Non specialist optometrist	Yes p. 263 Appendix U	No	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with	No	No	No	No	No	

specialist interest + training						
	General ophthalmologist	Specialist ophthalmologist	Certified optometrist with specialist interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

Matrix 3: Effectiveness of treatment by different healthcare professionals

General ophthalmologist						
Specialist ophthalmologist	Yes p. 271 Appendix U					
Certified optometrist with specialist interest	No	Yes p. 272 Appendix U				
Non specialist optometrist	Yes p. 268 Appendix U	Yes p. 270 Appendix U	No			
Orthoptist with specialist interest + training	No	No	No	No		
Nurse with specialist interest + training	No	No	No	No	No	
	General ophthalmologist	Specialist Ophthalmologist	Certified optometrist with specialist interest	Non specialist optometrist	Orthoptist with specialist interest + training	Nurse with specialist interest + training

2009

11.2.3 Effectiveness of diagnosis by different healthcare professionals

We searched for any studies comparing the agreement in the diagnosis of ocular hypertension or COAG between the different groups of healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

11.2.3.1 Non specialist optometrist compared to general ophthalmologist

See the study evidence tables in appendix H.

11.2.3.2 Clinical evidence

Table 92: Non-specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for vertical cup-to-disc ratio[51, 53]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	
Inter-observer agreement for optic disc haemorrhage[51, 53]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	

(a) Both studies were observer masked but both studies tested agreement in the ability to read 48 pairs of stereo photographs rather than clinical examination of patients. One study[52] did not report confidence intervals for the kappa statistic.

(b) There is variation between studies noted in number of participating optometrists and ophthalmologists and their experience and training.

Table 93: Non-specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for vertical cup-to-disc ratio	96	Range from: 0.31 fair (CI95%: 0.31 - 0.41) to 0.46 moderate	Low
Inter-observer agreement for optic disc haemorrhage	96	Range from: 0.42 moderate (CI95%: 0.37 – 0.47) to 0.77 substantial	Low

11.2.3.3 Economic evidence

No studies were identified.

11.2.3.4 Patient views evidence

No studies were identified.

2009

11.2.3.5 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical	There is fair to moderate agreement between non-specialist optometrists and general ophthalmologists in assessment of vertical cup-to-disc ratio assessment but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY) There is moderate to substantial agreement between non-specialist optometrists and general ophthalmologists in detecting the presence of optic disc haemorrhage but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared non-specialist optometrist to general ophthalmologist.

11.2.4 Non specialist optometrist compared to specialist ophthalmologist

See the study evidence tables in appendix H.

11.2.4.1 Clinical evidence

Table 94: Non-specialist optometrist compared to specialist ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for diagnosis decisions[11]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement for vertical cup-to-disc ratio[150]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement optic disc haemorrhage[150]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement for overall	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
health status of optic nerve head[150]						

(a) One study[11] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[150] was not observer masked, patients were not recruited in a random or consecutive fashion and only one consultant ophthalmologist participated in the study

(b) In one study[11] the community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist. In the other study,[150] the community optometrists participating in the study attended 2 hours of lectures on optic disc examination.

Table 95: Non-specialist optometrist compared to specialist ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for diagnosis decisions	100	0.70 substantial (CI95%: 0.54 - 0.87)	Moderate
Inter-observer agreement for vertical cup-to-disc ratio	50	0.84 almost perfect (CI95%: 0.81 - 0.87)	Moderate
Inter-observer agreement optic disc haemorrhage	50	0.67 substantial (CI95%: 0.45 - 0.89)	Moderate
Inter-observer agreement for overall health status of optic nerve head	50	0.62 substantial (CI95%: 0.53 - 0.70)	Moderate

2009

11.2.4.2 Economic evidence

No studies were identified.

11.2.4.3 Patient views evidence

No studies were identified.

11.2.4.4 Evidence statements - Non specialist optometrist compared to specialist ophthalmologist

Clinical	There is substantial agreement on the kappa scale between non-specialist optometrists with in-house training and specialist ophthalmologists in diagnostic management decisions from all test results. (MODERATE QUALITY) There is almost perfect agreement on the kappa scale between non-specialist optometrists with in-house training and specialist ophthalmologists in assessment of vertical cup-to-disc ratio. (MODERATE QUALITY) There is substantial agreement on the kappa scale between non-specialist optometrists with in-house training and specialist ophthalmologists in detecting the presence of optic disc haemorrhage. (MODERATE QUALITY) There is substantial agreement on the kappa scale between non-specialist optometrists with in-house training and specialist ophthalmologists in assessment of overall health status of the optic nerve head. (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared non-specialist optometrists to specialist ophthalmologists.

2009

11.2.5 Specialist ophthalmologist compared to general ophthalmologist

See the study evidence tables in appendix H.

11.2.5.1 Clinical evidence

Table 96: Specialist ophthalmologist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for diagnosis decisions[11]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) The study was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study.

(b) The community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist.

Table 97: Specialist ophthalmologist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for diagnosis decisions	100	0.54 moderate (CI95%: 0.35 - 0.73)	Moderate

11.2.5.2 Economic evidence

No studies were identified.

11.2.5.3 Patient views evidence

No studies were identified.

11.2.5.4 Evidence statements - Specialist ophthalmologist compared to general ophthalmologist

Clinical	There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in diagnostic management decisions from all test results. (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to general ophthalmologists.

2009

11.2.6 General ophthalmologist compared to certified optometrist with a special interest

See the evidence tables in appendix I.

11.2.6.1 Clinical evidence

No studies were identified.

11.2.6.2 Economic evidence

We found a cost analysis comparing a referral refinement scheme to normal practice in the UK. Patients in the scheme are referred from a community optometrist to an optometrist with a special interest who decides whether the patient needs to be referred to the Hospital Eye Service. In the comparative normal practice arm, patients are referred directly from the community optometrist to the Hospital Eye Service via a GP. See the economic evidence tables in appendix I for details.

Table 98: General ophthalmologist compared to certified optometrist with a special interest - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Henson 2003[56]	Serious limitations (a)	Partially applicable (b)	

(a) Not a full economic evaluation. Cost of false negatives was not included.

