6-year surveillance 2015 – Glaucoma (2009) NICE guideline CG85

Appendix A: decision matrix

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Diagnosis			
CG85 – 01. Is non-contact tonometry suitable as an alternative to Goldmann applanation Tonomotry for measuring intraocular pressure (IOP)? (1.1.1;1.1.6)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
CG85 – 02. Are disposable prisms suitable as an alternative to Goldmann prisms when using Goldmann Applanation Tonometry? (1.1.1;1.1.6)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
CG85 – 03. Are any other imaging tests suitable as alternatives to biomicroscopic slit lamp examination with stereophotography? (1.1.1;1.1.6)			

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No relevant evidence identified.	A systematic review[1] (number of studies unconfirmed) of colour doppler imaging of retrobulbar blood flow velocities in primary open-angle glaucoma (POAG) found that peak systolic velocity and end diastolic velocity were statistically significantly reduced in the ophthalmic artery, central retinal artery and short posterior ciliary artery. Colour Doppler imaging was considered to be a potential diagnostic tool for POAG. It should be noted that the number of studies and pooled sample size was not stated in the abstract, which limits the assessment of the impact of this meta-analysis on the guideline recommendations. The GATE study[2] (publication date to be confirmed) assessed the diagnostic performance and cost-effectiveness of imaging technologies, as triage tests, for identifying people with glaucoma. Heidelberg Retinal Tomogram, scanning laser polarimetry and optical coherence tomograph were compared. Heidelberg Retinal Tomogram had the highest sensitivity, but the lowest specificity. Scanning laser polarimetry had the highest specificity but the lowest sensitivity. The preliminary results also showed that introducing a composite triage station into the referral pathway to identify appropriate referrals was cost-effective.	Topic expert feedback indicated that there was new evidence related to diagnostics that may contradict recommendations. The following areas were highlighted: • Optical coherence tomography (OCT) disc and retinal imaging is currently being investigated as a potential tool to aid diagnosis and disease monitoring. The GATE study will provide new and potentially useful information regarding the role of 3 alternative optic nerve head imaging technologies, OCT being the newest. The results could feed into the glaucoma case finding / diagnostic scenario but these technologies alone were not considered to be sufficient as stand-alone tools for glaucoma screening / case finding / referral. As an element within a 'sequential test series cascade' however	New evidence was identified that may have a future impact on guideline recommendations. In CG85, biomicroscopic slit lamp examination by a trained clinician was considered to be the reference standard for optic nerve assessment. This is frequently combined with imaging, stereophotography being the imaging standard. New systematic review evidence identified through the 6-year surveillance review indicates that colour Doppler imaging is a potential diagnostic tool for POAG, but further research is necessary to confirm a definite impact on recommendation 1.1.1. The full results of the GATE study are awaited in order to assess the impact on recommendation 1.1.1 of three new imaging technologies for the diagnosis of glaucoma in secondary care. Preliminary reports from this new evidence suggest that introducing a composite triage station into the referral pathway to identify appropriate referrals is cost-effective. Further evidence is required on the

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		they could be valuable. • Many new devices and upgraded technologies for imaging the retinal nerve fibre layer have become available to optometrists and Hospital eye service (HES) departments	following diagnostic technologies highlighted by clinical feedback: • OCT disc and retinal imaging • new devices and upgraded technologies for imaging the retinal nerve fibre layer. **Surveillance decision** This review question should not be updated.
CG85 – 04. Are any other visual field tests suitable as alternatives to 24-2 SITA Humphrey perimetry for diagnosis of glaucomatous visual field damage? (1.1.1;1.1.6)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
CG85 – 05. Are other methods of assessing anterior chamber angles suitable as alternatives to gonioscopy? (1.1.1;1.1.6)			
No relevant evidence identified.	A systematic review[3] (30 studies) found that assessment of pupils using pupillary light reflex was a potential diagnostic tool in identifying persons with glaucoma, through the detection of relative afferent pupillary defect.	None identified relevant to this question.	No new evidence was identified that may change guideline recommendations. New systematic review evidence identified at the 6 year surveillance review suggests that assessment of pupils using pupillary light reflex was a potential diagnostic tool in identifying persons with glaucoma,

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			through the detection of relative afferent pupillary defect. Further evidence is necessary on specific instruments and approaches to confirm any definite impact on recommendation 1.1.1. **Surveillance decision** This review question should not be updated.
Monitoring			
CG85 – 06. Which diagnostic tools could be used at monitoring visits? (1.2.1)			
A systematic review[4] which evaluated the effectiveness of visual function tests in diagnosing glaucoma and in monitoring progression was identified. The review indicated that standard white-on-white automated perimetry remains the most commonly performed test for assessing the visual field, with the Swedish interactive threshold algorithm largely replacing full-threshold testing strategies. The review concluded that whilst advances in technology and newer analytic tools had provided more rapid and varied ways of assessing visual function in glaucoma, these techniques had not yet produced a definitive new direction for the diagnosis of glaucoma or its progression over time. The guideline currently recommends that automated perimetry should be offered for diagnosis and monitoring of patients with chronic open angle glaucoma (COAG), suspected COAG or possible COAG under investigation.	NICE Medtech Innovation briefing MIB14 was published in 2014. This covers the SENSIMED Triggerfish contact lens sensor for continuous 24-hour recording of ocular dimensional changes in people with or at risk of developing glaucoma. No evidence was identified to show that 24-hour recording with the SENSIMED Triggerfish leads to improved clinical outcomes for patients, such as control of intraocular pressure IOP, progression from ocular hypertension (OHT) to glaucoma, or vision loss. A systematic review and economic analysis[5] aiming to determine effective and efficient monitoring criteria for OHT included a systematic review of tonometers. 102 comparative studies assessed the agreement of at least one tonometer with GAT. The	None identified relevant to this question.	New evidence was identified that may change guideline recommendations. CG85 currently recommends (recommendation 1.2.5) that automated perimetry should be offered for diagnosis and monitoring of patients with COAG, suspected COAG or possible COAG under investigation. The evidence at the 3 year surveillance review identified supports the recommendations within the guideline. There was insufficient evidence to demonstrate that 24-hour recording with the SENSIMED Triggerfish leads to improved clinical outcomes for patients,

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The evidence identified at the 3-year surveillance review was considered to support the recommendations within CG85.	results indicated that due to sizeable measurement variability between tonometers, the same type of tonometer should be used to compare IOP measurements in an individual. However, the results also raise questions over the validity of GAT as the default standard as sizeable inter- and intraobserver variability was observed for all tonometers.		such as control of IOP, progression from OHT to glaucoma, or vision loss. Further evidence is required on this technology to establish any potential impact on recommendations. The new evidence indicated that, due to sizeable measurement variability between tonometers, the same type of tonometer should be used to compare IOP measurements in an individual. This is consistent with CG85, which recommends using GAT consistently at each monitoring assessment (1.2.1). However, there is a potential impact on recommendation 1.2.1 as the new evidence indicated that GAT may not be the most appropriate standard tonometer. **Surveillance decision** This review question should be updated. Overall, topic expert feedback indicated that it is not necessary to change the recommendation in relation to using the GAT as it is considered to be the gold standard. However, topic experts noted there would be value in clarifying the use of the GAT or other tonometers (such as Icare and Perkins) for different populations based on risk level. It was also considered

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			important to distinguish the value of the GAT for people with diagnosed glaucoma, and other tonometers for people with OHT and suspected glaucoma.

