Surveillance report – Glaucoma (2009) NICE guideline CG85

November 2015

Surveillance decision

We will plan a partial update of the following sections in the guideline: monitoring and treatment of chronic open angle glaucoma (COAG), ocular hypertension and suspected COAG. An extension to the scope will be required to incorporate case finding and referral from primary to secondary care.

We will also amend the guideline to include cross-referrals to the NICE guidelines on Medicines adherence and Medicines optimisation

Reason for the decision

We found 98 new studies relevant to the guideline through the surveillance process. New evidence that could affect recommendations was identified. Topic experts who helped to develop the guideline advised us about whether the following sections of the guideline should be updated and any new sections added:

Monitoring

- At what intervals should patients be offered monitoring?

A Health Technology Assessment (Burr et al. 2012), identified as ongoing at the 3-year surveillance review, is now published and has been selected for commentary in this 6-year surveillance review. The results indicated that there was no benefit from intensive monitoring, and that biennial monitoring is most cost effective.

The topic experts stated that the monitoring intervals within the guideline were intentionally broad to allow clinical judgment but it was recognised that these had been misinterpreted in some situations. There was also a view that the

recommendations as they stand, combined with the resulting misinterpretation in clinical practice, may be causing a strain on departments.

It was agreed that Table 4 'Monitoring intervals for people with OHT or suspected COAG who are recommended to receive medication' could be made clearer with further clarification of the monitoring information. 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 this area.

Decision: This question should be updated**.**

- Which diagnostic tools could be used at monitoring visits?

An additional focus of the Burr paper was that the Goldmann applanation tonometer (GAT) may not be the most appropriate standard tonometer (the instrument used to measure IOP). Currently the guideline recommends using the GAT consistently at each monitoring assessment. However, clinical feedback indicated that the GAT is not always used as standard in practice, because of the emergence of new tonometers, such as Icare.

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

Decision: This question should be updated**.**

Treatment for people with COAG, OHT and suspected COAG

- Treatment for people with OHT and suspected COAG
  - Is treatment overall clinically and cost effective?
- Treatment for people with COAG: effectiveness of IOP-lowering interventions

- Which are the most clinically and cost effective and least harmful pharmacological treatments from the following classes of drugs?
  - ◊ topical beta-blockers
  - ◊ topical prostaglandin analogues (PGAs)
  - ◊ topical sympathomimetics
  - ◊ topical and systemic carbonic anhydrase inhibitors
  - ◊ topical miotics

Although the evidence identified through the surveillance review search was not considered to have any impact on the guideline recommendations, clinical feedback and intelligence gathering 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.
- Preservative-free and fixed-combination solutions need to be included as additional interventions.

Decision: Both questions should be updated, with revised economic modelling.

Information for people with COAG, OHT and suspected COAG

It was also noted that information for pharmacists and GPs should be addressed in relation to discussing the different types of droppers to help patient choice decisions. It was suggested linking to published NICE guidelines on Medicines adherence and Medicines optimisation would help to address this.

Decision: The questions on treatment for people with COAG, OHT and suspected COAG should incorporate cross-references to the NICE guidelines on Medicines adherence and Medicines optimisation**.**

Case finding and referral

An issue identified in the surveillance review was confusion over referral criteria and consequent 'flooding' of hospital eye services with referrals of people at low risk of blindness. Topic experts indicated that this has drawn resources away from people with advanced glaucoma who are at a much higher risk of blindness. Because there are targets for seeing new patients, these people at low risk are given priority by NHS trusts ahead of people with advanced and potentially blinding glaucoma. There are no existing review questions in this area in the guideline, but as it has been an unintended consequence of the guidance, 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 or community care to secondary care.

Decision: A new review question should be added to the guideline about case finding and referral, including referral refinement, and possibly to include economic modelling.

Other clinical areas

We also found new evidence relating to the following areas, but it was not deemed to have an effect on current recommendations. These areas were:

- Diagnosis
- Provision of information

Overall decision

After considering all the new evidence and the views of topic experts, we decided that a partial update with a modified scope is necessary for this guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 1 study for further commentary.

