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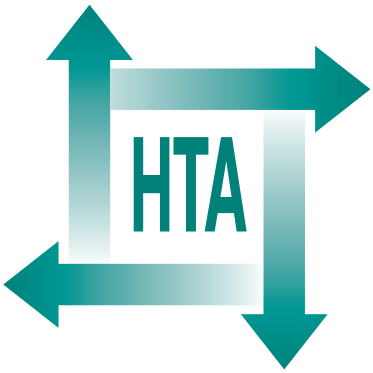

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J Carlton,[1] J Karnon,[1] C Czoski-Murray,[1*] KJ Smith[1] and J Marr[2]

[1] School of Health and Related Research (ScHARR), University of Sheffield, UK

[2] Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK

* Corresponding author

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 04/32/05. The contractual start date was in July 2005. The draft report began editorial review in January 2007 and was accepted for publication in December 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation

J Carlton,[1] J Karnon,[1] C Czoski-Murray,[1*] KJ Smith[1] and J Marr[2]

[1] School of Health and Related Research (ScHARR), University of Sheffield, UK

[2] Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK

* Corresponding author

Objectives: To estimate the cost-effectiveness of screening for amblyopia and strabismus in children aged up to 4–5 years, also identifying the major areas of uncertainty and so inform future research priorities in this disease area.

Data sources: Major electronic databases were searched in January 2006.

Review methods: Systematic literature reviews were undertaken to determine the prevalence and natural history, the screening methods, the effectiveness of treatment options and health-related quality of life issues relating to amblyopia and strabismus. The review of treatment interventions was restricted to high-quality reviews, meta-analyses and guidelines. The data derived from the review informed the structure and implementation of the decision-analytic model.

Results: The amblyopia screening model was analysed in detail to estimate the cost and effects of six alternative screening options comprising screening at different ages (3, 4 and 5 years) and using alternative sets of tests (visual acuity testing and the cover tests, with and without autorefraction). The reference case results showed that screening programmes that included autorefraction dominated screening programmes without autorefraction. Analyses based on the cost per case of amblyopia prevented showed screening at either 3 or 4 years prevented additional cases at a low absolute cost (£3000–6000). However, when these results were extrapolated to estimate the cost per quality-adjusted life-year (QALY) gained, the reference case analysis found that no form of screening is likely to be cost-effective at currently accepted values of a QALY. The wide-ranging sensitivity analyses found that the results were robust to most parameter changes. The only parameter that radically affected the results was the utility effect of loss of vision in one eye. No direct evidence of a utility effect was identified and the reference case assumed no effect. When a small effect is assumed (a reduction in utility of 2%), the incremental cost per QALY gained becomes extremely attractive for screening at both 3 and at 4 years. The expected value of perfect information was shown to be large when the unilateral vision loss utility parameter was allowed to vary, but not when it was kept constant at zero.

Conclusions: The results show that the cost-effectiveness of screening for amblyopia is dependent on the long-term utility effects of unilateral vision loss. There is limited evidence on any such effect, although our subjective interpretation of the available literature is that the utility effects are likely to be minimal. Any utility study investigating such effects would need to be careful to avoid introducing bias. The reference case model did not represent potential treatment-related utility effects, primarily due to an increased probability of treated children being bullied at school. The evidence indicates that this may be a problem, and additional sensitivity analyses show that small utility decrements from bullying would improve the cost-effectiveness of early screening significantly. A prospective study of the utility effects of bullying would usefully inform the analysis, although such a study would need to be carefully planned in order to distinguish whether the overall incidence of bullying decreases with reduced school-age treatment, or whether it is displaced to other children.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Disease/diagnosis/management terms

Amblyopia Reduced visual acuity in the absence of organic disease, which cannot be improved by glasses. It is usually uniocular. Amblyopia is believed to be reversible up to the age of 8 years of age.

Anisometropia A difference in refractive error between the two eyes.

Astigmatism A type of refractive error; a distortion of the image on the retina caused by irregularities in the cornea or lens.

Cover–uncover test A test used to detect strabismus, in which each eye is covered in turn while the child fixes on a specific target, and the tester observes the movements of the eyes.

Cycloplegic drugs These drugs block the action of the ciliary muscle, preventing accommodation. In addition, papillary dilation occurs.

Dioptre Unit of measurement of the power of the lens (D).

Esophoria A type of latent strabismus, a tendency of the eye to turn inwards.

Esotropia A type of manifest strabismus, where one of the eyes turns inwards.

Exophoria A type of latent strabismus, a tendency of the eye to turn outwards.

Exotropia A type of manifest strabismus, where one of the eyes turns outwards.

Heterophoria A tendency for one or both eyes to wander away from the position where both eyes are looking together in the same direction.

Hypermetropia Refractive error where the principal focus is behind the eye (so-called 'long sight').

Hyperopia See hypermetropia.

Latent strabismus With both eyes open, the visual axes are aligned. When one eye is covered, the eye under the cover deviates; when the cover is removed, it comes back into alignment. A small heterophoria is present in the majority of people without ocular symptoms.

LogMAR Scale used to measure visual acuity (logarithm of the minimum angle of resolution).

Manifest strabismus With both eyes open, the visual axis of one eye is deviated from the point of fixation. It may be constant or intermittent in nature.

Myopia A refractive error where the parallel rays of light focus in front of the retina when the eye is at rest (so-called 'short sight').

Occlusion Obscuring the vision of one eye, either totally or partially, to prevent or reduce visual stimulation.

Orthophoria An ideal condition in which the visual axes remain aligned with the object of fixation.

continued

Glossary *continued*

Refractive error An abnormal refractive index.

Snellen Scale used to measure visual acuity. This has now been superseded by the development of the LogMAR scale.