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CG85 – 07. At what intervals should patients be offered monitoring? (1.2.1; 1.2.10; 1.2.12; 1.2.14) **What is the optimal frequency of monitoring visits for patients with OHT and COAG suspects?** **What is the optimal frequency of monitoring visits for patients with COAG?**			
No relevant evidence identified.	An economic modelling evaluation[5] aimed to determine effective and efficient monitoring criteria for raised IOP through (i) identification and validation of glaucoma risk prediction models; and (ii) development of models to determine optimal surveillance pathways. Five pathways were compared including 'NICE intensive' (4-monthly to annual monitoring) and 'NICE conservative' (6-monthly to biennial monitoring). Results showed that the best available glaucoma risk prediction model estimated the 5-year risk based on age and ocular predictors. The results also showed that there was no clear benefit from intensive monitoring. A cohort study was recommended to provide data to refine the glaucoma risk prediction model, determine the optimum type and frequency of serial glaucoma tests and estimate costs and patient preferences for monitoring and treatment.	Clinical feedback highlighted the questionable value of yearly visual field testing for the majority of stable patients, as it could be time consuming, costly and distressing for some patients. Following the CG85 guidelines may increase pressure on most departments and could potentially lead to patients who are getting worse being missed. The clinical feedback indicated, therefore, that there may be value in revisiting the currently recommended monitoring interval frequencies in the light of many glaucoma departments struggling even to provide appointments under current financial and resource constraints. Clinical feedback further indicated that the CG85 monitoring criteria are very	New evidence was identified that may change guideline recommendations. There is a potential impact on CG85 recommendations 1.2.10 and 1.2.12, and Table 4, which advise monitoring at regular intervals from 1-24 months according to risk, to be clinically judged in terms of age, IOP, CCT, appearance and size of optic nerve head. Although the findings are consistent with CG85 criteria for biennial IOP monitoring for untreated or stable treated OHT, the authors also concluded that that there was no clear benefit from intensive monitoring for raised IOP. However, the limitations highlighted indicate that further research is required in the form of a prospective cohort study using a representative sample of newly diagnosed OHT patients. Clinical feedback stated that CG85 monitoring criteria are deliberately broad to cater for the wide variations in case mix. Intensive monitoring is amongst the range of possible options. Excluding it as an

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		broad to cater for the wide variations in case mix. Intensive monitoring is amongst the range of possible options. Excluding it as an option would potentially place the small but significant minority of individuals who are in the high risk subgroup at risk of conversion and subsequent vision loss. It should be recognised that OHT risk is a continuous spectrum from minimal to significant. One size will not fit all which is why clinical knowledge and experience are required when taking care of high risk people. They are, however, very much present in the real world environment in which NICE guidance must be applied. Clinical risk assessment would be part of the decision and no glaucoma clinician would institute an intensive regime in a blanket manner. The feedback indicated that the results must therefore be interpreted with	option would potentially place the high risk subgroup at risk of conversion and subsequent vision loss. Further clinical feedback indicated that the biggest resource in terms of time and equipment is optic nerve imaging and visual field testing. The new evidence does not make recommendations relating to frequency of these tests, which is the aspect of the service that most contributes to the capacity problems. However, the collective clinical feedback indicated that risk prediction and monitoring intervals in CG85 require review in the light of the new evidence. **Surveillance decision** This review question should be updated. It was agreed with topic experts that Table 4 'Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication' could be made clearer. It was suggested that this was more about further clarification of the monitoring information rather than changing it. Furthermore, there may be an opportunity to develop research recommendations to encourage further research to define risk levels that could further inform future recommendations in

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		caution. Further clinical feedback indicated that the biggest resource in terms of time and equipment is optic nerve imaging and visual field testing. This study does not make recommendations relating to frequency of these tests, which is the aspect of the service that most contributes to the capacity problems. However, additional clinical feedback indicated that risk prediction and monitoring intervals in CG85 require review in the light of this study.	this area.
Treatment for people with OHT and suspected COAG			
CG85 – 08. Is treatment overall clinically and cost effective? (1.3.1-1.3.7)			
A meta-analysis[6] to estimate the effect of reducing IOP on the incidence of POAG in patients with OHT, and the progression of glaucoma was identified. The resulting meta-analysis of ten trials indicated that OHT therapy reduces the risk of conversion to glaucoma with the risk reduction increasing with greater IOP reduction. Two further studies were identified[7,8]. One RCT	A systematic review and meta analysis[9] (8 studies, n=841) evaluated the efficacy and tolerability of the fixed combinations latanoprost/timolol versus dorzolamide/timolol in patients with elevated IOP. Latanoprost/timolol was found to have equivalent efficacy in IOP lowering but was better tolerated. A meta analysis[10] (7 studies, n=582) evaluated the	Clinical feedback indicated that Xalatan (latanoprost) has come off patent and several other agents (not specified) including combined preparations are available as generics. For CG85, economic modelling was	New evidence was identified that may change guideline recommendations 1.3.1, 1.3.4, 1.3.5, 1.3.7 The evidence identified at the 3 year review was not considered to have any impact on current guideline

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
compared earlier against later treatment with topical ocular hypertensive medication in preventing POAG in individuals with OHT. This study found that treatment reduced the risk of development of POAG with absolute reduction greatest among participants at the highest baseline risk of developing POAG. However, a six year follow up of a cohort of patients from the no treatment arm of a RCT indicated that in patients with early glaucoma, IOP remained stable without treatment regardless of baseline IOP, except for patients with exfoliation glaucoma. The conclusions and economic model within CG85 indicated that the treatment for all individuals with OHT was not cost effective. However, it was cost effective in preventing eventual vision loss from COAG in patients in higher risk OHT subgroups. The evidence identified at the 3-year surveillance review was felt to support these conclusions.	efficacy and tolerability of the fixed-combination brimonidine 0.2%/timolol 0.5% (FCBT) compared with the fixed-combination dorzolamide 2%/timolol 0.5% (FCDT) in the treatment of patients with elevated IOP. Both FCBT and FCDT were found to lower IOP in patients with elevated IOP, and the IOP-lowering efficacy of FCBT was noninferior to that of FCDT. FCBT was reported to cause less burning or stinging, although it was not confirmed in the abstract whether this was statistically significant.	conducted to identify the most cost-effective treatment options for people with OHT and suspected COAG, and people with COAG. The original model constructed for the guideline was sensitive to changes in costs associated with referral, diagnosis and treatment. Feedback from clinicians, the NCC and the NICE health economist team indicate that the unit cost changes are highly likely to alter the recommendations for the treatment of OHT and suspected COAG. Clinical feedback also highlighted that with fixed dose combination treatment there is less exposure to preservatives and their associated risks. Stakeholder feedback stated that since Xalatan came off patent, different generic	recommendations. The new systematic review evidence identified at the 6 year review was consistent with CG85 recommendation 1.3.1 which advises treatment based on risk. Further evidence is required on fixed combination drug treatments to establish a definite impact on CG85. Clinical feedback and intelligence gathering at the 6 year review indicated that as a PGA available on the NHS (latanoprost) is now generically available, the expected cost of medical treatment of PGAs is likely to change. Several other agents will be off patent soon and others are being remarketed at different concentrations. Both the fixed dose combinations latanoprost/timolol and dorzolamide/timolol are available as generics. There are also more expensive preservative free preparations which are increasingly required for patients on long term topical medications. There is therefore a potential impact on the economic modelling and on

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		versions are being offered to patients with different types of droppers. Patient experience indicates that some droppers are easier to use than others. The stakeholder feedback highlighted the need for clinicians to discuss the different types of droppers and help patients select the one that is right for them - or at least spend time showing the patient how to use the new dropper. This feedback is also relevant to question CG85-20.	recommendations 1.3.1, 1.3.4, 1.3.5, 1.3.7 Stakeholder feedback indicated that different generic versions of latanoprost are being offered to patients with different types of droppers and this has created a need for patient information in this area. CG85 already states that the healthcare professional should offer people the opportunity to discuss their treatment and provide them with relevant information. This was stated to include how to apply eye drops, and technique(s) (punctal occlusion and devices). However, this specific area of patient information was considered to have a potential impact on CG85 recommendation 1.6.1. **Surveillance decision** This review question should be updated. The evidence identified through the surveillance review was not considered to have any impact on the guideline recommendations. However, clinical feedback and intelligence gathering through the surveillance review indicated that as a PGA available on the NHS (latanoprost) is now available in multiple generic products, the expected cost of medical treatment with PGAs is likely to