(b) Patients were referred from community optometrists to either an optometrist with special interest or a GP and the Hospital Eye Service. Hence, this study does not entirely answer the clinical question.

Table 99: General ophthalmologist compared to certified optometrist with a special interest - Economic summary of findings

Study	Incremental cost (2001 £) for 3 years of referral scheme	Incremental effects	ICER	Uncertainty
Henson2003[56]	13,426	NR	NR	If 23 patients per month are referred to the certified optometrist, the scheme saves approximately £16 per patient.

2009

11.2.6.3 Patient views evidence

No studies were identified.

11.2.6.4 Evidence statements - General ophthalmologist compared to certified optometrist with a special interest

Clinical	No studies were identified where the statistical agreement between general ophthalmologist and certified optometrist with a specialist interest was either moderate or better.
Economic	Referring patients to accredited optometrists could decrease costs compared to a direct referral to ophthalmologists. The evidence has serious limitations and only partial applicability.

11.2.7 Recommendations and link to evidence

Recommendation	**54. Diagnosis of OHT and suspected COAG and formulation of a management plan should be made by a suitably trained healthcare professional with:** • **a specialist qualification and** • **relevant experience. [2009, amended 2017]**
Relative values of different outcomes	Accurate measurement of visual field, optic nerve, IOP and the anterior chamber drainage angle are all considered as equally important outcomes because COAG is defined by all four. Further studies are needed to show agreement between different types of clinicians in the assessment of these parameters.

2009

Trade off between clinical benefits and harms	Patients may receive their diagnosis sooner if evaluated in a community setting. Diagnosis of OHT and COAG suspects by staff other than consultant ophthalmologists may increase access to consultants' care for patients requiring formal COAG diagnosis. Refer to section 1.8 in appendix U for assumptions for OHT and COAG suspect.
Economic considerations	Diagnosis by healthcare professionals other than ophthalmologists could be cost saving even when the cost of referrals to ophthalmologists is taken into account.
Quality of evidence	The clinical evidence was of variable quality due to the following limitations: studies were not carried out in a systematic and controlled way, and there was the potential for selection bias, as some patients were volunteers. The economic evidence has serious limitations because the only study identified was not a full economic evaluation, the cost of false negatives were not estimated and the capital cost of necessary equipment for accredited optometrists was not included. The economic evidence has partial applicability, as it does not directly answer the clinical question.
Other considerations	Although not addressed as a clinical question the GDG noted that there is not always a high level of agreement between specialist ophthalmologists. However specialist ophthalmologists are considered to be the reference standard in this review. Therefore, the reliability of our reference standard could be questionable. Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical staff. The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available. Patient preference for assessment at hospital or in the community should be considered.

2009

11.2.8 Supporting recommendations

Recommendation	**55. Refer people with suspected optic nerve damage or repeatable visual field defect, or both, to a consultant ophthalmologist for consideration of a definitive diagnosis and formulation of a management plan. [2009]**
Trade off between clinical benefits and harms	The consequence of either failing to identify COAG or incorrect diagnosis may lead to irreversible blindness and visual disability.
Economic considerations	There are high costs associated with false negative and false positive diagnoses of COAG. It is important to obtain the most accurate diagnosis.

Other considerations	None

Recommendation	**56. Healthcare professionals involved in the diagnosis of OHT and COAG suspect status and preliminary identification of COAG should be trained in case detection and referral refinement and be able to identify abnormalities based on relevant clinical tests and assessments. They should understand the principles of diagnosis of OHT and COAG and be able to perform and interpret all of the following:** • **medical and ocular history** • **differential diagnosis** • **Goldmann applanation tonometry (slit lamp mounted)** • **standard automated perimetry (central thresholding test)** • **central supra-threshold perimetry** • **stereoscopic slit lamp biomicroscopic examination of anterior segment** • **examination of the posterior segment using a slit lamp binocular indirect ophthalmoscopy** • **gonioscopy** • **van Herick peripheral anterior chamber depth assessment** • **CCT measurement. [2009]**
Trade off between clinical benefits and harms	Training is likely to improve quality of care by increasing the healthcare professional's knowledge of discriminatory power (sensitivity and specificity).
Economic considerations	None
Other considerations	The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available.

2009

11.3 Effectiveness of monitoring by different healthcare professionals

We searched for any studies comparing the agreement in the monitoring of ocular hypertension or COAG between the different groups healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

11.3.1 Non specialist optometrist compared to general ophthalmologist

See the study evidence tables in appendix H and the economic evidence in appendix I.

11.3.1.1 Clinical evidence

Table 100: Non-specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for visual field assessment for right and left eyes[13]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	
Inter-observer agreement for follow up intervals[13]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	
Inter-observer agreement (ICC) for visual field assessment for right and left eyes[49, 142]	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)
Inter-observer agreement (ICC) for vertical cup-to-disc ratio assessment for right and left eyes[49,142]	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)
Inter-observer agreement (ICC) for IOP measurement for right	1	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	(c)

2009

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
and left eyes[49,142]						
Inter-observer agreement for vertical cup-to-disc ratio[51,53]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	
Inter-observer agreement for optic disc haemorrhage[51,53]	2	Retrospective observational	Serious limitations (a)	Serious inconsistency (b)	No serious indirectness	

(a) One study[13] was observer masked but it was not clear whether the patients were recruited in a randomised or consecutive fashion. Only one general ophthalmologist (research fellow) and one senior optometrist participated in the study and confidence intervals for the kappa statistic were not reported. Both the studies[51,53] were observer masked but tested agreement in the ability to read 48 pairs of stereo photographs rather than clinical examination of patients. One study[52] did not report confidence intervals for the kappa statistic. The RCT study[49,142] did not report confidence intervals for the ICC agreement statistic.

(b) For the studies[51,53] there is variation between studies noted in number of participating optometrists and ophthalmologists and their experience and training.

(c) For the RCT study[49,142] participating community optometrists received in-house training through lectures and demonstrations. An adjusted Intraclass Correlation Coefficient (ICC) was used in place of the kappa statistic, which provides and equivalent scale to measure agreement between the community optometrists and the general ophthalmologists in the Hospital Eye Service setting.