Strabismus The misalignment of the visual axis of the two eyes. It may be manifest or latent.

Visual acuity (VA) The limit of spatial visual discrimination, commonly measured using letter or other geometric forms. Two of the scales used to measure visual acuity are Snellen and LogMAR scales.

Epidemiological terms

False-negative A test result that indicates that a person does not have a specific disease or condition when the person actually does have the disease or condition.

False-positive A test result that indicates that a person does have a specific disease or condition when the person actually does not have the disease or condition.

Negative predictive value (NPV) The proportion of individuals who test negative who do not have a target condition.

Positive predictive value (PPV) The proportion of individuals with a positive test result who have a target condition.

Screening A health service in which members of a defined population, who do not necessarily perceive that they are at risk of a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment.

Sensitivity (true-positive rate) The proportion of individuals with the target condition in a population who are correctly identified by a screening test.

Specificity (true-negative rate) The proportion of individuals free of the target condition in a population who are correctly identified by a screening test.

List of abbreviations

A&SQ	Amblyopia and Strabismus Questionnaire
ALSPAC	Avon Longitudinal Study of Parents and Children
A/V	A or V pattern
BE	best Eye
BSAG	Bristol Social Adjustment Guide
BT	botulinum toxin
BV	best vision
CC	Cardiff Cards
CG	control group
Conv exc	convergence excess
CI	confidence interval
CMO	clinical medical officer
CR	corneal reflections
CT	cover test
Cyl	cylinder
DC	dioptre cylinder
DS	dioptres
E	esophoria
EE	either eye
EOM	extra ocular movements
ESVP	Enhanced Vision Screening Programme
ET	esotropia
EVPI	expected value of perfect information
FH	family history
FTA	failed to attend
GAC	Glasgow Acuity Cards
GP	general practitioner
GPSC	General Practitioner Screening Clinic
GSE	gold standard examination
HES	hospital eye service
HRQoL	health-related quality of life
HSC	Hopkins Symptoms Checklist
HV	health visitor
HVSC	Health Visitor Screening Clinic
ICER	incremental cost-effectiveness ratio
IG	intervention group
Int XT	intermittent exotropia
MLE	maximum likelihood estimation
MOTAS	Monitored Occlusion Treatment for Amblyopia Study
NAD	no apparent deviation
NCR	non cyclo refraction
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NSC	National Screening Committee
ODM	occlusion dose monitor
OM	ocular movements
OR	odds ratio
OSC	Orthoptist Screening Clinic
PCT	Primary Care Trust
PEDIG	Paediatric Eye Disease Investigator Group
PMT	Protection Motivation Theory
PPQ	Perceived Psychosocial Questionnaire
PPV	positive predictive value
PRK	photoreactive keratectomy
PSA	probabilistic sensitivity analysis

continued

List of abbreviations *continued*

PSI	Perceived Stress Index
PST	polaroid suppression test
PSVS	pre-school vision screening
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RDES	random dot E stereo test
ROTAS	Randomized Occlusion Treatment for Amblyopia Study
SD	standard deviation
SF-12	Short Form with 12 Items
SG	Sheridan Gardner
Sn	Snellen
SN	school nurse
SSG	Single Sheridan Gardner
Stycar	stereo acuity by the Lang-stereo test
VA	visual acuity
VFQ-25	Visual Function Questionnaire-25
VIP	Vision in Preschoolers
WPI	whole person impairment (index)
X	exophoria
XT	exotropia

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Amblyopia and strabismus are both common conditions in childhood. A Health Technology Assessment report published in 1997 concluded that the evidence for the value of screening for such conditions did not support any expansion of the current screening programme; indeed, it recommended that the National Screening Committee should consider halting the existing programme. The authors specifically highlighted the lack of evidence on the long-term impact of amblyopia, the extent of disability that amblyopia and strabismus have and their impact on quality of life. This study aims to re-examine the literature and to use this to inform a decision-analytic model to determine the cost-effectiveness of screening for amblyopia and strabismus.

There are several well-defined criteria informing the suitability of screening for a condition. The condition must be important and the natural history and epidemiology of the condition must also be understood. The screening tests used should be simple, safe, precise and acceptable to the general population, and there should be a defined diagnostic process following a test. Treatment for screened conditions should lead to better outcomes than treatment provided at the point of clinical diagnosis.

Aims and objectives

The aim of this study was to estimate the cost-effectiveness of screening for amblyopia and strabismus in children up to the ages of 4–5 years by developing a decision-analytic model that incorporates and assesses all of the above criteria. At the outset it was recognised that there was likely to be significant uncertainty in key areas of the model, and an objective of the study was to identify the major areas of uncertainty and so inform future research priorities in this disease area.

Methods

Systematic literature reviews were undertaken of the prevalence and natural history of amblyopia and strabismus, the screening methods used in detecting amblyopia and strabismus, the effectiveness of treatment options for amblyopia and strabismus and health-related quality of life issues relating to amblyopia and strabismus. The review of treatment interventions for amblyopia and strabismus was restricted to high-quality reviews, meta-analyses and guidelines. The literature searches were undertaken in the period 18–24 January 2006. The data derived from the review informed the structure and implementation of the decision-analytic model. This was calibrated with screening data from Birmingham.

Results

The amblyopia screening model was analysed in detail to estimate the cost and effects of six alternative screening options comprising screening at different ages (3, 4 and 5 years) and using alternative sets of tests (visual acuity testing and the cover tests, with and without autorefraction). The reference case results showed that screening programmes that included autorefraction dominated screening programmes without autorefraction. Analyses based on the cost per case of amblyopia prevented showed that screening at either 3 or 4 years prevented additional cases at a low absolute cost (£3000–6000). However, when these results were extrapolated to estimate the cost per quality-adjusted life-year (QALY) gained, the reference case analysis found that no form of screening is likely to be cost-effective at currently accepted values of a QALY.