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			change. The topic experts agreed that this would have an impact on the economic modelling as a result of this, and the following aspects should be considered in an updated economic analysis: • Treating lower risk groups and including visual field measurement in the cost-effectiveness analysis. • Adverse effects of eye drops, particularly as a result of switching treatments, over the short and long term. An economic evaluation also highlighted this area. • Preservative-free and fixed-combination solutions need to be included as additional comparators. Topic experts advised that information for pharmacists and GPs should be addressed in relation to discussing the different types of droppers to help people select the one that is right for them, or at least spend time showing the patient how to use a new dropper. It was suggested linking to published NICE guidelines on Medicines adherence and Medicines

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			optimisation would help to address this.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Treatment for people with COAG - Effectiveness of IOP-lowering interventions			
CG85 – 09. Which are the most clinically and cost effective and least harmful pharmacological treatments from the following classes of drugs? (1.4.1; 1.4.2, 1.4.5; 1.4.6; 1.4.8; 1.4.9; 1.4.10) • **topical beta-blockers** • **topical prostaglandin analogues (PGAs)** • **topical sympathomimetics** • **topical and systemic carbonic anhydrase inhibitors** • **topical miotics**			
In total 14 studies (including 1 systematic review and three meta-analyses) were identified that compared the effectiveness of different pharmacological interventions for the treatment of OHT, suspected COAG or COAG. A network meta-analysis[11] which compared the effectiveness of topical pharmacological treatment for POAG or OHT in lowering IOP was identified. The study, which combined direct and indirect estimates of the effect of eight drugs and placebo from 28 RCTs, indicated that all drugs were more effective than placebo in lowering IOP. The rank order from high to low in treatment effects in terms of the mean IOP reduction was bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, brinzolamide at peak effect. In addition the following studies were identified which compared different classes of drugs:	**Preservative free preparations** A meta-analysis[28] (21 studies) assessed the relative efficacy and tolerability of preservative-free latanoprost (T2345) compared with other PGAs for the treatment of open-angle glaucoma and ocular hypertension. There were no statistically significant differences between T2345 and other PGAs in terms of efficacy on IOP. T2345 showed statistically significant superiority over BAK-tafluprost. The risk of hyperaemia was statistically significantly lower with T2345 than with all the other PGAs. A systematic review[29] (5 studies) explored the safety and efficacy of eye drops without benzalkonium chloride (BAK) in treating glaucoma and ocular hypertension. There was found to be no difference between the eye drops with or without BAK in lowering IOP, but there were more adverse effects of eyedrops without BAK.	Clinical feedback indicated that Xalatan (latanoprost) has come off patent and several other agents (not specified) including combined preparations are available as generics. For CG85, economic modelling was conducted to identify the most cost-effective treatment options for people with OHT and suspected COAG, and people with COAG. The original model constructed for the guideline was sensitive to changes in costs associated with referral, diagnosis and treatment.	New evidence was identified which may change recommendations 1.4.2, 1.4.6, 1.4.8, 1.4.9. The evidence identified at the 3 year review was not considered to have any impact on current guideline recommendations. On the whole, the identified new evidence at the 6 year review in relation to pharmacological treatments supports the efficacy of currently recommended treatments. However, factoring other data into the health economic model may influence current guideline recommendations.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
PGA versus PGA Two meta-analyses[12,13] compared the efficacy and tolerability of travoprost and latanoprost in patients with OAG or OHT. The results indicated that these agents had similar efficacy in reducing IOP and both agents were generally well tolerated. One RCT[14] reported that there was no significant difference in efficacy or tolerance of three PGAs, bimatoprost, latanoprost and travoprost, in patients with previously untreated OAG and OHT following six months of treatment. One RCT[15] found that daily doses of bimatoprost 0.03% and travoprost 0.004% were equally effective at lowering IOP in patients with POAG or OHT. One RCT[16] evaluated the dosing of bimatoprost in patients with COAG or OHT. Bimatoprost 0.01% was found to have equivalent efficacy to bimatoprost 0.03% or 0.0125% in lowering IOP and demonstrated improved tolerability. **Beta- blocker versus sympathomimetrics** One RCT[17] indicated that brimonidine tartrate 0.2% was more effective in preserving visual function than timolol maleate 0.5% in patients with low-pressure COAG. However, brimonidine treatment had significantly more	**Prostaglandin analogues** A systematic review[30] (32 studies) comparing the efficacy and tolerability of 4 PGAs as first-line monotherapies for IOP lowering in adult patients with primary open-angle glaucoma or ocular hypertension. The PGAs included in the comparison were bimatoprost, latanoprost, tafluprost, and travoprost, in addition to PGA with timolol. The results showed that bimatoprost achieved the highest efficacy in terms of IOP reduction but was associated with the highest risk of developing hyperaemia, whereas latanoprost had the most favourable tolerability profile. A systematic review[31] (5 studies n=528) examined the efficacy and tolerability of latanoprost compared with timolol in the treatment of patients with COAG. Latanoprost was found to provide greater IOP-lowering efficacy than timolol in the treatment of patients with chronic angle-closure glaucoma. Latanoprost caused conjunctival hyperaemia in more patients than timolol. **Long term medical management** An economic evaluation[32] based on systematic review data assessed the long-term economic consequences of the medical management of	Feedback from clinicians, the NCC and the NICE health economist team indicate that the unit cost changes are highly likely to alter the recommendations for the treatment of OHT and suspected COAG. Stakeholder feedback indicated that any update to the economic model for CG85 should take into account the feasibility of cost comparisons based on the medium to long-term benefits of preservative-free formulations. The cost consequences of ocular surface disease relating to the use of preservative-containing products should also be considered when updating the economic model. The emerging body of evidence demonstrates that approximately 50% of glaucoma patients suffer from concurrent ocular surface disease, and that preservatives contribute to,	CG85 does not currently recommend any specific PGA in priority over others. Recommendation 1.4.8 advises offering alternative pharmacological treatments or preservative free preparations to people with COAG who are intolerant to a prescribed medication. The new systematic review evidence on preservative free treatments is consistent with this recommendation. The new systematic review evidence identified at the 6 year review comparing PGA monotherapies demonstrated a trade-off between benefits and harms that does not favour any specific drug. However, Clinical feedback and intelligence gathering indicated that as a PGA available on the NHS (latanoprost) is now generically available, the expected cost of medical treatment of PGA is likely to change. Several other agents will be off patent soon and others are being remarketed at different concentrations. There are also more expensive preservative free preparations which are increasingly required for patients on long term topical medications, to prevent ocular surface

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patients discontinuing treatment due to drug-related adverse events. **Beta- blockers v PGA** A post hoc analysis of three 6-month RCTs[18] reported that latanoprost results in fewer patients with high IOP fluctuation compared to timolol in patients with COAG or OHT. **Combination therapy** One small RCT[19] compared the effects of latanoprost/timolol versus dorzolamide/timolol fixed combinations on IOP in patients with OAG. One year of either treatment regime resulted in similar IOP lowering effects as well as stable visual function and structure. A non-inferiority RCT[20] compared the IOP-lowering efficacy of twice daily dosing of two fixed combination products, brinzolamide/timolol suspension and dorzolamide / timolol solution in patients with OAG or OHT who required a therapy change due to elevated IOP. The treatments were found to have comparable IOP-lowering efficacy, however brinzolamide/timolol suspension showed significantly less ocular irritation. Three fixed combinations of latanoprost /timolol, bimatoprost /timolol, or travoprost/timolol were all found to be effective at lowering IOP in an RCT[21] in patients	glaucoma in the UK. The results indicated that drug acquisition costs are not a key driver of the total cost of glaucoma management and the cost of medical therapy is offset by avoiding the cost of managing low vision. Long term consequences of treatment were found to affect cost effectiveness due to minimising therapy switches.	and exacerbate this. However, the cited observational studies did not meet the inclusion criteria for the 6 year review and were not included. Stakeholder feedback also stated that since Xalatan came off patent, different generic versions are being offered to patients with different types of droppers. Patient experience indicates that some droppers are easier to use than others. The stakeholder feedback highlighted the need for clinicians to discuss the different types of droppers and help patients select the one that is right for them - or at least spend time showing the patient how to use the new dropper. This feedback is also relevant to question CG85-20.	disease. There is therefore a potential impact on the economic modelling and on recommendations 1.4.2, 1.4.6, 1.4.8, 1.4.9. New economic evaluation evidence indicated that the economic models of glaucoma should include the long-term consequences of treatment as these will affect cost-effectiveness. Stakeholder feedback indicated that different generic versions of latanoprost are being offered to patients with different types of droppers and this has created a need for patient information in this area. CG85 already states that the healthcare professional should offer people the opportunity to discuss their treatment and provide them with relevant information. This was stated to include how to apply eye drops, and technique(s) (punctal occlusion and devices). However, this specific area of patient information was considered to have a potential impact on CG85 recommendation 1.6.1.