2009

Table 101: Non-specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for visual field assessment for right and left eyes	54	0.81 almost perfect (right eye) 0.80 substantial (left eye)	Moderate
Inter-observer agreement for follow up intervals	54	0.97 almost perfect	Moderate
Inter-observer agreement (ICC) for visual field assessment for right and left eyes	403	0.55 moderate (right eye) 0.61 substantial (left eye)	High
Inter-observer agreement (ICC) for vertical cup-to-disc ratio	403	0.50 moderate (right eye) 0.54 moderate (left eye)	High

Outcome	Number of patients	Mean kappa statistic	Quality
assessment for right and left eyes			
Inter-observer agreement (ICC) for IOP measurement for right and left eyes	403	0.45 moderate (right eye) 0.40 fair (left eye)	High
Inter-observer agreement for vertical cup-to-disc ratio	96	Range from: 0.31 fair (CI95%: 0.31 - 0.41) to 0.46 moderate	Low
Inter-observer agreement for optic disc haemorrhage	96	Range from: 0.42 moderate (CI95%: 0.37 – 0.47) to 0.77 substantial	Low

11.3.1.2 Economic evidence

We found a UK study where patients with COAG were randomised to either follow-up by the Hospital Eye Service or community optometrists. See economic evidence tables in appendix I for details.

Table 102: Non-specialist optometrist compared to general ophthalmologist - Economic study characteristics

Study	Limitations	Applicability	Other Comments
Coast 1997[28] (a)	Serious limitations (b)	Partially applicable (c)	

(a) Based on a RCT[49,141]
(b) Not a full economic evaluation; cost of false positives and false negatives was not included and optometrists fees were probably underestimated.
(c) Optometrists were volunteers from community optometrists. It is a shared care scheme rather than a comparison between two alternative healthcare professionals.

Table 103: Non-specialist optometrist compared to general ophthalmologist - Economic summary of findings

Study	Incremental full cost (£) per year per patient	Incremental effects	ICER	Uncertainty
Coast 1997[28]	13 (a)	NR	NR	When follow up interval in with optometrist was similar to that with ophthalmologist, monitoring by optometrist costs £14 less per patient.

(a) Costs include cost of staff, training of optometrists, consumables, referrals from optometrists to ophthalmologist (19% patients), and overheads.

11.3.1.3 Patient views evidence

No studies were identified.

2009

11.3.1.4 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical	There is almost perfect and substantial agreement on the kappa scale between non-specialist optometrists and general ophthalmologists in visual field assessment for the right and left eyes respectively. (MODERATE QUALITY) There is almost perfect agreement on the kappa scale between non-specialist optometrists and general ophthalmologists in follow-up intervals. (MODERATE QUALITY) There is moderate and substantial agreement on the ICC scale between non-specialist optometrists with in-house training and general ophthalmologists in visual field assessment for the right and left eyes respectively. (HIGH QUALITY) There is moderate and substantial agreement on the ICC scale between non-specialist optometrists with in-house training and general ophthalmologists in assessment of vertical cup-to-disc ratio for both eyes. (HIGH QUALITY) There is moderate and fair agreement on the ICC scale between non-specialist optometrists with in-house training and general ophthalmologists in IOP measurement for the right and left eyes respectively. (HIGH QUALITY) There is fair to moderate agreement between non-specialist optometrists and general ophthalmologists in assessment of vertical cup-to-disc ratio assessment but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY) There is moderate to substantial agreement between non-specialist optometrists and general ophthalmologists in detecting the presence of optic disc haemorrhage but the evidence is from retrospective examination from stereo photograph pairs. (LOW QUALITY)
Economic	Monitoring by non-specialist optometrist is more costly than monitoring by general ophthalmologist unless the follow-up intervals are similar. The evidence has serious limitations and partial applicability.

2009

11.3.2 Recommendations and link to evidence

Recommendation	**57. People with a confirmed diagnosis of OHT or suspected COAG and who have an established management plan may have monitoring (but not treatment) from a suitably trained healthcare professional with knowledge of OHT and COAG, relevant experience and ability to detect a change in clinical status. The healthcare professional should be able to perform and interpret all of the following:** • **Goldmann applanation tonometry (slit lamp mounted)** • **standard automated perimetry (central thresholding test)** • **central supra-threshold perimetry (this visual field strategy may be used for monitoring OHT or suspected COAG when the visual field is normal)** • **stereoscopic slit lamp biomicroscopic examination of the anterior segment** • **van Herick peripheral anterior chamber depth assessment** • **examination of the posterior segment using slit lamp binocular indirect ophthalmoscopy. [2009]**
Relative values of different outcomes	The most important aspects of monitoring are: Progression Detection of changes in clinical status Diagnosis, including being alert to ocular and systemic comorbidities Starting treatment Changing treatment Tests at each visit Follow up interval
Trade off between clinical benefits and harms	Factors to be considered during monitoring are: Prevention of sight loss Side effects of treatment Interactions with other medications Incorrect treatment (absent or inadequate) leading to sight loss Incorrect diagnosis leading to sight loss Incorrect diagnosis leading to over treatment
Economic considerations	Monitoring by trained healthcare professionals other than ophthalmologists could be cost saving even when the cost of referrals is taken into account.
Quality of evidence	The clinical evidence was of variable quality due to the following limitations: studies were not carried out in a systematic and controlled way, and there was the potential for selection bias, as some patients

2009

	were volunteers. The economic evidence has serious limitations and partial applicability because the only study identified was not a full economic evaluation, the cost of false positives and false negatives was not included, and there was potential selection bias, as some patients were volunteers. The optometrists in the study were volunteers. The study was a shared care scheme rather than a comparison between the care of two alternative healthcare professionals.
Other considerations	Specialist ophthalmologists are considered to be the reference standard in this review. Although not addressed as a clinical question the GDG noted that there is not always a high level of agreement between specialist ophthalmologists themselves. Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical staff. The GDG noted that the correct equipment to complete diagnostic assessments in keeping with the reference standards for tonometry, standard automated central thresholding perimetry and biomicroscopic slit lamp examination are required for healthcare professionals to perform diagnosis in a community setting and should be available. Patient preference for assessment at hospital or in the community should be considered.