Monitoring

We selected the health technology assessment by Burr et al. (2012) for a full commentary because the study was identified as ongoing at the previous surveillance review, with a potential impact on the recommendations in NICE CG85 about monitoring intervals. The results of this study showed that there was no clear benefit from intensive monitoring, and that biennial monitoring is most cost effective. Clinical feedback indicated that monitoring intervals in the guideline need revision because of the pressure on resources resulting from following the current recommendations, which could potentially result in more urgent cases being missed.

What the guideline recommends

NICE CG85 recommends that people with OHT or suspected COAG, who are recommended to receive medication according to their risk of conversion to COAG, are monitored at regular intervals. IOP is measured using a tonometer. Use of the GAT (slit lamp mounted) is recommended at each monitoring assessment. In current practice, the GAT is the most commonly used tonometer for estimating IOP.

The recommended monitoring interval frequencies for IOP are 1–24 months based on the person's risk of conversion to COAG. Risk of conversion to COAG should be clinically judged in terms of age, IOP, central corneal thickness (CCT), appearance and size of optic nerve head, and visual field. OHT is defined as consistently or recurrently elevated IOP (greater than 21 mmHg) in the absence of clinical evidence of optic nerve damage or visual field defect. Intensive monitoring at 1–4-month intervals is recommended only when the IOP is not at the target IOP. Once the target IOP has been achieved with treatment, monitoring is recommended at 6–12-months or 12–24-month intervals according to perceived risk.

Methods

Burr et al. (2012) conducted a systematic review and economic analysis aiming to determine effective and efficient monitoring criteria for OHT through:

- identification and validation of glaucoma risk prediction models and
- development of models to determine optimal surveillance pathways.

The study comprised three interlinked substudies, which covered risk prediction models, monitoring frequency and an economic evaluation that compared 5 surveillance pathways for OHT (including two based on NICE CG85).

Risk prediction models

The inclusion criteria for the systematic review of risk prediction models were prospective studies and studies in which patients were identified retrospectively but followed up prospectively. These studies were included if:

- The patients were exclusively those with confirmed OHT, or where they could be distinguished from the rest of the study cohort and separate models were fitted for them.
- They were conducted from 1988 onwards, when reliable computerised perimetry, which measures the visual field, became the standard of care for detecting vision loss.
- It was possible to obtain a prediction equation for the development of OAG.
- The reported model included a minimum of 2 variables to predict risk, one of which was IOP.
- The performance of the model was reported in a longitudinal follow-up of a cohort initially free of OAG, irrespective of the length of follow-up.
- The population was adults 18 years or older with OHT (defined as elevated IOP but no evidence of glaucomatous optic nerve damage or visual field loss).

The main outcome was the predictive ability of the model to discriminate between patients who did or did not develop OAG. This was assessed using Harrell's *c*-index. A *c*-index of 1.0 indicates perfect discrimination (for

example, predicted risks for those with OAG are all greater than for those without OAG) whereas a *c*-index of 0.5 indicates random discrimination.

Optimal monitoring criteria

The inclusion criteria for the systematic review of tonometers were direct comparative studies (in English) that assessed the agreement of one or more tonometers with the reference standard tonometer (GAT) in the same group of people. Adults over 16, including those with a diagnosis of OHT or glaucoma, were included. All studies including types of tonometers that could be used in a monitoring context were eligible.

Studies comparing both an eligible and a non-eligible tonometer with the GAT were also included. Studies were excluded if they compared manometry (an invasive procedure) with tonometry, or if tonometers either were used primarily as a research device or were unavailable in a clinical setting. The primary outcome was the agreement between a tonometer and the reference standard, measured by mean difference and limits of agreement.

To determine the optimal monitoring criteria for IOP and visual fields, data from 2 placebo-controlled RCTs were included. The participants had OHT with repeated monitoring over long-term follow-up. No inclusion criteria were stipulated. The selection of trials was based on suitability of the data for quantifying the signal-to-noise ratio of IOP and visual fields, which would inform the monitoring pathway.

Health economic evaluation

The inclusion criteria for selecting economic studies were full economic evaluations of surveillance strategies for adult patients with OHT.

Data used to structure and populate the economic model were obtained from:

- The systematic reviews (see methods above) of risk prediction models (3 models) and agreement between tonometers (102 comparative studies).
- Secondary analyses of existing datasets (statistical modelling n=153 and validation n=132) to validate identified risk models and determine optimal monitoring criteria.