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with POAG or OHT. However after 1 year of treatment latanoprost /timolol and bimatoprost /timolol were more effective than travoprost/timolol. The latanoprost /timolol treatment showed less hyperaemia than bimatoprost /timolol throughout the study. A post hoc analysis[22] from two RCTs indicated that patients with OHT or COAG treated with fixed-combination brimonidine/timolol were more likely than patients treated with either brimonidine or timolol alone to achieve a combination of low mean IOP and low short-term (daily) or long-term (intervisit) IOP fluctuation. A post hoc analysis[23] of an RCT evaluated differences in diurnal IOP fluctuation in COAG or OHT patients treated with once-daily fixed-combination latanoprost/timolol, once-daily latanoprost or twice-daily timolol. The fixed-combination latanoprost/timolol resulted in lower diurnal IOP fluctuation and significantly fewer patients with a high fluctuation than treatment with latanoprost or timolol monotherapy. One RCT[24] found that the daytime efficacy of a fixed combination of timolol and brimonidine was equivalent to a timolol and dorzolamide fixed combination in patients with pseudoexfoliation glaucoma in reducing daytime diurnal IOP. **Adverse events associated with pharmacological**			**Surveillance decision** This review question should be updated. The evidence identified through the surveillance review was not considered to have any impact on the guideline recommendations. However, clinical feedback and intelligence gathering through the surveillance review indicated that as a PGA available on the NHS (latanoprost) is now available in multiple generic products, the expected cost of medical treatment with PGAs is likely to change. The topic experts agreed that this would have an impact on the economic modelling as a result of this, and the following aspects should be considered in an updated economic analysis: • Treating lower risk groups and including visual field measurement in the cost-effectiveness analysis. • Adverse effects of eye drops, particularly as a result of switching treatments, over the short and long term. An economic evaluation also highlighted this area.

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treatments A meta-analysis[25] of the safety and tolerability from two RCTs for thrice daily brimonidine purite 0.1% and brimonidine purite 0.15%, for reducing IOP in patients with OAG or OHT was identified. The study indicated that brimonidine 0.1% had an improved systemic safety and tolerability compared with brimonidine purite 0.15% however the ocular safety and tolerability of the formulations are similar. A second meta-analysis[26] investigated the occurrence of conjunctival hyperaemia in patients with OHT or OAG using latanoprost versus travoprost and bimatoprost.The results indicated that the use of latanoprost was associated with a lower incidence of conjunctival hyperaemia when compared with travoprost and bimatoprost. In addition, a pooled analysis[27] of six RCTs indicated that once daily compared to twice daily bimatoprost 0.03% has a favourable safety and tolerability profile. Adverse events reported were conjunctival hyperaemia, increased eyelash growth, eye pruritus, periocular skin hyperpigmentation, eye irritation, dry eye, and hypertrichosis. **Summary** The recommendations for treatment options in CG85 were based on a health economics model which resulted in algorithms for treatment stratified by condition and severity of disease along with the age of patients. Pharmacological treatment options in the current			• Preservative-free and fixed-combination solutions need to be included as additional comparators. Topic experts advised that information for pharmacists and GPs should be addressed in relation to discussing the different types of droppers to help people select the one that is right for them, or at least spend time showing the patient how to use a new dropper. It was suggested linking to published NICE guidelines on Medicines adherence and Medicines optimisation would help to address this.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
guideline are restricted to two classes of medication, PGAs and beta-blockers, with no individual drugs named as the recommended medication. On the whole, the evidence identified at the 3-year surveillance in relation to pharmacological treatments was considered to support the efficacy of currently recommended treatments. There was new evidence from direct head to head comparisons that PGAs have similar levels of effectiveness. In addition, there was new evidence relating to comparative efficacy of different fixed combination therapies, however it was felt that this data did not provide a consensus as to the most effective combination due to the large number of potential comparators. Two additional studies relating to fixed versus monotherapy were also identified. These studies provided evidence that contradicted the evidence in the current guideline.			
CG85 – 10. Which is the most effective and least harmful concentration of timolol between 0.5% and 0.25%? (1.4.6; 1.4.10)			
No relevant evidence identified	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
CG85 – 11. Are combinations of topical medications (pre-prepared in one bottle or as separate bottles) more effective and less harmful than single medications? (1.4.6; 1.4.10)			

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified	The NICE Evidence Summary ESNM56 (brinzolamide/brimonidine for glaucoma) was retrieved which found that in 2 RCTs in people with glaucoma, brinzolamide/brimonidine combination eye drops were significantly superior to either constituent drug administered alone as monotherapy in reducing IOP at 3 months. The combination eye drops were non-inferior to brinzolamide plus brimonidine administered concomitantly. Most reported adverse events were mild to moderate and localised, but these were higher in number with the combination eye drops compared with the individual constituent drugs. There were no published studies comparing brinzolamide/brimonidine combination eye drops with other drug treatments for managing glaucoma and ocular hypertension. ESNM56 reported that brinzolamide/brimonidine may be an alternative treatment option for some people, for whom PGAs and beta-blockers are unsuitable. A systematic review[33] (41 studies) evaluated the IOP-lowering effect of the commonly used fixed-combination drugs containing 0.5% timolol. All six commonly used fixed-combination drugs containing timolol were found to effectively lower IOP in patients with POAG and OHT, and both latanoprost/timolol and travoprost/timolol might achieve better IOP-lowering effects.	None identified relevant to this question.	No new evidence was identified that may change guideline recommendations. Further research is required on the comparative effectiveness of brinzolamide/brimonidine combination treatment with other combination and monotherapy treatments, before any potential impact on CG85 recommendations can be established. The other new systematic review evidence identified on commonly used fixed-combination treatments is consistent with CG85 recommendation 1.4.6, which does not stipulate prioritising a specific combination but advises that more than one agent may be needed concurrently to achieve target IOP. **Surveillance decision** This review question should not be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	A systematic review[34] (11 studies, n=1493) evaluated the efficacy of brimonidine, dorzolamide and brinzolamide in reducing IOP when used as adjunctive therapy to beta-blockers or PGAs in patients with POAG. Brimonidine was found to provide greater IOP-lowering efficacy than topical carbonic anhydrase inhibitors as adjunctive therapy. A systematic review[35] (18 studies) assessed the IOP-lowering effect of PGAs administered in combination with beta-blockers to patients with glaucoma or ocular hypertension. Fixed combinations were found to be more efficacious than their individual components but less efficacious than their respective unfixed combinations. However, the fixed combinations led to a lower hyperaemia risk than both unfixed combinations and monotherapy. A systematic review[36] (number of studies unconfirmed in the abstract) assessed the effects of the fixed combination of 0.005% latanoprost and 0.5% timolol (FCLT) vs the individual components for POAG. The results showed FCLT had a greater IOP lowering effect than monotherapy, but that there was no statistical difference in the outcomes of visual field defect and optic atrophy.		