2009

11.4 Effectiveness of treatment by different healthcare professionals

We searched for any studies comparing the agreement in the decisions to treat patients with ocular hypertension or COAG between the different groups healthcare professionals listed in the matrix at the beginning of this chapter. We did not compare agreement within groups.

11.4.1 Non specialist optometrist compared to general ophthalmologist

See the study evidence tables in appendix H.

11.4.1.1 Clinical evidence

Table 104: Non-specialist optometrist compared to general ophthalmologist - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
to treat[11]						
Inter-observer agreement for treatment decisions (start/increase/reduce) for right and left eyes[13]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	

(a) One study[11] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[13] was observer masked but it was not clear whether the patients were recruited in a randomised or consecutive fashion. Only one general ophthalmologist (research fellow) and one senior optometrist participated in the study and confidence intervals for the kappa statistic were not reported.

2009

Table 105: Non-specialist optometrist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for decision to treat	100	0.62 substantial (CI95%: 0.45 - 0.79)	Moderate
Inter-observer agreement for treatment decisions (start/increase/reduce) for right and left eyes	54	1.00 perfect (right eye) 0.93 almost perfect (left eye)	Moderate

11.4.1.2 Economic evidence

No studies were identified.

11.4.1.3 Patient views evidence

No studies were identified.

11.4.1.4 Evidence statements - Non specialist optometrist compared to general ophthalmologist

Clinical	There is substantial agreement on the kappa scale between non-specialist optometrists with in-house training and general ophthalmologists in decision to treat. (MODERATE QUALITY) There is perfect and almost perfect agreement on the kappa scale between non-specialist optometrists and general ophthalmologists in treatment decisions (start/increase/reduce) for the right and left eyes respectively. (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared non-specialist optometrists to general ophthalmologists.

11.4.2 Non specialist optometrist compared to specialist ophthalmologist

See the study evidence tables in appendix H.

11.4.2.1 Clinical evidence

Table 106: Non-specialist optometrist compared to specialist ophthalmologist - Clinical study characteristics

Table Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision to treat[11]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) The study was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study

(b) The community optometrists participating in the study received in-house training through glaucoma clinic attendance with the consultant ophthalmologist.

Table 107: Non-specialist optometrist compared to specialist ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for decision to treat	100	0.72 substantial (CI95%: 0.57 - 0.86)	Moderate

11.4.2.2 Economic evidence

No studies were identified.

11.4.2.3 Patient views evidence

No studies were identified.

11.4.2.4 Evidence statements - Non specialist optometrist compared to specialist ophthalmologist

Clinical	There is substantial agreement on the kappa scale between non-specialist optometrists with in-house training and specialist ophthalmologists in decision to treat. (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared non-specialist optometrists to specialist ophthalmologists.

11.4.3 Specialist ophthalmologist compared to general ophthalmologist

See the study evidence tables in appendix H.

11.4.3.1 Clinical evidence

Table 108: Specialist ophthalmologist compared to general ophthalmologist - Clinical study characteristics

Table Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for decision to treat[11]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)
Inter-observer agreement for treatment decisions (start/increase/reduce)[12]	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

(a) One study[11] was observer masked and patients randomly selected from community optometrist referrals but only one consultant ophthalmologist and one trainee general ophthalmologist participated in the study. The other study[12] was observer masked and patients were recruited sequentially but confidence intervals for the kappa statistic are not reported and kappa statistics are only reported for one specialist ophthalmologist.

(b) The community optometrists participating in one study[11] received in-house training through glaucoma clinic attendance with the consultant ophthalmologist. The certified optometrists in the other study[12] also received in-house training through patient assessments with a consultant.

2009

Table 109: Specialist ophthalmologist compared to general ophthalmologist - Clinical summary of findings

Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for decision to treat	100	0.55 moderate (CI95%: 0.37 - 0.73)	Moderate
Inter-observer agreement for treatment decisions (start/increase/reduce)	350	0.52 moderate	Moderate

11.4.3.2 Economic evidence

No studies were identified.

11.4.3.3 Patient views evidence

No studies were identified.

11.4.3.4 Evidence statements - Specialist ophthalmologist compared to general ophthalmologist

Clinical	There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in decision to treat. (MODERATE QUALITY) There is moderate agreement on the kappa scale between specialist ophthalmologists and general ophthalmologists in treatment decisions (start/increase/reduce). (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to general ophthalmologists.

2009

11.4.4 Specialist ophthalmologist compared to certified optometrist with a special interest

See the study evidence tables in appendix H.

11.4.4.1 Clinical evidence

Table 110: Specialist ophthalmologist compared to certified optometrist with a special interest - Clinical study characteristics

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
Inter-observer agreement for	1	Prospective observational	Serious limitations (a)	No serious inconsistency	No serious indirectness	(b)

Outcome	Number of studies	Design	Limitations	Inconsistency	Directness	Other considerations
treatment decisions (start/increase/reduce) [12]						

(a) The study was observer masked and patients were recruited sequentially but confidence intervals for the kappa statistic are not reported and kappa statistics are only reported for one specialist ophthalmologist.

(b) The certified optometrists participating in the study received in-house training through patient assessments with a consultant.

Table 111: Specialist ophthalmologist compared to certified optometrist with a special interest - Clinical summary of findings

Table Outcome	Number of patients	Mean kappa statistic	Quality
Inter-observer agreement for treatment decisions (start/increase/reduce)	350	0.67 substantial	Moderate

2009

11.4.4.2 Economic evidence

No studies were identified.

11.4.4.3 Patient views evidence

No studies were identified.

11.4.4.4 Evidence statements - Specialist ophthalmologist compared to certified optometrist with a special interest

Clinical	There is substantial agreement on the kappa scale between specialist ophthalmologists and certified optometrists with a specialist interest in treatment decisions (start/increase/reduce). (MODERATE QUALITY)
Economic	No studies meeting the inclusion criteria were identified which compared specialist ophthalmologists to certified optometrists with a special interest.