- Public preferences for an optimal monitoring service, in terms of preferred attributes and willingness to pay for these (pilot n=184, web based survey n=814). The attributes considered were 10-year risk of developing glaucoma or severe glaucoma, risk of developing visual impairment, unwanted effects of treatment, communication and understanding, location and cost/price proxy (to determine willingness to pay).

The main outcome measures were public preferences, willingness to pay, costs and quality-adjusted life-years (QALYs).

Results

Risk prediction models

- 3 models were identified, which estimated 5-year risk of glaucoma based on routinely collected data (age, IOP, CCT, vertical cup-to-disc ratio and pattern standard deviation). One of the models, the Ocular Hypertension Study-European Glaucoma Prevention Study (OHTS-EGPS) means model, had a higher predictive probability as measured by a *c*-index ranging between 0.69 and 0.83 across 4 cohorts. This indicated a strong discriminatory ability of the model to distinguish between patients with OHT who developed OAG and those who did not, in all four cohorts. The model was therefore considered the most robust.

Optimal monitoring criteria

- In the systematic review of tonometers, a total of 102 comparative studies assessed the agreement of at least one tonometer with the GAT. Overall, the reporting in the included studies was considered to be poor. The agreement in IOP varied across tonometers, from 0.2 mmHg [95% confidence interval (CI) −3.8 to 4.3 mmHg] for non-contact tonometer to 2.7 mmHg (95% CI −care4.1 to 9.6 mmHg) for Ocuton S. The study noted that the results potentially raise questions over the validity of the GAT as the default standard, as sizeable inter-observer and intra-observer variability was observed for all tonometers.
- For assessing optimal frequency of monitoring IOP and tests to detect glaucoma, statistical modelling was performed on ocular measures from an

RCT [n=153, mean IOP 24.4 mmHg, standard deviation (SD) 3.5 mmHg] and validation was performed using data from another RCT [n=132, mean IOP 25.7 mmHg, SD 2.5 mmHg]. The average change in IOP over time for the whole group was less than 1 mmHg over a period of 3 years. When lower baseline IOP (less than 26 mmHg) was considered in the model, the results suggested that a true change in IOP would be unlikely within 3 years.

Health economic evaluation

- In the discrete choice experiment, there was a general public preference for monitoring OHT. The value of alternative services was predicted by good communication with the health professional and understanding of the testing process.
- In the economic modelling evaluation 5 pathways were compared:
  - 'NICE intensive' – defined by Burr et al. (2012) as 4-monthly to annual monitoring based on initial risk stratification, with treatment according to baseline risk stratification by age, IOP and CCT.
  - 'NICE conservative' – defined by Burr et al. (2012) as 6-monthly to biennial monitoring based on initial risk stratification, with treatment according to baseline risk stratification by age, IOP and CCT.
  - Two further pathways, differing in primary or secondary care settings, included monitoring biennially with treatment initiated for at least a 6% 5-year glaucoma risk in primary.
  - A 'treat all' pathway involving treatment if IOP was higher than 21 mmHg, measurement of IOP annually in community optometry and referral to secondary care if treatment response was inadequate (less than 15% reduction in IOP).
- The results of the economic modelling indicated that 'treat all' was the least costly and 'NICE intensive' the most costly pathway. Both biennial monitoring and the 'NICE intensive' pathway reduced the number of cases of glaucoma conversion compared with a 'treat all' pathway. Biennial monitoring provided more QALYs, but the incremental cost-effectiveness ratio (ICER) was considerably more than £30,000 per QALY gained. NICE-

based pathways were either dominated (more costly and less effective) by biennial hospital monitoring or had ICERs higher than £30,000 per QALY.

Strengths and limitations

Strengths

- The systematic review and economic evaluation sub–studies addressed clear questions and were supported by reproducible eligibility criteria.
- The systematic reviews were robust in terms of study identification, selection, data extraction and data synthesis.
- For the economic evaluation, the authors adopted an NHS perspective and discounted costs and QALYs at the recommended 3.5% discount rate.
- The ICER used in the economic evaluation is appropriate for the NHS context.