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG85 – 12. Which is the most effective and least harmful laser treatment between argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT)? (1.4.6; 1.4.8; 1.4.9; 1.4.10)			
One RCT[37] indicated that SLT and ALT had a similar effect over 5 years in patients with OAG on maximal tolerated medical therapy with no significant change in IOP in either of the two groups. Whereas, a second RCT[38] comparing SLT to ALT as treatment in patients with uncontrolled OAG on maximally tolerated medication therapy showed that both treatments were equally effective in lowering IOP. One RCT[39] found that titanium: sapphire laser trabeculoplasty had similar efficacy to ALT in IOP reduction in patients with uncontrolled OAG. Excimer laser trabeculotomy ab interno was shown to be as effective as SLT in patients with POAG refractory to medical therapy for reduction of IOP[40]. One RCT[41] indicated that pneumatic trabeculoplasty was less effective than ALT in POAG uncontrolled with two topical therapies.	A systematic review and meta analysis[42] (6 studies n=482) compared outcomes between SLT and ALT in open-angle glaucoma at different times post-treatment. The results showed that SLT had equivalent efficacy to ALT with a similar rate of side effects. A statistically significant difference in favour of SLT was found when comparing the IOP reduction at 3 months after intervention, but not at any other timepoint (1 hour, 1 week, 1 month, 6 months, and successive annual points 1-5 years). A meta analysis[43] (6 Studies) evaluated the efficacy and tolerability of SLT and ALT in the treatment of open-angle glaucoma. The results showed that there was no significant difference in therapeutic IOP responses between SLT and ALT. When compared in patients with previous failed laser treatment, SLT was more effective in IOP reduction than ALT but the statistical significance was not reported in the abstract. The difference in tolerability of the 2 lasers was not significant. A systemic review[44] (17 studies) compared SLT to other glaucoma treatment options in terms of their IOP-lowering effect finding no difference between SLT and ALT. Three trials indicated no difference between 360degree SLT and medical therapy, with	None identified relevant to this question.	No new evidence was identified that would affect recommendations. The new systematic review evidence indicates equivalent efficacy and tolerability between argon and SLT. This is consistent with CG85 which advises laser trabeculoplasty treatment but does not prioritise between argon and selective techniques (recommendations 1.4.6, 1.4.8, 1.4.9, 1.4.10). **Surveillance decision** This review question should not be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
	one of the trials indicating greater IOP reduction with latanoprost over 90degree and 180degree SLT. Three trials indicated no difference between 180degree SLT and 360degree SLT. It was inconclusive whether 90degree was less efficacious than 180degree SLT. It should be noted, from an assessment of the abstract, that the authors did not conduct a quantitative synthesis of the evidence identified.		
CG85 – 13. Which is the most effective and least harmful surgical treatment between trabeculectomy, deep sclerectomy and viscocanalostomy? (1.4.3; 1.4.6; 1.4.7; 1.4.8; 1.4.9)			
Surgery The surgical treatments considered in CG85 were classified as penetrating (trabeculectomy) and non-penetrating (deep sclerectomy and viscocanalostomy). **Surgery type** Four studies comparing different classes of surgery were identified. A meta analysis[45] which compared the efficacy of non-penetrating trabecular surgery and trabeculectomy for the treatment of OAG was identified. The analysis showed that compared with the non-penetrating trabeculectomy, the traditional trabeculectomy could reduce IOP more and had a higher success rate while the non-penetrating trabecular surgery was associated with lower postoperative complications.	NICE IPG396 was issued in May 2011 on trabecular stent bypass microsurgery for open angle glaucoma. This procedure is only recommended for use with special arrangements for clinical governance, consent and audit or research. There is insufficient evidence on efficacy to consider the procedure for inclusion in the guideline at this time. A systematic review[64] (5 studies, n=247) compared the effectiveness of non-penetrating filtration surgery, specifically viscocanalostomy or deep sclerectomy, with conventional trabeculectomy in people with glaucoma. The results showed limited evidence that control of IOP is better with trabeculectomy than viscocanalostomy. For deep sclerectomy, the evidence was inconclusive. The	Clinical feedback highlighted the increasing use of new surgical techniques not recommended in CG85 (e.g. deep sclerectomy, viscocanalostomy). A non-randomised controlled trial and an observational study were cited, but were out of scope of the 6 year review and did not meet the study design eligibility criteria for this clinical area in CG85.	No new evidence was identified that may change guideline recommendations. The current guideline makes no specific recommendations, with the exception of MMC or 5-FU augmentation, around the type or method of surgery for the COAG population. The evidence identified supported the use of surgery with MMC augmentation and the use of surgery for those with more advanced disease. In addition, evidence was identified that indicated that penetrating surgery may be more effective than non-penetrating surgery.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Two studies specifically compared viscocanalostomy and trabeculectomy. A meta-analysis[46] found trabeculectomy was more effective at lowering IOP than viscocanalostomy in uncontrolled glaucoma. However, viscocanalostomy had a significantly better risk profile. One RCT[47] found trabeculectomy to be more effective at lowering IOP than viscocanalostomy in POAG patients. Additionally, a systematic review and meta analysis[48] was identified which evaluated the efficacy and tolerability of non-penetrating glaucoma surgery augmented with mitomycin C (MMC) compared with trabeculectomy plus MMC in the treatment of patients with OAG. The study indicated that whilst non-penetrating glaucoma surgery augmented with MMC was better tolerated, it was equally as effective as trabeculectomy plus MMC in lowering IOP. **Surgical method** A meta- analysis[49] found that there was no significant difference in IOP reduction between 1- and 2-site phaco-trabeculectomy. One small scale RCT[50] found that there were comparable results for patients receiving trabeculectomy and phaco-trabeculectomy with or without a routine peripheral iridectomy.	authors highlighted the lack of use of quality of life outcomes in the included trials. A systematic review[65] (18 studies) compared the hypotensive effect and safety of nonpenetrating surgery and trabeculectomy in terms of IOP reduction and incidence of complications. The considered interventions were trabeculectomy, deep sclerectomy, viscocanalostomy, and canaloplasty. Trabeculectomy was found to be the most effective surgical procedure. However, the absolute risk of hypotony, choroidal effusion, cataract, and flat or shallow anterior chamber was higher in the trabeculectomy group than in the NPS group. **EX-PRESS Implantation** A systematic review[66] (4 studies, n=200) evaluated the efficacy and safety of Ex-PRESS implantation (Ex-PRESS) compared to trabeculectomy in the treatment of patients with open-angle glaucoma. The results showed that Ex-PRESS and trabeculectomy provided similar IOP control, but Ex-PRESS was more likely to achieve complete success at one year, with fewer postoperative interventions. Complication rates were similar for the two types of surgery, except for a lower frequency of hyphema in the Ex-PRESS group.		A range of small scale studies were identified that investigated various methods indicating that there may be varying efficacy for different surgical techniques. The use of stents and implants was not discreetly considered in the original clinical guideline. The new evidence identified with regard to these devices indicates that they may offer benefits in surgical outcome for patients. The evidence was insufficient to impact on guideline recommendations. Clinical feedback highlighted the increasing use of new surgical techniques not recommended in CG85 (e.g. deep sclerectomy, viscocanalostomy). Further evidence is required on nonpenetrating very deep sclerectomy to establish any potential impact on recommendations. The new systematic review evidence on EX-PRESS implantation, a minimally penetrating surgical method, suggested comparable efficacy with trabeculectomy with fewer complications of hypotony and hyphema. Further evidence is required on its cost effectiveness to establish its