11.4.5 Recommendations and link to evidence

Recommendation	**58. People with OHT, suspected COAG or COAG should have monitoring and treatment from a trained healthcare professional who has all of the following:** • **a specialist qualification** • **relevant experience**

	• **ability to detect a change in clinical status. [2009, amended 2017]**
Relative values of different outcomes	Treatment decisions are dependent upon: Diagnosis, including being alert to ocular and systemic comorbidities Severity of COAG or level of conversion risk Effectiveness, contra-indications, precautions and interactions of existing anti-COAG medications Tolerance of current anti-COAG medications Systemic conditions and medications
Trade off between clinical benefits and harms	Treatment by non-medical healthcare professionals or non-ophthalmologists will increase the number of healthcare professionals available from which care may be accessed.
Economic considerations	None
Quality of evidence	The clinical evidence was of moderate quality. Studies were not carried out in a systematic and controlled way and there was the potential for selection bias, as some patients were volunteers.
Other considerations	There are not enough ophthalmologists at present to do all the work required so the work needs to be shared. Currently hospital lists are full and this results in delayed appointments. Evidence is only available for optometrists, with no studies available for other non-medical healthcare professionals or non-ophthalmologist medical staff.

2009

11.4.6 Supporting recommendations

Recommendation	**59. Be aware that holding an independent or non-medical prescribing qualification alone (without a specialist qualification relevant to the case complexity of glaucoma being managed) is insufficient for managing glaucoma and related conditions. [2017]**
Trade off between clinical benefits and harms	The committee for the guideline update believed that clarification was needed to specify that practitioners who hold an independent prescribing license are not qualified to manage people being treated for OHT, suspected COAG or COAG unless they also hold a specialist glaucoma-related qualification. They wished to reinforce that the prescribing licence only covers prescribing treatment and does not qualify them to diagnose, assess or manage people on treatment with respect to deciding appropriate reassessment visits for evaluating control of IOP and risk of conversion to or progression of glaucoma.
Economic considerations	None
Other considerations	None

Recommendation	**60. Healthcare professionals involved in the monitoring and treatment of OHT, suspected COAG and established COAG should be trained to make management decisions on all of the following:** • **risk factors for conversion to COAG** • **coexisting pathology** • **risk of sight loss** • **monitoring and detecting a change in clinical status (for example, visual field changes, stereoscopic slit lamp biomicroscopic examination of anterior segment and posterior segment)** • **pharmacology of IOP-lowering drugs** • **treatment changes for COAG, suspected COAG and OHT (with consideration given to relevant contraindications and interactions). [2009]**
Trade off between clinical benefits and harms	All clinical tests need to be performed correctly to inform decisions based upon results properly. A clear understanding of the nature of the test and how to interpret results is necessary. Decision-making should be based upon clinical circumstances and current examination.
Economic considerations	Training is costly but essential to ensure quality care.
Other considerations	Training healthcare professionals takes time.

2009

Recommendation	**61. Healthcare professionals who diagnose, treat or monitor independently of consultant ophthalmologist supervision should take full responsibility for the care they provide. [2009]**
Trade off between clinical benefits and harms	Clinical governance applies to all NHS services. Although a consultant ophthalmologist may be responsible for the care of a patient they may delegate the task diagnosis, treatment and monitoring to another suitably trained healthcare professional under their supervision. When healthcare professionals provide care independently of consultant supervision they should practice within the limits of their competence. Patients should clearly understand who is responsible for their care.
Economic considerations	None
Other considerations	None

12 Provision of information for patients

12.1 Introduction

The way patients are provided with information could affect the outcome of their treatment. Improved patient understanding of OHT and COAG and involvement in its management could reduce stress and uncertainty for patients and potentially improve adherence with medical treatment. This in turn could help prolong sighted lifetime.

12.1.1 Comparison of methods of giving information to patients

We searched for studies comparing the effectiveness of different ways of providing information to COAG patients in improving the outcome for patients e.g. a greater reduction in intraocular pressure, a difference in visual field progression, better adherence with medications.

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12.1.1.1 Clinical evidence

No studies were identified.

12.1.1.2 Economic evidence

No studies were identified.

12.1.1.3 Patient views evidence

No studies were identified.

12.1.2 Supporting recommendation

Recommendation	**62. 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 (see NICE's guideline on medicines optimisation).** • **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)** • **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. [2009, amended 2017]**
Trade off between clinical benefits and harms	The GDG considered it important that patients are fully aware of their condition and its management. Information is important in allowing patients to become fully aware of their condition and its management. Opportunities for raising concerns must also be given. There is potential for harm if this is not provided, for example resulting in low adherence with treatment or monitoring appointments. Improved understanding has the potential to reduce anxiety, with the potential of affecting the patient's quality of life.
Economic considerations	There is potentially a significant increase in cost effectiveness by improving COAG management. For example, if drops are instilled correctly the drug is likely to be more effective with no change in its cost.
Other considerations	The recommendation was amended slightly for the update of this guideline. The committee added that patient information should also include: • reassurance that most people having treatment for COAG will have a good quality of life

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	• reference to the eye clinic liaison officer (ECLO) as these now available in many clinics • reference to support organisations. The committee also noted that since the publication of CG85, the NHS Accessible Information Standard (2016) had been published which provides information regarding patient access to information in a format suitable for them. (https://www.england.nhs.uk/ourwork/accessibleinfo/) <u>Patient choice</u> Pharmacists and GPs can discuss with patients the different types of droppers available as this may help patient decisions. Health professionals can refer to the Medicines Optimisation guideline (NG5; https://www.nice.org.uk/guidance/ng5) and the Medicines Adherence guideline (CG76; https://www.nice.org.uk/guidance/cg76) to help address these options in discussion with patients.

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14 Acronyms and abbreviations

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

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

Acronym or abbreviation	Description
VCD	Vertical cup-to-disc ratio
VF	Visual field

15 Glossary

The NICE Glossary can be found at www.nice.org.uk/glossary.