Limitations

Limitations of the study, most of which were reported by the authors, included:

- For the risk prediction models, both trial and observational validation cohorts were highly selected and none satisfactorily covered the full spectrum of risk.
- The 5-year prediction horizon adopted for the risk prediction models may not be fully representative of long-term risk.
- Definitions of glaucoma were not standardised across the cohorts, and missing data for the predictors was considerable.
- Optimal monitoring intervals were based on IOP data from a small sample, which may not have incorporated the full spectrum of risk.
- It was not possible to determine the optimal frequency of measurement of the visual field or optic nerve head for identifying glaucoma as there was insufficient data.
- The economic modelling took a 20-year time horizon which may be insufficient to capture long-term benefits.
- Uncertainty surrounding parameter estimates may not have been fully captured by the sensitivity analyses.

- Patient views were consulted when developing the discrete choice experiment, but the results were based on public preferences and these may differ from those of patients.
- Results of the economic analysis were not sensitive to the risk threshold for starting surveillance, but were sensitive to the risk threshold for starting treatment, NHS costs and treatment adherence.

Impact on guideline

Risk prediction models

The authors concluded that the best available prediction model (OHTS-EGPS means model) estimates the 5-year risk of glaucoma based on age and the ocular predictors IOP, CCT, vertical cup-disc ratio and pattern standard deviation. This may have a potential impact on NICE CG85 recommendation 1.2.10. The guideline does not recommend a specific risk prediction model, but advises that risk should be judged clinically in terms of age, IOP, CCT, appearance and size of optic nerve head.

Optimal monitoring criteria and surveillance pathways

The authors concluded that, because of the sizeable measurement variability between tonometers, the same type of tonometer should be used to compare IOP measurements in an individual. This is consistent with NICE CG85, which recommends using the GAT at each monitoring assessment. However, there is a potential impact on NICE CG85 recommendation 1.2.1 as the authors concluded that the GAT may not be the most appropriate standard tonometer.

There is also a potential impact on CG85 recommendations 1.2.10 and 1.2.12. These advise monitoring at regular intervals between 1 and 24 months according to risk, which is judged clinically in terms of age, IOP, CCT, appearance and size of optic nerve head. Although the findings are consistent with the criteria in NICE CG85 for biennial IOP monitoring for people with 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 indicate that further research is needed in the form of a prospective

cohort study using a representative sample of people newly diagnosed with OHT.

Topic expert feedback obtained through the surveillance process indicated that the study misclassified the monitoring intervals in NICE CG85, particularly intensive and non-intensive monitoring intervals. The 4-monthly monitoring of IOP recommended in the guideline relates to treatment change, and once this is stable or a result of treatment is achieved, the person would move to longer monitoring intervals.

The monitoring criteria in NICE CG85 were stated as being deliberately broad to cater for the wide variations in case mix. Intensive monitoring is among the range of possible options. It was stated that excluding it as an option would potentially place the small but significant minority of high risk people at even greater risk of conversion to COAG and subsequent vision loss. Risk of OHT is considered to be a continuous spectrum from minimal to significant and clinical judgement is considered essential in assessing individual patients. Further clinical feedback indicated that the biggest resource in terms of time and equipment is optic nerve imaging and visual field testing. The study does not make recommendations relating to frequency of these tests, which is the aspect of the service that contributes most to the capacity problems. However, the collective clinical feedback indicated that risk prediction and monitoring intervals in NICE CG85 may need to be reviewed in the light of this study and potential misinterpretation of the guidance.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 6 years after the publication of Glaucoma (2009) NICE guideline CG85.

For details of the process and update decisions that are available, see Ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 37 new studies in a search for systematic reviews published between 1 March 2012 and 11 March 2015. We also considered 3 additional studies identified by members of the Guideline Committee who originally worked on this guideline.

Evidence identified in previous surveillance 3 years after publication of the guideline was also considered. This included 57 studies identified by search and 1 study identified in comments received during consultation on the 3-year surveillance decision.

From all sources, 98 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 6-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

NICE Surveillance Programme project team

Sarah Willett
Associate Director

Philip Alderson
Consultant Clinical Adviser

Emma McFarlane
Technical Adviser

Stephen Sharp
Technical Analyst

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