The wide-ranging sensitivity analyses found that the results were robust to most parameter changes. The only parameter that radically affected the results was the utility effect of loss of vision in one eye. No direct evidence of a utility effect was identified and the reference case assumed no effect. When a small effect is assumed (a reduction in utility of 2%), the incremental cost per QALY gained becomes extremely attractive for screening at both 3 and at 4 years. The expected value of perfect information was shown to be large when the unilateral vision loss utility parameter was allowed to vary, but not when it was kept constant at zero.

Conclusions

The cost-effectiveness results from the amblyopia screening and lifetime models show that the cost-effectiveness of screening for amblyopia is dependent on the long-term utility effects of unilateral vision loss. There is limited evidence on any such effect, although our subjective interpretation of the available literature is that the utility effects are likely to be minimal. Any utility study investigating such effects would need to be careful to avoid introducing bias.

The reference case model did not represent potential treatment-related utility effects, primarily due to an increased probability of treated children being bullied at school. The evidence indicates that this may be a problem, and additional sensitivity analyses show that small utility decrements from bullying would improve the cost-effectiveness of early screening significantly.

Recommendations for future research

A prospective study of the utility effects of bullying would usefully inform the analysis, although such a study would need to be carefully planned in order to distinguish whether the overall incidence of bullying decreases with reduced school-age treatment, or whether it is displaced to other children.

Chapter 1
Introduction

Amblyopia and strabismus are conditions which occur in childhood and, if left untreated, will remain detectable throughout adult life. Amblyopia is a sensory anomaly defined as defective unilateral or bilateral visual acuity (VA), which cannot be attributed to a pathological cause. There are a number of classifications of amblyopia, based on the aetiological cause(s). Strabismus is a condition where the two eyes are not aligned, that is, the visual axes of the eyes are not parallel. Strabismus can be classified into manifest and latent. Manifest strabismus can be further subclassified into constant and intermittent. As with amblyopia, a number of subclassifications of strabismus exist, which differ in their aetiological factors and clinical characteristics. There are a number of recognised causal factors for amblyopia and strabismus. It is accepted that the aetiological factors are often multifactorial in nature.

Vision screening of children in the UK during the 1960s and 1970s was driven by health professionals' perceived need for surveillance programmes. A number of screening programmes existed within UK from the 1980s and current practice remains varied in different parts of the country. The Health Technology Assessment (HTA) report published in 1997[1] concluded that the evidence on the value of vision screening did not support any expansion of the existing screening programme. The authors recommended that the UK National Screening Committee (NSC) should consider halting the existing programme, highlighting the lack of evidence on the long-term impact of amblyopia specifically.

The impact of removing vision screening programmes in the UK is not proven. Cosmetically obvious strabismus should still be identifiable by parents or health professionals, and treatment initiated accordingly. Amblyopia and small-angle strabismus would not be easily identified by parents or health professionals unless a suspicion of their existence was evident. It could therefore be argued that the removal of vision screening programmes in the UK would result in an increase in the prevalence of amblyopia and strabismus.

Epidemiology

This study was concerned with a screening programme; therefore, population-based epidemiological studies which were either UK centred or were similar to the UK population were included. There is some evidence to suggest that amblyopia, strabismus and refractive error are more prevalent in different ethnic populations.[2] This distinction is less important in the context of screening in the UK, as the prompt to take part in any screening programme would be related to age and not to ethnicity.

The incidence of amblyopia and strabismus increases with age, particularly around the age of 2–3 years. The presence of refractive error is a recognised contributory factor to the development of amblyopia and/or strabismus. To this end, the development of refractive error has been examined in this study.

General rationale for screening

The purpose of screening is to classify persons as being at either greater or lesser risk of developing a particular condition. The NSC[3] described screening as "a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications". The NSC has established criteria for appraising the viability, effectiveness and appropriateness of screening programmes. The criteria address four factors: the condition, the test, the treatment and the screening programme. The NSC stated that ideally all criteria should be met before screening for a condition is indicated.

The condition should be an important health problem, and the epidemiology and natural history of the condition must be understood. The screening test should be simple, safe and precise and be acceptable to the general population. In addition, there should be an agreed policy on

further diagnostic investigation following a positive test. The treatment of the screened condition should be effective, and intervention for those identified through screening should lead to better outcomes than late detection and treatment. The screening programme should be clinically, socially and ethically acceptable in terms of the test, diagnostic procedures and treatment/intervention. Plans for monitoring the programme should be clearly defined, with adequate staffing and facilities available to cope with expected demand. The benefit from the screening programme should outweigh the physical and psychological harm caused by the test, diagnostic procedures and treatment.

Screening should also be cost-effective and, if screening is found to be cost-effective, then the most cost-effective form of screening should be implemented. Monitoring of the screening programme is necessary to allow the confirmation of cost-effectiveness. The cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be value for money, as compared with other areas of medical expenditure. The need for cost-effectiveness in terms of a generic outcome measure in practice requires the estimation of quality-adjusted life-years (QALYs). "The QALY is a measure of health outcome which assigns to each period of time a weight, ranging from 0 to 1, corresponding to the quality of life during that period, where a weight of 1 corresponds to perfect health and a weight of 0 corresponds to a health state judged equivalent to death. The number of quality-adjusted life-years, then, represents the number of healthy years of life that are valued equivalently to the actual health outcome."[5]

The criteria also stated that "there should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity". If such data are available, it is possible to assess the cost–utility of alternative screening programmes alongside the relevant trials. However, there are examples where no clinical evidence is available, and where clinical trial evidence is available, this may not inform all aspects of a screening programme. In this situation, modelling is necessary to inform cost–utility analyses of screening programmes.