15.1 Guideline-specific terms

Term	Definition
Absolute risk reduction (Risk difference)	The difference in the risk of an event between 2 groups (one subtracted from the other) in a comparative study.
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Adherence	The extent to which the patient's behaviour matches the prescriber's recommendations. Adherence emphasises the need for agreement and that the patient is free to decide whether or not to adhere to the doctor's recommendation.[100]
Adjustment	A statistical procedure in which the effects of differences in composition of the populations being compared (or treatment given at the same time) have been minimised by statistical methods.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in a RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	The degree to which the results of an observation, study or review are likely to hold true in a particular clinical practice setting.
Appraisal of Guidelines Research and Evaluation, (AGREE)	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreecollaboration.org). The AGREE instrument, developed by the group, is designed to assess the quality of clinical guidelines.
Aqueous humour	"Clear, colourless fluid that fills the anterior and posterior chambers of the eye. It is a carrier of nutrients for the lens and for part of the cornea. It contributes to the maintenance of the intraocular pressure. It is formed in the ciliary processes, flows into the posterior chamber, then through the pupil into the anterior chamber and leaves the eye through the trabecular meshwork passing to the canal of Schlemm and then to veins in the deep scleral pleral plexus." [93]
Arm (of a clinical study)	Sub-section of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.

Term	Definition
Audit	See 'Clinical audit'.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results that is caused by the way the study is designed or conducted.
Blinding (masking)	Keeping the study participants, caregivers, researchers and outcome assessors unaware about the interventions to which the participants have been allocated in a study.
Blindness	1. Inability to see. 2. Absence or loss of sight severe enough for someone to be unable to perform any work for which eyesight is essential.[93] The World Health Organisation definition of blindness is less than 3/60 in the better seeing eye. This means that the better seeing eye cannot read the top letter on the Snellen visual acuity chart at three metres. (Cochrane Eyes and Vision Group, http://www.cochraneeyes.org/glossary.htm) For the purposes of the economic analysis in this guideline, the committee considered the definition of severe visual impairment to be Mean Defect <-20 dB. It was further assumed that both eyes were similar.
Capital costs	Costs of purchasing major capital assets (usually land, buildings or equipment). Capital costs represent investments at one point in time.
Carer (caregiver)	Someone other than a health professional who is involved in caring for a person with a medical condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Case-control study	Comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and others who have not (controls), and then collects data to determine previous exposure to a possible cause.
Chronic open-angle glaucoma (COAG)	See glaucoma, chronic open-angle
Clinical audit	A quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change.
Clinical effectiveness	The extent to which an intervention produces an overall health benefit in routine clinical practice.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.

Term	Definition
Clinical impact	The effect that a guideline recommendation is likely to have on the treatment or treatment outcomes, of the target population.
Clinical question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Clinically acceptable IOP	A dynamic, clinical judgement about what level of intraocular pressure is considered by the healthcare professional treating the patient to be sufficiently low to minimise or arrest disease progression or onset and avoid disability from sight loss within a person's expected lifetime.
Clinician	A healthcare professional providing direct patient care, for example doctor, nurse or physiotherapist.
Cluster	A closely grouped series of events or cases of a disease or other related health phenomena with well-defined distribution patterns, in relation to time or place or both. Alternatively, a grouped unit for randomisation.
Cochrane Library	A regularly updated electronic collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews.
Cochrane Review	A systematic review of the evidence from randomised controlled trials relating to a particular health problem or healthcare intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Cohort study	A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined based on presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case 2 or more groups are selected based on differences in their exposure to the agent of interest.
Co-morbidity	Co-existence of more than one disease or an additional disease (other than that being studied or treated) in an individual.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.[100]
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.[100]
Conference proceedings	Compilation of papers presented at a conference.

Term	Definition
Confidence interval (CI)	A range of values for an unknown population parameter with a stated 'confidence' (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The 'confidence' value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted as a result of an association between the population or intervention or outcome and another factor (the 'confounding variable') that can influence the outcome independently of the intervention under study.
Consensus methods	Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.
Control group	A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) – in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Controlled clinical trial(CCT)	A study testing a specific drug or other treatment involving 2 (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The 2 groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a randomised controlled trial.
Conversion	Worsening of suspected COAG or OHT with the development of visual field loss in keeping with optic nerve head appearance. To make this judgement the healthcare professional must know the eye's earlier clinical state.
Cost benefit analysis	A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.
Cost-consequences analysis (CCA)	A type of economic evaluation where various health outcomes are reported in addition to cost for each intervention, but there is no overall measure of health gain.
Cost-effectiveness analysis (CEA)	An economic study design in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

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

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

Term	Definition
Glaucoma	A disease of the optic nerve with characteristic changes in the optic nerve head (optic disc) and typical defects in the visual field with or without raised intraocular pressure. (*see also types of glaucoma listed below*)
Glaucoma, angle-closure	Glaucoma in which the angle of the anterior chamber is blocked by the root of the iris which is in apposition to the trabecular meshwork.[93]
Glaucoma, chronic open-angle	Glaucoma without evident secondary cause which follows a chronic time course and occurs in the presence of an open anterior chamber angle (the trabecular meshwork is visible on gonioscopy). In this guideline, the term COAG is used regardless of the level of intraocular pressure and has been extended to include COAG associated with pseudoexfoliation and pigment dispersion (unless specifically stated otherwise).
Glaucoma, normal tension /glaucoma, low tension	A type of chronic open-angle glaucoma where intraocular pressure has rarely been recorded above 21 mmHg (a figure frequently taken as the 'statistical' upper limit of the normal range).
Glaucoma, open-angle	When the anterior chamber angle (defined by gonioscopy) is open.
Glaucoma, pigmentary	Glaucoma caused by the deposition of pigment in the trabecular meshwork as a result of pigment dispersion syndrome.
Glaucoma, primary open-angle (POAG)	Chronic open-angle glaucoma in the absence of any other ocular, systemic or pharmacological cause and accompanied by elevated intraocular pressure.
Glaucoma, pseudoexfoliative	Glaucoma in the presence of pseudoexfoliative material.
Glaucoma, secondary	Glaucoma associated with raised intraocular pressure due to a recognised or systemic disease or pharmacological treatment.
Glaucoma, suspected	When, regardless of the level of the IOP, the optic nerve head (optic disc) and/or visual field show changes that suggest possible glaucomatous damage.
Glaucomatous optic neuropathy	Characteristic morphological changes within the optic nerve head associated with specific patterns of visual field loss.
Gold standard	See 'Reference standard'.
Gonioscope	Mirrored contact lens (goniolens), used with slit lamp biomicroscopy, or a contact prism lens (gonioprism) to enable observation of the anterior chamber angle.
Gonioscopy	Examination of the anterior chamber angle using a gonioscope to observe angle structures and estimate depth of angle.
Goodness-of-fit	How well a statistical model or distribution compares with the observed data.