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
One RCT[51] investigated found that scleral flap size had no significant effect on the medium-term IOP control and complication rates after augmented trabeculectomy. One RCT[52] evaluated early conjunctival suture removal following trabeculectomy on postoperative outcome in comparison to routine practice. Early suture removal increased postoperative visual acuity and resulted in significantly lower IOP. An RCT[53] (Kobayashi) which compared the IOP lowering effect of adjustable sutures and laser suture lysis for trabeculectomy in eyes with POAG found no significant difference in hypotensive efficacy between the two suture type. One RCT[54] suggested that very deep sclerectomy with collagen implant was as effective as standard deep sclerectomy with collagen implant in lowering IOP in patients with medically uncontrolled glaucoma. **Valve/stent/implant** Two reports[55,56] of an RCT which compared the Ahmed glaucoma valve and the Baerveldt glaucoma implant in refractory glaucoma were identified. Both studies indicated that after a one year follow up, IOP was lower with the Baerveldt glaucoma implant than the Ahmed	A systematic review[67] (8 studies, n=559) and a meta-analysis[68] (4 studies, n=292 eyes) evaluated the efficacy, tolerability and safety of Ex-PRESS implantation compared with trabeculectomy in the treatment of patients with uncontrolled glaucoma. Ex-Press was associated with numerically greater, but nonsignificant, IOP lowering efficacy than trabeculectomy. Ex-Press was associated with a significantly lower frequency of hypotony and hyphema than trabeculectomy. **Other Surgical methods** A meta-analysis[69] (13 studies, n=266 eyes) compared the effect of trabeculectomy, cyclophotocoagulation (CPC), and glaucoma drainage device (GDD) on IOP control and corneal graft survival in patients with postkeratoplasty glaucoma. GDD resulted in greater IOP control, the lowest glaucoma surgery failure rate, and less vision loss compared with other forms of glaucoma surgery. However, GDD surgery resulted in a higher rate of graft failure. A systematic review[70] (1 study) found that, based on one small RCT, needling encapsulated blebs in people with encapsulated trabeculectomy blebs was not significantly better than medical treatment in reducing IOP.		potential impact on the CG85 economic modelling and recommendations for treatment of COAG. The new systematic review evidence comparing trabeculectomy with non-penetrating surgery indicates that trabeculectomy is the most effective surgical procedure, but also causes a higher incidence of complications. The new systematic review evidence indicates that the glaucoma drainage device was more effective than trabeculectomy, but with a higher rate of graft failure. There is insufficient evidence on efficacy to consider trabecular stent bypass microsurgery for open angle glaucoma for inclusion in the guideline at this time. Collectively, the new evidence is consistent with CG85, which does not recommend a specific type or method of surgery for the COAG population due to the potential risks of complications and the need to consider patient preferences.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
glaucoma valve. However there were fewer early and serious postoperative complications associated with the use of the Ahmed glaucoma valve. One RCT[57] was identified that compared the Ahmed valve implantation with the Molteno single-plate implantation surgical treatment in patients with refractory glaucoma. Whilst both implants successfully preserved visual field, IOP control was more pronounced in patients with the Molteno implant. One study[58] evaluating the safety and efficacy of the Ologen implant as adjuvant compared with low-dosage MMC in trabeculectomy found that both methods were equivalent in efficacy for lowering IOP in patients with glaucoma. However, bleb height was higher in those treated with Ologen implant compared to MMC treatment. In another RCT[59], trabeculectomy with an Ologen implant was found not to offer any advantages compared with trabeculectomy alone in patients requiring glaucoma surgery for uncontrolled IOP. Additionally, a small scale RCT[60] which assessed the efficacy and complications of trabeculectomy with an Ologen implant in comparison to trabeculectomy using MMC in patients with medically uncontrolled OAG was identified. Whilst one year after surgery, both interventions had lowered IOP, anti-glaucomatous medication was necessary in a large proportion in the Ologen group. The 3-year results of a Baerveldt glaucoma implant	A systematic review[71] (16 studies, n=1392) evaluated the efficacy and tolerability of limbus-based (LBCF) compared with fornix-based conjunctival flaps (FBCF) for trabeculectomy in the treatment of patients with uncontrolled glaucoma. The results showed that there was no significant difference in IOP lowering, number of glaucoma medications, or proportion of patients who reached the IOP target between LBCF and FBCF trabeculectomy. There was also no significant difference in adverse events between the two incision techniques.		**Surveillance decision** This review question should not be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
surgery versus trabeculectomy with MMC in patients who have had previous trabeculectomy, cataract extraction with intraocular lens implantation, or both and uncontrolled glaucoma RCT[61] was identified. Tube shunt surgery had a higher success rate compared to trabeculectomy with MMC. However both procedures were associated with similar IOP reduction and use of supplemental medical therapy at 3 years. Two reports[62,63] from the Ex-PRESS study were identified which provided data from 1 year and 5 year follow up points which evaluated the efficacy and safety of the Ex-PRESS mini glaucoma shunt in patients with POAG in comparison to trabeculectomy. At one year follow-up, the Ex-PRESS mini glaucoma shunt implant produced significantly higher success rates, and a similar complication rate, compared with trabeculectomy. At five years compared with trabeculectomy, EX-PRESS provided better IOP control in the first three years, and patients required fewer IOP medications and fewer surgical interventions. **Summary** The recommendations for non-pharmacological options in CG85 were based on a health economics model which resulted in this option for patients with COAG stratified by condition severity, level of control of IOP and disease progression. On the whole, the identified new evidence in relation to			

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
non-pharmacological treatments was considered, at the 3-year surveillance review, to support the efficacy of currently recommended treatments. Overall, new evidence was identified indicating that laser therapy in the treatment of adults with glaucoma had beneficial effects on the outcomes measured**.** One study was identified that may address a research recommendation in the guideline on the clinical effectiveness of initial argon, diode or SLT compared with prostaglandin analogues alone in people with COAG. The current guideline makes no specific recommendations, with the exception of MMC or 5-FU augmentation, around the type or method of surgery for this patient population. Evidence was identified at the 3-year surveillance review, which indicated that penetrating surgery may be more effective than non-penetrating surgery. A range of small scale studies were identified that investigated various methods indicating that there may be varying efficacy for different surgical techniques. The use of stents and implants was not discreetly considered in the original clinical guideline. The evidence identified at the 3-year surveillance review with regard to these devices indicated that they may offer benefits in surgical outcome for patients.			