Rationale for screening for amblyopia and strabismus

The purpose of this research was to define the extent to which current screening practice for amblyopia and strabismus meets the NSC's criteria.[3] To achieve this, the research addressed each criterion individually.

Study aims and objectives

The decision problem addressed by this report is based on the definition that a screening programme for amblyopia and strabismus aims to detect amblyogenic factors that are known to increase the risk of children developing amblyopia. These risk factors include spherical error, astigmatism and strabismus. Detected risk factors may be treated with the intention of removing them as amblyogenic factors. Alternatively, amblyopia may be detected at an earlier stage, at which point treatment is more effective than at later stages.

It is assumed that cases of cosmetically apparent strabismus will be detected outside a screening programme (that is, through parents, GPs or health visitors), and that the only impact of cases of non-cosmetically apparent strabismus is via an increased risk of developing amblyopia.

The analysis considers the relative cost-effectiveness of mass population screening programmes for amblyopia and strabismus at the ages of 3, 4, and 5 years, compared with no screening, defining the QALY as the unit of outcome measurement. The minimum and maximum age ranges were chosen because it was not considered feasible to screen children accurately before the age of 3 years, and disease present at 6 years is likely to be less amenable to treatment and correction.

The specific objectives of the study were:

1. To develop a model of natural history for amblyopia, strabismus and refractive error. The description of natural history for each condition required estimates of disease-specific incidence for each condition.
2. Analysis of treatment effectiveness for amblyopia, strabismus and refractive error, including the possibility of disease regression when treatment is implemented at different stages of each condition.
3. To identify a range of potential screening programmes and, with clinical input, further evaluate those programmes that appear to be the most viable, effective and cost-effective options. These programmes were fully evaluated using the defined decision-analytic

modelling framework, which incorporates the net benefits of screening and measures the opportunity cost of the programme.
4. The economic aspects of amblyopia and strabismus that required consideration include the estimation of the impact of amblyopia and strabismus (and loss of vision) on people's quality of life (QoL) (utility).

It is recognised that the causal effects, treatment pathway and ultimately prognosis of specific strabismus and/or amblyopia may differ. This study does not aim to provide clinical guidelines for the treatment of each type of strabismus and/or amblyopia.

Research methods

The planned methods of this study consisted of three main sections. First, a literature review was undertaken covering all aspects referred to above. Second, following analysis of the data identified in the literature, areas in which no usable data were available, expert elicitation was used to obtain relevant estimates. Finally, a full expected value of perfect information (EVPI) analysis was undertaken using a decision-analytic framework to estimate the costs of uncertainty associated with the decision to screen for amblyopia and strabismus in the UK, and also to prioritise research by costing the individual parameters affecting the cost-effectiveness of screening.

Literature review

A comprehensive literature search was undertaken to identify literature pertaining to screening for amblyopia and strabismus. Major searches were conducted which were designed to retrieve papers demonstrating:

- trial and observational evidence describing the natural history of amblyopia and strabismus
- high-level evidence [clinical guidelines, systematic reviews, randomised controlled trials (RCTs)] on the effectiveness of treatment of amblyopia and strabismus
- evidence describing the effectiveness of screening tests for amblyopia and strabismus
- empirical estimates of health-related quality of life (HRQoL) and patient utilities relating to amblyopia and strabismus and screening.

The first review looked at epidemiological studies that inform our understanding of the development of amblyopia and strabismus and their disease progression. The second review examined studies that evaluated or reviewed the effectiveness of treatment options for amblyopia and strabismus. The third review looked for evidence describing the effectiveness of established screening programmes and the acceptability of screening tests for amblyopia and strabismus. The final review focused on the data describing the impact of amblyopia and strabismus and screening on HRQoL and utility.

Expert elicitation

Elicitation is the process by which an expert person expresses prior knowledge in probabilistic form. Since the expert rarely has a deep understanding of probability, the formal involvement of a facilitator becomes essential.

It was expected that few data would be identified for areas of the screening process that are potentially key to the estimation of cost-effectiveness. It was therefore necessary to elicit estimates of the required data from experts in the relevant field. Consultation with clinicians highlighted the presence of existing primary data, which were then used to populate the model.

EVPI analysis

The EVPI is a measure of the costs of uncertainty around the results of an evaluation, in this case the incremental cost-effectiveness of screening for amblyopia. The EVPI is estimated using the results of a probabilistic sensitivity analysis (PSA), in which the uncertainty around all input parameters to an evaluation is represented, and the outputs are a large number of separate estimates of cost-effectiveness (informed by alternative sampled sets of input parameters). If all of the iterations find the same intervention to be the most cost-effective (for a given value of the chosen outcome, e.g. the QALY), then there is no value in collecting additional information and the EVPI is zero. If there is some variation in the iterations, and different iterations find alternative interventions to be the most cost-effective option, then there is potential value in collecting more data to be able to identify the most cost-effective option with certainty.

The estimation of the EVPI treats each iteration of the PSA as a potential state of the world. In the absence of perfect information, a single decision is made regarding the choice of intervention that is applied to all states of the world. With perfect information, a separate choice of intervention can be made for each state of the world. The EVPI is the difference between the expected net benefits across all states of the world (iterations) with and without perfect information. The interpretation of

the EVPI is that it is the additional expected net benefits derived from eliminating uncertainty from the policy decision about which form of screening is most cost-effective (including no screening). The EVPI can also be viewed as an upper bound for the value of any partial information.

Systematic review

Separate systematic reviews of the literature were undertaken in the following areas relating to amblyopia and strabismus: natural history; epidemiology; diagnosis; screening tests; treatments; and QoL.