Term	Definition
Grey literature	Reports that are unpublished or have limited distribution and are not included in the common bibliographic retrieval systems.
Harms	Adverse effects of an intervention.
Health economics	The study of the allocation of scarce resources among alternative healthcare treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.
Healthcare professional	For the purposes of this guideline, the term 'healthcare professional' refers to a trained individual involved in glaucoma related care including: ophthalmologists, optometrists, orthoptists, pharmacists, nurses and general practitioners.
Health-related quality of life	A combination of an individual's physical, mental and social well-being; not merely the absence of disease.
Heidelberg retina tomography	A confocal laser scanning system providing 3-D images of the posterior segment of the eye to enable quantitative topographical assessment of ocular structures and changes over time.
Heterogeneity	Or lack of homogeneity. The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	This means that the results of studies included in a systematic review or meta-analysis are similar and there is no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hospital-based triage	A hospital-based risk assessment shortly after referral. Initial tests are performed to determine what happens next. For example, people at a low risk following initial testing by a nurse or technician may be discharged whereas those at higher risk may be directed to a more senior member of the assessment and diagnostic team, such as a consultant ophthalmologist.
Hypothesis	A supposition made as a starting point for further investigation.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

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

Term	Definition
	glaucoma.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life-years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Literature review	An article that summarises the evidence contained in a number of different individual studies and draws conclusions about their findings. It may or may not be systematically researched and developed.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Medical devices	All products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or handicap.
Medicines and Healthcare Products Regulatory Agency (MHRA)	The Executive Agency of the Department of Health protecting and promoting public health and patient safety by ensuring that medicines, healthcare products and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely.
Meta-analysis	A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Narrative summary	Summary of findings given as a written description.
Nerve fibre layer (NFL)	"The layer of the retina composed of the unmyelinated axons of the ganglion cells which converge towards the optic disc where they exit the eye and form the optic nerve."[93]
Normal-tension glaucoma (NTG; low-tension glaucoma)	See Glaucoma, normal-tension.
Number needed to treat (NNT)	The number of patients that who on average must be treated to prevent a single occurrence of the outcome of interest.
Observational study	Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups; for example, cohort studies and case–control studies.
Ocular hypertension	Consistently or recurrently elevated intraocular pressure (greater than 21

Term	Definition
	mmHg) in the absence of clinical evidence of optic nerve damage or visual field defect.
Odds ratio	A measure of treatment effectiveness. The odds of an event happening in the treatment group, expressed as a proportion of the odds of it happening in the control group. The 'odds' is the ratio of events to non-events.
Off-label	A drug or device used treat a condition or disease for which it is not specifically licensed.
Older people	People over the age of 65 years.
Open-angle glaucoma	See Glaucoma, open-angle.
Operating costs	Ongoing costs of carrying out an intervention, excluding capital costs.
Ophthalmic nurse	A nursing professional with specialist training and expertise in the care of conditions of the eye.
Ophthalmologist	A medically qualified specialist with expert knowledge of conditions affecting the eye and orbit, including diagnosis, management and surgery.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the loss of other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Optometrist	A healthcare professional with specialist training and expertise in conditions of the eye, especially measurement of vision and refractive error, prescription and dispensing of spectacles and contact lenses. Extended role optometrists or optometrists with a specialist interest increasingly participate in delivery of healthcare services for eye disease.
Orthoptist	A healthcare professional with specialist training and expertise in the care of conditions of the eye, especially measurement of vision in children and binocular function in children and adults.
Outcome	Measure of the possible results that may stem from exposure to a preventive or therapeutic intervention. Outcome measures may be intermediate endpoints or they can be final endpoints. See 'Intermediate outcome'.
P value	The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be 'statistically significant'.
Peer review	A process where research is scrutinised by experts that have not been involved in the design or execution of the studies.
Perimetry	The systematic measurement of visual field function using different types

Term	Definition
	and intensities of stimuli.
Perioperative	The period from admission through surgery until discharge, encompassing preoperative and post-operative periods.
Pigment dispersion syndrome (PDS)	"A degenerative process in the iris and ciliary body epithelium in which pigment granules are disseminated and deposited on the back surface of the cornea, the lens, the zonules and within the trabecular meshwork." "Deposition of pigment in the trabecular meshwork may give rise to glaucoma (called pigmentary glaucoma)."[93]
Pigmentary glaucoma	See Glaucoma, pigmentary.
Placebo	An inactive and physically identical medication or procedure used as a comparator in controlled clinical trials.
Placebo effect	A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	Pertaining to the period before surgery commences.
Primary care	Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.
Primary open-angle glaucoma (POAG)	See Glaucoma, primary open-angle
Primary research	Study generating original data rather than analysing data from existing studies (which is called secondary research).
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Progression	The worsening of COAG as clinically judged by the healthcare professional caring for the patient based on the assessment of visual field loss and optic nerve head appearance. To make this judgement, the healthcare professional must know the eye's earlier clinical state.
Prospective study	A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective.*
Pseudoexfoliation	"Deposition of grayish-white, flake-like basement membrane material on the anterior lens capsule, the iris and the ciliary processes with free-floating

Term	Definition
	particles in the anterior chamber."[93]
Pseudoexfoliative glaucoma	See Glaucoma, pseudoexfoliative
Qualitative research	Research concerned with subjective outcomes relating to social, emotional and experiential phenomena in health and social care.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost-utility analysis. The QALYs gained are the mean QALYs associated with one treatment minus the mean QALYs associated with an alternative treatment.
Quantitative research	Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census, which counts people and households.
Quick Reference Guide	An abridged version of NICE guidance, which presents the key priorities for implementation and summarises the recommendations for the core clinical audience.
Randomisation	Allocation of participants in a research study to 2 or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.
Randomised controlled trial (RCT)	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
RCT	See 'Randomised controlled trial'.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Referral filtering	A general term for any type of accuracy checking before referral to hospital eye services. Referral filtering may take the form of 'repeat measures', 'enhanced case finding', 'referral refinement', 'hospital-based triage' or 'administrative paper-based triage'.
Referral refinement	A 2-tier assessment in which initial evidence of abnormality found during case finding or screening is validated by an enhanced assessment, which adds value beyond that achieved through a simple 'repeat measures' scheme. A referral refinement service performs tests to diagnose OHT and suspected COAG and interprets the results in the light of clinical findings. Specialist practitioners who deliver this service independently have the