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG85 – 14. Does pharmacological augmentation to surgery with fluorouracil (5-FU) or mitomycin C (MMC) improve outcomes? (1.4.3; 1.4.6; 1.4.7; 1.4.8)			
Surgery augmented with pharmacological augmentation A systematic review and meta analysis[72] that identified eight trials found that non-penetrating glaucoma surgery with MMC was associated with greater complete success rates compared with non-penetrating glaucoma surgery without intraoperative MMC in the treatment of patients with OAG. No difference in effectiveness or safety was found in the application of MMC in deep sclerectomy with collagen implant applied under the superficial scleral flap or under the deep scleral flap in one RCT[73]. One RCT[74] indicated that the efficacy of augmenting trabeculectomy with subconjunctival MMC or 5-fluorouracil in lowering IOP in patients with high-risk OAG was equivalent. One study[75] found that the long-term efficacy of intraoperative 5-fluorouracil and MMC in primary trabeculectomy were equivalent in reducing IOP of eyes undergoing primary trabeculectomy. One RCT[76] showed that trabeculectomy with subconjunctival bevacizumab was not as effective as trabeculectomy with MMC in controlling the IOP profile of	An updated systematic review[79] (4 studies, n=551) on the effectiveness of beta radiation during glaucoma surgery found that trabeculectomy with beta irradiation has a lower risk of surgical failure compared to trabeculectomy alone. However, beta irradiation was associated with an increased risk of cataract. A systematic review[80] (8 studies) compared the efficacy and tolerability between nonpenetrating filtering surgery with and without intraoperative MMC application for treatment of open angle glaucoma. Intraoperative mitomycin C was associated with significantly greater complete remission rates without drug-induced complications. A systematic review[81] (7 studies, n=227 eyes) found that the application of the Ologen implant was comparable with MMC for trabeculectomy, in the outomes of IOP-lowering efficacy, reduction in the number of glaucoma medications, success rates, and tolerability. A systematic review[82] (9 studies, 349 patients) evaluated the intraoperative application of antimetabolites compared with anti-vascular endothelial growth factor agents with or without	None identified relevant to this question.	No new evidence was identified that may change guideline recommendations. The evidence identified supported the use of surgery with MMC augmentation and the use of surgery for those with more advanced disease. The new systematic review evidence identified was consistent with CG85 recommendations 1.4.3, 1.4.6, 1.4.7, and 1.4.8 which advise augmentation of surgery with MMC or 5-FU as indicated. MMC and 5-FU continue to be used off label for the COAG population. **Surveillance decision** This review question should not be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
patients with uncontrolled glaucoma. One RCT[77] indicated that preoperative treatment with either topical non-steroidal anti-inflammatory drug (ketorolac) or steroid (fluorometholone) treatment was associated with improved trabeculectomy outcomes in terms of likelihood of postoperative needling in comparison to placebo. One study[78] indicated that postoperative topical cyclosporine had no effect compared to placebo on bleb function and IOP following trabeculectomy in patients with uncontrolled glaucoma requiring filtration surgery.	antimetabolites in trabeculectomy for glaucoma. The results showed that antimetabolites were more effective in lowering IOP in trabeculectomy, while the intraoperative application of these two types of agents did not indicate significant differences in the complete success rate, qualified success rate, or incidence of adverse events. A systematic review[83] (12 studies, n=1319) assessed the effects of both intraoperative application and postoperative injections of 5-FU in eyes of people undergoing surgery for glaucoma at one year. The participants were divided into three separate subgroup populations (high risk of failure, combined surgery and primary trabeculectomy). The results showed a small but significant reduction in surgical failures and IOP at one year in the primary trabeculectomy group and high-risk group. However, none of the trials reported on the participants' perspective of care for this invasive procedure. No evidence was found of an increased risk of serious sight-threatening complications, but other complications were more common after 5-FU injections. A systematic review[84] found no RCTs to test the effectiveness of antimetabolites with cataract surgery in individuals with the intention of preventing failure of a previous trabeculectomy.		

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG85 – 15. Which is the most clinically and cost effective and least harmful treatment between medications, laser and surgery? (1.4.1-1.4.10)			
Medication versus surgery An RCT[85] which evaluated the effect of SLT in comparison with latanoprost therapy on IOP control and diurnal tension curves of patients with OAG and OHT found that both SLT and latanoprost reduced IOP with latanoprost deceasing IOP fluctuation more. Three reports[86-88] from the Collaborative Initial Glaucoma Treatment Study which compared medical or surgical treatment of inpatients with OAG were identified. Two reports[86-87] focused on visual field progression, the first of which indicated that the intervention protocol led to a lowering of IOP that persisted over time in both treatment groups at 8 years of follow-up. However, progression of visual function loss was seen in a subset, increasing to more than 20% of the subjects. The effect of initial treatment on subsequent visual field loss was modified by time, baseline mean deviation and diabetes with the findings suggesting that initial surgery was more beneficial for subjects with more advanced visual field loss at presentation, but detrimental for patients with diabetes. The second report indicated that inadequate IOP control as measured by higher maximum, greater standard deviation and range of IOP is associated with progression of visual fields loss. The third report[88] concentrated on the effect of IOP	An updated systematic review[89] (4 studies, n=888) assessed the effects of medication compared with initial surgery in adults with open angle glaucoma. Primary surgery was found to lower IOP more than primary medication but was associated with more eye discomfort. In three trials the risk of developing cataract was higher with trabeculectomy. Evidence from one trial suggests that, beyond five years, the risk of needing cataract surgery did not differ according to initial treatment policy. The clinical and cost-effectiveness of contemporary medication (prostaglandin analogues, alpha2-agonists and topical carbonic anhydrase inhibitors) compared with primary surgery was not covered by the included trials. A systematic review[90] found evidence that medical, laser, and surgical treatments decrease IOP and that medical treatment and trabeculectomy reduce the risk for optic nerve damage and visual field loss compared with no treatment. The direct effect of treatments on visual impairment and the comparative efficacy of different treatments were not clear. Harms of medical treatment were primarily local (ocular redness, irritation) and surgical treatment carried a small risk for more serious complications. Two ongoing studies were identified:	Clinical feedback highlighted new RCT evidence that interrogates whether one treatment recommended as second-line in the initial guideline (it was an emerging technology at the time), SLT may be effective as a primary treatment. The cited study[91] (n=69) compared outcomes of SLT with drug therapy for glaucoma patients. IOP reduction was similar in both arms after 9 to 12-months follow-up. More treatment steps were necessary to maintain target IOP in the medication group, although there was not a significant difference between groups.	No new evidence was identified that may change guideline recommendations. **SLT in comparison with latanoprost** The RCT evidence identified at the 3-year surveillance point indicated that both SLT and latanoprost reduced IOP with latanoprost decreasing IOP fluctuation more. This evidence was considered to address research recommendation 4.3: What is the clinical and cost effectiveness of initial argon, diode or SLT compared with PGAs alone or laser trabeculoplasty plus PGAs in combination, in people with COAG? However, the RCT evidence was limited by the small sample size, differing baseline IOP values between treatment groups, and lack of sham laser treatment. **Medication versus surgery** The collective new systematic review evidence indicates that medical treatment and trabeculectomy are effective but that the comparative efficacy of different treatments remains unclear and requires further research. Surgical treatment carries a risk for more serious complications. This is consistent with CG85 recommendations,