Search strategies

A comprehensive literature search was undertaken in the period 18–24 January 2006 to identify relevant literature pertaining to screening for amblyopia and strabismus (squint) (Appendix 1). Major searches were conducted which were designed to retrieve:

- high-level evidence (i.e. guidelines, systematic reviews and RCTs) concerning amblyopia and strabismus
- papers describing the screening of amblyopia and strabismus
- papers describing the epidemiology of amblyopia and strabismus
- papers describing the natural history of amblyopia and strabismus
- papers describing the diagnosis and diagnostic tests associated with amblyopia and strabismus
- papers describing the treatment of amblyopia and strabismus
- cost-effectiveness and health utility literature in the field.

The following electronic bibliographic databases were searched:

- Cochrane Database of Systematic Reviews (CDSR) (searched 24 January 2006)
- Cochrane Central Register of Controlled Trials (CENTRAL) (searched 24 January 2006)
- EMBASE (searched 20–24 January 2006)
- MEDLINE (searched 18–20 January 2006)
- MEDLINE in Process (searched 20 January 2006)
- BIOSIS (searched 23 January 2006)
- Cinahl (searched 20 January 2006)
- NHS Economic Evaluations Database (NHS EED) (searched 24 January 2006)
- Office for Health Economics, Health Economics Evaluations Database (OHE HEED) (searched 24 January 2006)
- Science Citation Index (searched 23 January 2006)
- NHS Database of Abstracts of Reviews of Effects (DARE) (searched 24 January 2006)
- NHS HTA database (searched 24 January 2006)

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. Health Management Information Consortium, Index to Theses, Dissertation Abstracts), current research registers (e.g. National Research Register, Research Findings Register, Current Controlled Trials) and relevant websites (e.g. Royal College of Ophthalmologists, British and Irish Orthoptic Society, Department of Health).

The reference lists of included studies and relevant review articles were also checked. No date or language restrictions were applied to the searches. The search strategy was to combine searches of

- "amblyopia and strabismus terms" and "screening" terms
- "amblyopia and strabismus terms" and "diagnosis" terms
- "amblyopia and strabismus terms" and "treatment" terms
- "amblyopia and strabismus terms" and "natural history" terms
- "amblyopia and strabismus terms" and "epidemiology" terms
- "amblyopia and strabismus terms" and "economics and quality of life" terms.

Inclusion and exclusion

The team devised the criteria for inclusion and exclusion. References were retrieved by one reviewer selecting from a specific subject heading and then checked by a second reviewer. In the first round of sifting the retrieved references, we used the following criteria. The papers identified as part of this review have been separated into the following categories:

Prevalence and incidence

- Inclusion: Primary research, systematic review or high-quality review
  Representative population-based sample
  Data reported
- Exclusion: Non-UK based

Risk factors

- Inclusion: Primary research, systematic review or high-quality review
  Data reported

- Exclusion: Risk factors not applicable to a screening population, e.g. genetic risk markers

Natural history progression
- Inclusion: Primary research, systematic review or high-quality review
- Exclusion: Highly selected population (such as ethnic group or screened population)

Treatment studies
- Inclusion: Primary research, high-quality reviews (recent and well-referenced publications) or guidelines
  Data reported

Quality of life studies
- Inclusion: Primary research
  Utility data or appropriate HRQoL measures used and the data reported

Economic studies
- Inclusion: Screening evaluations
  Resource and cost data presented

Screening studies
- Inclusion: Potential screening test
  Data reported

Diagnostic test studies
- Inclusion: Potential diagnostic test
  Data reported

The data were extracted by one reviewer and checked by a second reviewer using specially designed data extraction tables.

Results of the systematic review

The search resulted in 134 studies. The number of studies identified in each category is presented in Appendix 2. Lists of the studies included in the review are given in Appendices 3–7.

Six papers were identified in the literature search which were categorised as being systematic reviews or guidelines.[1,6–10] These included a Cochrane Review of screening for correctable visual acuity deficits in school-age children and adolescents[10] and a previous HTA report on preschool vision screening.[1] The papers identified were used as a basis to inform any additional literature searches. However, the systematic reviews and guidelines were excluded from further review in this report for two reasons: their inclusion and exclusion criteria differed from our own, and no results of meta-analyses were provided. These papers were therefore excluded from further review.

Chapter 2

Prevalence and incidence of amblyopia, strabismus and refractive error

A systematic literature review was undertaken to identify papers describing the prevalence and incidence of amblyopia, strabismus and refractive error (Appendix 1). The purpose of the review was to inform the model. Seven papers were identified and reviewed.[11–17] This chapter summarises the data relating to the prevalence of amblyopia, strabismus and refractive error. Four papers were identified relating to prevalence of amblyopia,[11–14] three papers reporting the prevalence of strabismus[15–17] and one paper reporting the prevalence of refractive errors.[17] It can be seen that the literature searches elicited few data regarding the prevalence or incidence of amblyopia, strabismus and refractive error. The assumptions of prevalence for amblyopia, strabismus and refractive error used for the model are summarised below.

Prevalence of amblyopia

Flom and Neumaier[11] reviewed previous literature detailing amblyopia prevalence and acknowledged that the definition of amblyopia affects the prevalence rates reported (*Table 1*). The authors demonstrated prevalence differences reported in military inductees, clinical samples and studies of school and preschool children. Prevalence rates of amblyopia ranged from 0.6 to 5.3% of the population in the studies reviewed. Studies carried out specifically within the UK demonstrated prevalence rates of 1.7–5.3%.[18–20] In the studies which reported prevalence of amblyopia in military inductees, each describes prevalence in a US cohort.[21–25] Such papers cannot be used to inform the prevalence of amblyopia within the UK due to differences in population characteristics.