Term	Definition
	qualifications and experience set out in NICE guidance. Practitioners providing a referral refinement service should be qualified to make a diagnosis of OHT and suspected glaucoma, and to carry out gonioscopy to exclude angle-closure glaucoma.
Relative risk (RR)	The number of times more likely or less likely an event is to happen in one group compared with another (calculated as the risk of the event in group A/the risk of the event in group B).
Remit	The brief given by the Department of Health and Welsh Assembly Government at the beginning of the guideline development process. This defines core areas of care that the guideline needs to address.
Repeat measures	The repeated measurement of parameters related to the diagnosis of glaucoma. A simple repeat measures scheme may involve repeat measurement of IOP only. Other repeat measures schemes may also include repeated measurement of visual fields and other relevant ocular parameters when clinically necessary.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A retrospective study deals with the present or past and does not involve studying future events. This contrasts with studies that are *prospective.*
Secondary benefits	Benefits resulting from a treatment in addition to the primary, intended outcome.
Secondary glaucoma	See Glaucoma, secondary.
Selection bias (also allocation bias)	A systematic bias in selecting participants for study groups, so that the groups have differences in prognosis and/or therapeutic sensitivities at baseline. Randomisation (with concealed allocation) of patients protects against this bias.
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Sensitivity	Sensitivity or recall rate is the proportion of true positives that are correctly identified as such. For example, in diagnostic testing, it is the proportion of true cases that the test detects. See the related term 'Specificity'.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on

Term	Definition
	the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Sight loss	Sight loss in glaucoma is visual damage that manifests as blind spots in the field of vision. Early on, these are mostly asymptomatic with many people being unaware of a problem. Sight loss may progress and become symptomatic and eventually cause visual impairment.
Sight test	A sight test determines whether or not a person has a sight defect, and if so what is needed to correct, remedy or relieve it. An optometrist performing a sight test has to conduct the examinations specified in the Sight Testing (Examination and Prescription; No 2) Regulations 1989. These include an internal and external examination of the eyes and any other examinations needed to detect signs of injury, disease or abnormality in the eye or elsewhere.
Specificity	The proportion of true negatives that a correctly identified as such. For example, in diagnostic testing the specificity is the proportion of non-cases incorrectly diagnosed as cases? See related term 'Sensitivity'. In terms of literature searching, a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	Those with an interest in the use of the guideline. Stakeholders include manufacturers, sponsors, healthcare professionals, and patient and carer groups.
Statistical power	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Synthesis of evidence	A generic term to describe methods used for summarising (comparing and contrasting) evidence into a clinically meaningful conclusion in order to answer a defined clinical question. This can include systematic review (with or without meta-analysis), qualitative and narrative summaries.
Systematic review	Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and

Term	Definition
	report their findings. It may or may not use statistical meta-analysis.
Time horizon	The time span used in the NICE appraisal that reflects the period over which the main differences between interventions in health effects and use of healthcare resources are expected to be experienced, and taking into account the limitations of supportive evidence.
Tonometry	A test to measure intraocular pressure using an instrument called a tonometer.
Trabecular meshwork	"Meshwork of connective tissue located at the angle of the anterior chamber of the eye and containing endothelium-lined spaces through which passes the aqueous humor to Schlemm's canal."[93]
Trabeculectomy	A surgical procedure that lowers IOP by creating a fistula, which allows aqueous outflow from the anterior chamber to the sub-tenon space.[67]
Treatment allocation	Assigning a participant to a particular arm of the trial.
Treatment options	The choices of intervention available.
Unacceptable IOP	Intraocular pressure not at clinically acceptable level.
Utility	A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.
van Herick Test	The van Herick's peripheral anterior chamber depth assessment test is a slit lamp estimation of the depth of the peripheral anterior chamber of the eye and is used as a proxy measure for judging whether the anterior chamber angle is open.
Visual field	The area that can be seen when the eye is directed forward, including both central and peripheral vision.
Visual impairment	A severe reduction in vision, which cannot be corrected with standard glasses or contact lenses and reduces a person's ability to function in a visual environment.

15.2 General terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.

Term	Definition
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples, see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise

Term	Definition
	as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population.

Term	Definition
	The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that "based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110". In such a case, the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore, age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost-benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost-consequences analysis (CCA)	Cost-consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).

Term	Definition
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost-utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis.
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequences analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%.

Term	Definition
	The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore cost-effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.

Term	Definition
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as (£20,000 × QALYs gained) − Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms, this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See ‘Product licence’.
Life years gained	Mean average years of life gained per person as a result of the intervention

Term	Definition
	compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease and can be interpreted as the probability that a negative test result is correct. It is calculated as follows: TN/(TN+FN).
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Non-randomised intervention study	A quantitative study investigating the effectiveness of an intervention that does not use randomisation to allocate patients (or units) to treatment groups. Non-randomised studies include observational studies, where allocation to groups occurs through usual treatment decisions or people's preferences. Non-randomised studies can also be experimental, where the investigator has some degree of control over the allocation of treatments. Non-randomized intervention studies can use a number of different study designs, and include cohort studies, case-control studies, controlled before-and-after studies, interrupted-time-series studies and quasi-randomised controlled trials.

Term	Definition
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant.

Term	Definition
	For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics, this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows: TP/(TP+FP).
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics, this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists

Term	Definition
	and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and do not publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a

Term	Definition
	positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Risk ratio (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the risk ratio is 1. If the first group had a risk ratio of 2, subjects in that group would be twice as likely to have the event happen. A risk ratio of less than 1 means the outcome is less likely in the first group. The risk ratio is sometimes referred to as relative risk.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who do not have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative').

Term	Definition
	Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who do not have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example, in diagnostic testing, the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching, a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a

Term	Definition
	decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis that separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).