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
lowering on the optic disc at a five year follow up point. Optic disc progression was higher in the medicine group than in the surgical group with visual field worsening being associated with progression of optic disc cupping. In addition the incidence of reversal of cupping was higher in the surgical group than the medicine group which was associated with lower postoperative IOP. Reversal of cupping was not associated with improvement of visual function.	Treatment of Advanced Glaucoma Study (TAGS): A multicentre randomised controlled trial comparing primary medical treatment with primary trabeculectomy for people with newly diagnosed advanced glaucoma. This RCT aims to clarify which treatment option is best for advanced glaucoma. This trial has only just started recruiting and will not be reporting for 3-5 years. Another trial which has just completed recruitment is the HTA Funded multi-centre Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. This is to address the question of whether laser first or drops first is the best option for pressure lowering and glaucoma control and importantly includes QoL outcome. This trial still has 2 years to run with an expected publication date of 2017.		which are guided by patient preferences and needs (1.4.2-1.4.10). Specifically recommendation 1.4.2 advises offering initial pharmacological treatment for people with early or moderate COAG, and recommendation 1.4.4 advises offering surgery for advanced COAG with information on the risks and benefits associated with surgery. Recommendations 1.4.6-1.4.8 advise offering surgery where medication is ineffective or inappropriate. Further evidence will be considered at the next surveillance review, including the ongoing TAGS trial and the LiGHT trial. **Surveillance decision** This review question should not be updated. Topic experts agreed that further research is needed to address the research recommendation 4.3. Ongoing research (Laser in Glaucoma and Ocular Hypertension (LiGHT) trial) and an update to a Cochrane review on laser trabeculoplasty for open angle glaucoma (Rolim de Moura et al.) will provide more conclusive evidence to address the research recommendation in the future.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG85 – 16. Is there evidence that complementary or alternative treatments can be used for treating patients with ocular hypertension or chronic open angle glaucoma? (1.3.1; 1.3.4; 1.3.5; 1.4.6; 1.4.8; 1.4.10)			
A Cochrane systematic review[92] which assessed the effectiveness and safety of acupuncture in people with glaucoma found that therapeutic efficacy could not be established as no RCTs and only a few case series studies of small sample size were identified. **Summary** The current guideline found no objective scientific evidence or accepted practice supporting the use of alternative or complementary therapies. In light of this the consensus of the GDG was to make no recommendations for their use in the treatment of glaucoma. The identified study from the 3-year surveillance review was considered not to provide evidence that would alter the current guideline conclusions.	An updated systematic review[93] (1 completed study, 1 ongoing) assessed the effectiveness and safety of acupuncture in people with glaucoma The one completed trial compared auricular acupressure-a nonstandard acupuncture technique-with the sham procedure for glaucoma. The difference in IOP in the acupressure group was significantly less than that in the sham group at four weeks, but not at any other time point. No significant difference in visual acuity was noted at any follow-up time points. The ongoing trial was registered with the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization, but was not recruiting at the time of publication of the Cochrane review. A systematic review[94] (10 studies) assessed the effect of acute aerobic exercise on IOP to verify the influence of participant characteristics, exercise intensity, and duration. Results showed a robust effect of exercise on IOP for sedentary participants. However, the heterogeneity across study parameters, such as exercise protocol, IOP measurement, and participant selection, prohibited the inclusion of studies in this analysis that may have influenced the results.	None identified relevant to this question.	No new evidence was identified that may change guideline recommendations. New evidence identified at the 3 year review was not considered to have any impact on current guideline recommendations. The new systematic review evidence identified at the 6 year review on acupuncture and aerobic exercise for glaucoma is insufficient to impact on CG85 recommendations. Further evidence on the benefits and harms of these and other alternative or complementary therapies is needed before considering for inclusion in the guideline. **Surveillance decision** This review question should not be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
CG85 – 17. Is there evidence that neuroprotective agents are effective alone or in addition to IOP lowering treatments? (1.3.1; 1.3.4; 1.3.5; 1.4.6; 1.4.8; 1.4.10)			
A Cochrane systematic review[95] found no RCT evidence regarding the effectiveness of topical or oral neuroprotective agents for slowing the progression of COAG. Hence they concluded that the evidence that neuroprotective agents are effective in preventing retinal ganglion cell death and thus preserving vision in patients with OAG has not been demonstrated.	An updated systematic review[96] (1 study) examined the effectiveness of neuroprotective agents for slowing the progression of OAG in adults. The one included trial, comparing brimonidine with timolol, did not provide evidence that they are effective in preventing retinal ganglion cell death, and thus preserving vision in people with OAG. The most frequent adverse event was ocular allergy to study drug, which occurred more frequently in the brimonidine group than the timolol group.	None identified relevant to this question.	No new evidence was identified that may change guideline recommendations. The current evidence in this area does not demonstrate that neuroprotective agents are effective in preventing retinal ganglion cell death. Further research in this area demonstrating the benefits and harms of neuroprotective agents is needed before recommendations can be made in this area. **Surveillance decision** This review question should not be updated.
Organisation of care			
CG85 – 18. What evidence is there that risk factors affect the number of patients converting from ocular hypertension, to COAG? (1.5.5)			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This review question should not be updated.
CG85 – 19. Can professionals other than consultant ophthalmologists diagnose, monitor and/or treat ocular hypertension and/or COAG? (1.5.1-1.5.7)			

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
No relevant evidence identified.	A study[2] (publication date to be confirmed) assessed the diagnostic performance and cost-effectiveness of imaging technologies, as triage tests, for identifying people with glaucoma. Heidelberg Retinal Tomogram, scanning laser polarimetry and optical coherence tomograph were compared. Heidelberg Retinal Tomogram had the highest sensitivity, but the lowest specificity. Scanning laser polarimetry had the highest specificity but the lowest sensitivity. The preliminary results also showed that introducing a composite triage station into the referral pathway to identify appropriate referrals was cost-effective.	Referral was not included in the original guideline scope, but clinical feedback highlighted ongoing uncertainty relating to referral criteria and indicated that a guideline revision could embed the referral principles set out by the NICE quality standard, which may be beneficial to service delivery. The unmanageable increase in referrals to hospital eye services may have been related to: • Clarity of the criteria in the NICE guideline on when to refer patients to the hospital eye service • Expectations about when to refer patients at the lower threshold to the hospital eye service. A study[97] was cited relating to managing glaucoma referrals in secondary care. It describes a referral refinement model in a hospital eye department that triages	New evidence was identified which may change recommendations 1.5.1-1.5.7. The full results of the GATE study are awaited in order to assess the impact CG85 of three new imaging technologies for the diagnosis of glaucoma in secondary care. Preliminary reports from this new evidence suggest that introducing a composite triage station into the referral pathway to identify appropriate referrals is cost-effective. New evidence on referral refinement adds to the clinical feedback that has highlighted the need to clarify referral criteria, manage referrals more efficiently and increase capacity for more urgent cases. There is a potential impact on recommendations 1.5.1-1.5.7 relating to case detection and referral refinement. Specifically, the clarification of referral criteria (1.5.1) and training of healthcare professionals (1.5.2-1.5.7) should be considered for updating. **Surveillance decision** This area should be updated.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
		referrals to increase capacity for more urgent cases.	However, there are no existing specific review questions in this area in the guideline and so a potential new question is needed to: • cover case finding, particularly in high-risk groups • clarify the threshold for referral to the hospital eye service, to enable efficient management and greater capacity for more cases • define and clarify repeat measures and referral refinement • incorporate new technologies, including Icare tonometry • clarify the role of optometrists. Screening will not be included because it is outside the remit of NICE and is covered by the National Screening Committee. New evidence on referral refinement, including a local practice model and an ongoing study (Glaucoma automated tests evaluation [GATE]), adds to the clinical feedback that has highlighted the need to manage referrals more efficiently. An extension to the scope of the guideline will be needed to incorporate case finding and referral from primary to secondary care.

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
Provision of information			
CG85 – 20. What are the most effective ways of providing information to patients? (1.6.1)			
No relevant evidence identified.	A systematic review[98] (16 studies n=1565) assessed the effects of interventions for improving adherence to ocular hypotensive therapy in people with OHT or glaucoma. The results showed that complex interventions consisting of patient education combined with personalised behavioural change interventions, including tailoring daily routines to promote adherence to eye drops, may improve adherence to glaucoma medication. However there was insufficient evidence to favour one intervention. None of the included studies reported on the cost of the intervention.	See CG85-09 for related stakeholder feedback.	No new evidence was identified that may change guideline recommendations. The new systematic review evidence identified at the 6 year surveillance indicated that complex interventions including patient education may improve adherence to glaucoma medication. However, further research demonstrating the cost effectiveness of interventions to improve adherence is needed before recommendations can be made in this area. **Surveillance decision** This review question should not be updated.
Research Recommendations			
RR – 01. What is the clinical effectiveness and cost effectiveness of using different monitoring intervals to detect disease progression in people with COAG who are at risk of progression?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
			considered again at the next surveillance point.
RR – 02. What are the current NHS national benchmarks for surgical success and complications in people with COAG undergoing trabeculectomy drainage surgery with and without pharmacological augmentation?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 03. What is the clinical effectiveness and cost effectiveness of initial argon, diode or selective laser trabeculoplasty compared with prostaglandin analogues alone or laser trabeculoplasty plus prostaglandin analogues in combination in people with COAG?			
See evidence under CG85-12	See CG85-15	None identified relevant to this question.	See CG85-15
RR – 04. In people identified on primary examination as exhibiting possible COAG, OHT or suspected COAG, what is the comparative effectiveness of diagnosis by different healthcare professions?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.
RR – 05. What is the clinical effectiveness and cost effectiveness of providing people with COAG with a 'glaucoma card' or individual record of care compared with standard			

Conclusions from previous 3-year surveillance	Summary of new evidence from 6-year surveillance	Summary of new intelligence from 6-year surveillance	Impact
treatment?			
No relevant evidence identified.	No relevant evidence identified.	None identified relevant to this question.	No new evidence was identified that would affect recommendations. **Surveillance decision** This research recommendation will be considered again at the next surveillance point.

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