TABLE 1 *Studies reporting amblyopia prevalence*[11]

Study	Percentage of population
Military inductees	
Theodore *et al.*, 1944[21]	4.0
Downing, 1945[22]	3.2
Glover and Brewer, 1944[23]	2.4
Agaston, 1944[24]	1.8
Helveston, 1965[25]	1.0
Clinical samples	
Cole, 1959[19]	5.3
Cholst *et al.*, 1962[26]	4.7
De Rotth, 1945[27]	4.5
School and preschool children	
McNeil, 1955[18]	2.7
Da Cunha and Jenkins, 1961[20]	1.7
Russell *et al.*, 1965[28]	1.3
Vaughan *et al.*, 1960[29]	0.6

Two UK studies, described by Flom and Neumaier,[11] reported on the prevalence of amblyopia within school and preschool children. McNeil[18] estimated the prevalence of vision defects (including amblyopia) among all children in an area of approximately 75,000 people, by reviewing the records of children referred to an ophthalmic clinic as a result of school screening. A prevalence of 2.7% was reported; however, it was noted that attendance to the ophthalmic clinic was not required. Children referred with a suspected visual problem could have received treatment elsewhere, and as such the reported prevalence of amblyopia could be low. Da Cunha and Jenkins[20] determined the prevalence of amblyopia in 3-year-olds. For this study, amblyopia was defined as a difference of more than one Snellen type line between the two eyes. The sample of 301 children revealed five could be diagnosed as having amblyopia (three detected by VA testing and two by the cover–uncover test). This represents a prevalence of 1.7% from the sample of children included in the study.

One UK study reported on the prevalence of amblyopia within a clinical sample. Cole[19] reported on 10,000 consecutive patients who were referred to the ophthalmic service with a suspected ocular complaint. The criterion for amblyopia was 20/50 or worse for one eye, with the other eye at least two Snellen lines better. An observed prevalence of amblyopia was 5.3%, although exact numbers of cases detected were not disclosed in the Flom and Neumaier paper.[11] The prevalence of amblyopia within a clinical sample is likely to be an overestimate of that which occurs

within the general population. The characteristics of a clinical population are such that people are under clinical investigation for suspected and/or diagnosed ocular complaints, and cannot be deemed representative of the general population as a whole.

Flom and Neumaier[11] continued by retrospectively examining the prevalence of amblyopia in schoolchildren and from a university eye clinic in the USA. The prevalence of amblyopia was also calculated using different acuity criteria set for amblyopia diagnosis. Amblyopia prevalence in the schoolchildren sample was calculated as 1.0–1.4%, whereas unsurprisingly prevalence within the university eye clinic sample was reported as 1.7–9.0%, according to amblyopia definition (*Table 2*).

Hopkisson and colleagues[12] reported on the prevalence of amblyopia in British Army recruits, and examined whether prevalence has altered since the introduction of screening programmes. The authors selected a 20% random sample of recruits' medical records for two years (1965 and 1976) and examined the number of recruits with amblyopia (defined as a difference between the two eyes of two or more lines on the Snellen acuity chart, with the good eye having vision of 6/9 or better). Potential recruits with appreciable ocular disease were excluded from the study. Their results demonstrated no significant difference in the prevalence of amblyopia between the two years. A prevalence of 3.1–4.7% was cited, with non-significant variations of prevalence between males and females. The prevalence of amblyopia from the 1965 cohort was 4.8% (n = 1199; n with amblyopia = 216). It can be seen from the results that the prevalence of amblyopia decreased between the years 1965 and 1976; however, this was of low statistical value [not statistically significant for men and only just significant for women ($p < 0.5$)]. When the results were combined, mean prevalences of 0.044% [95% confidence interval (CI) 0.035 to 0.053%] in men and 0.046% (95% CI 0.031 to 0.061%) in females were cited (*Table 3*).

Stewart-Brown and Butler[13] reported the VA in a national sample of 10-year-old children from a 1970 birth cohort (n = 13,871). They categorised defects into isolated distant vision defect, isolated near vision defects and defects of both near and distant vision (mixed defects). VA data were available for a large proportion of the cohort (n = 12,583). The results demonstrated that 2.0% of the cohort had significant unilateral mixed defects (assumed to be a proxy amblyopia), with a definition of vision defect being 6/9 or worse (*Table 4*).

The authors compared the results of the study with prevalence rates published from a 1958 birth cohort by Alberman and colleagues,[30] where significant unilateral mixed defects (proxy amblyopia) were found in 3.0% of the cohort. The introduction of vision screening could account for the differences in the proportion of distance vision defects seen between the two cohorts.

TABLE 2 *Amblyopia prevalence according to definition[11]*

Amblyopia definition	Prevalence of amblyopia in schoolchildren population	Prevalence of amblyopia in eye clinic population (%)
20/50 or worse and difference of ⩾1 Snellen lines	1.4	–
20/40 or worse and difference of ⩾1 Snellen lines	1.0	1.7
20/40 or worse	0.7	–
20/30 or worse	–	3.5
20/25 or worse	–	9.0

TABLE 3 *Prevalence and depth of amblyopia in military recruits in 1965 and 1976[12]*

	Men 1965	Men 1976	Women 1965	Women 1976
Total *N* in sample	4000	3746	499	325
No. (%) with amblyopia	188 (4.7)	153 (4.1)	28 (5.6)	10 (3.1)
No. (%) with ⩽2 line difference	88 (46.8)	66 (43.1)	10 (35.7)	5 (50.0)
No. (%) with >2 line difference	100 (53.2)	87 (56.9)	18 (64.3)	5 (50.0)
No. (%) with left eye weaker	109 (58.0)	77 (50.3)	15 (53.6)	1 (10.0)

TABLE 4 *Prevalence at 10 years by category of vision defect*[13]

Category of defect	Prevalence at 10 years (%)
Minimal (6/9)	0.8
Mild (6/12–6/18)	0.8
Moderate (6/24–6/36)	0.8
Severe (6/60 or worse)	0.4
Total	2.0

Prevalence of amblyopia among defaulters of preschool vision screening was reported by Newman and East,[14] which was compared with prevalence rates of amblyopia within preschool vision screening attenders. In this study, amblyopia was defined as 6/9 or worse vision in either eye with an interocular difference of one Snellen line or more. The authors reported a prevalence of amblyopia among screening defaulters as 1.3% (95% CI 0.2 to 4.5%) and a prevalence of 2.5% (95% CI 1.4 to 4.1%) among screening attenders. The difference in the prevalence of amblyopia between the two groups was not significant ($p = 0.53$). Considering the total population ($n = 754$, number with amblyopia = 17), the prevalence of amblyopia was 2.3%. The prevalence rate in the non-screened population could be used as representative of prevalence at 5.5 years, although the finding of a lower rate in the non-screened population is counterintuitive. It is also noted that the CIs are wide.

Prevalence of strabismus

Three papers reported prevalence of strabismus. Graham[15] reported the prevalence of strabismus and significant heterophoria in 4784 children born in Cardiff in one year, at age 5 years. The author reported 339 cases as having strabismus or significant heterophoria, giving a prevalence of 7.1%. Considering strabismus alone, the author reported a prevalence of 5.66%.

Stidwill[16] established the incidence of binocular anomalies from approximately 60,000 routine general optometric consultations over a 15-year period. Within this clinical survey, a total of 3075 cases, including patients of all ages, were recorded who were diagnosed with some form of binocular anomaly. This included strabismus, decompensated heterophoria, nystagmus and anomalies of accommodation and vergence. The author reported a mean period prevalence (per 1000) of all types of strabismus as being 50.00. That is, within a stated period of time, 50 people aged 6 years will have a diagnosis of strabismus. It is important to recognise that within this figure, there may be a number of adult patients with acquired strabismus, and therefore the mean period prevalence reported by Stidwill could overestimate the prevalence of strabismus in childhood.

Bruce and colleagues[17] reported the incidence of binocular vision anomalies within a group of 699 infants in the UK. Infants were recruited to the study from GPs' registers in a random manner, although the exact method of randomisation is not disclosed to the reader. The results were examined in two age groups: infants aged 9–12 months and infants aged 33–36 months, with incidence reported for each group. Within the younger cohort, an incidence of 1.38% for some form of binocular anomaly was reported, compared with an incidence of 5.1% in the older cohort (*Table 5*).

From the papers reviewed, the prevalence of strabismus within the population cannot be determined accurately. Strabismus can be assumed to be more prevalent within different age groups, due to changes occurring within the visual system.

TABLE 5 *Type and incidence of binocular anomaly in infants up to 36 months*[17]

	No. (%)	
Binocular anomaly	**9–12 months**	**33–36 months**
Orthophoria	341 (94.7)	202 (59.5)
Heterophoria	14 (3.9)	120 (35.4)
Intermittent esotropia	0 (0)	3 (0.9)
Intermittent exotropia	4 (1.1)	1 (0.3)
Constant esotropia	1 (0.3)	7 (2.1)
Constant exotropia	0 (0)	3 (0.9)
Other	0 (0)	3 (0.9)

Prevalence of refractive error

Only one paper was identified relating to the prevalence of refractive error. As a second part to the paper by Bruce and colleagues,[17] the authors also reported the incidence of refractive error in the 9–12 and 33–36 months age groups (*Table 6*). Incidence is reported with respect to type of refractive error. A slightly higher incidence of refractive error was reported in the younger cohort (9.5% compared with 8.1%). In both groups, when refractive error was present, this was hypermetropic in nature. Refractive error was determined by the use of a Cambridge paediatric videorefractor (VPR-1). Cycloplegia was not used in the assessment of refractive error.

Conclusions

From the papers reviewed, amblyopia prevalence within the UK could be taken as:

- McNeil (1955)[18] 2.7%
- Cole (1959)[19] 5.3%
- da Cunha and Jenkins (1961)[20] 1.7%
- Hopkisson and colleagues (1982)[12] 4.8%
- Stewart-Brown and Butler (1985)[13] 2.0%
- Newman and East (2000)[14] 2.3%

For the purpose of the model, a prevalence of 4.8% is assumed. This was chosen as it represents a non-clinical sample of the population, reporting amblyopia incidence in people aged 18 years or older. The remaining papers were discounted as they either report amblyopia prevalence in a clinical sample, a sample of screened children, children aged less than 7 years or by proxy amblyopia definition. The prevalence of amblyopia is taken from a 1960s cohort, and the ethnic diversity of the UK population is known to have altered since then. The Commission for Racial Equality[31] reported increasing ethnic diversity over the past 50 years (*Table 7*). It is therefore possible that the prevalence of amblyopia, strabismus and/or refractive error has also increased over time, as such conditions are believed to be more prevalent in non-Caucasian populations.

TABLE 7 *The non-white population of Great Britain, 1951–2001*[31]

Year	Non-white population
1951	30,000 (estimate)
1961	400,000 (estimate)
1971	1.4 million
1981	2.1 million
1991	3.0 million
2001	4.6 million

For the purpose of the model, prevalence of strabismus has been taken at two time points: that at 33–36 months and that at 5 years. This assumption was made due to differences in the incidence of binocular anomalies between a younger and older cohort, as reported by Bruce and colleagues.[17] Their data suggest that binocular anomalies are more prevalent with increasing age. The prevalence of strabismus at 33–36 months as reported by Bruce and colleagues[17] was used to inform the model. For the purpose of the model, the prevalence of strabismus at 5 years was informed by Graham.[15] A prevalence of 7.1% was assumed for the model as this included significant heterophorias. The presence of significant heterophoria does not result in decompensation of the condition to a manifest strabismus; neither are all significant heterophorias problematic. However, the presence of a significant heterophoria detected at screening may warrant concern, and hence initiate a referral. It is acknowledged that the prevalence used of 7.1% is likely to be an overestimate.

Surgical rates for strabismus correction in children have been reported to be on the decline.[32,33]

TABLE 6 *Type and incidence of refractive error in infants aged of up to 36 months*[17]

	No. (%)	
Refractive anomaly	**9–12 months**	**33–36 months**
No significant refractive error	326 (90.5)	306 (91.9)
Hypermetropia	22 (6.1)	17 (5.1)
Myopia	1 (0.3)	1 (0.3)
Hypermetropic astigmatism	8 (2.2)	7 (2.1)
Myopic astigmatism	1 (0.3)	0 (0)
Mixed astigmatism	2 (0.6)	2 (0.6)

Although the reason for the decline cannot be accurately determined, several theories have emerged to explain the fall in extraocular surgery (introduction of preschool screening; better/earlier management of refractive errors). Some may argue that the actual prevalence of strabismus is decreasing, and that the surgical rates for strabismus correction reflect this change in prevalence. Others would state that prevalence of strabismus has remained constant, and merely better and/or earlier intervention can account for changes in surgical rates.

In the absence of any additional studies, the prevalence of refractive error at 33–36 months as reported by Bruce and colleagues[17] was used to inform the model. Assessment of refractive error using photorefraction (of any method) without cycloplegia is not 100% reliable. Therefore, the prevalence rates of refractive error as reported by Bruce and colleagues[17] must be treated with caution.

The prevalence of any condition (i.e. amblyopia, strabismus or refractive error) is dependent on the definition used. This can vary from study to study, and to an extent from one person's opinion to another. The difference between theoretical amblyopia and the presence of clinically significant amblyopia may result in a varied clinical approach in referral and/or treatment of that condition. Similarly, the definition of a 'normal' VA or binocular status may also vary with age and/or with the diagnostic test used to ascertain the presence of that condition. As such, it is difficult to state accurately the exact prevalence rates of amblyopia, strabismus or refractive error within the UK. Existing studies can be used to inform prevalence; however, flaws exist within specific studies and caution must be exercised. There remains little robust evidence as to the UK prevalence of amblyopia, strabismus and refractive error in children aged up to 7 years. For the basis of the model, assumptions of prevalence for each condition are shown in *Table 8*.

TABLE 8 *Assumed prevalence of amblyopia, strabismus and refractive error*

Condition	Assumed prevalence (%)
Amblyopia	4.8
Strabismus at 33–36 months	5.1
Strabismus at 5 years	7.1
Refractive error at 33–36 months	8.1

Chapter 3

Natural history and risk factors

A systematic search of the literature was undertaken to inform the description of the natural history of amblyopia, and to inform model parameters used to represent the natural history. Details of the search strategy are presented in Appendix 1. A total of 17 papers[34–50] were identified relating to natural history and two papers[51,52] were identified relating to risk factors. The general information from the review informed the iterative process of model development that is described in Chapter 8. The following sections describe the data extracted from the literature review, split into two broad categories. The first section presents data from studies concerned with the progression of amblyopia and amblyogenic factors within early childhood, to the point at which amblyopia incidence is close to zero. The second part reviews the evidence around the consequences of amblyopia in terms of binocular vision loss.

Natural history

To model the impact of an intervention, it is necessary to know the natural history of the disease(s). For this, studies are required to report upon changes in refractive error, VA and binocular status over time. However, the literature search could not identify any papers which adequately addressed these issues. Many included individuals who had received some form of intervention (i.e. glasses or other treatment). What these studies actually report is the natural history of the condition(s) following the instigation of treatment. The literature was examined to explore the early childhood natural history of amblyopia and amblyogenic factors. The papers identified examine the natural history of one or more amblyogenic factor(s). These will be considered in turn.

Refractive error alone

The papers identified which addressed the natural history of refractive error appeared to focus on the changes which occurred in cases of astigmatism. Dobson and colleagues[34] reported on the changes observed in a group of children with astigmatism over time. Specifically, they examined the prevalence of against-the-rule, with-the-rule and oblique-axis astigmatism between infancy and childhood. Retrospective data on 979 patients were used to show higher rates of against-the-rule astigmatism in younger infants. A subgroup of 11 children aged <18 months were followed up 5–11 years after initial examination to demonstrate changes in observed refractive error over time. Ten of the 11 children initially had against-the-rule astigmatism, 6/22 eyes had astigmatism at follow-up and the six remaining cases continued with against-the-rule astigmatism. The data reported indicate the changes which occur with astigmatism over time. During the time of initial examination and follow-up, the refractive error states changed. The natural history of astigmatic changes described by the authors may be able to be generalised to changes which occur within the general population at a similar age. These data therefore provided some indication of the rate at which astigmatism spontaneously resolves over the period of emmetropisation.

Gwiazda and colleagues[35] also reported on refractive error changes in infants over time. They examined 72 children before the age of 6 months. They found that children with positive spherical equivalent in the first 6 months with against-the-rule astigmatism were more hypermetropic during childhood than those with early with-the-rule astigmatism or no astigmatism. Children with negative spherical equivalent in the first 6 months with against-the-rule astigmatism became myopic at an earlier age than children with no astigmatism. Children with early with-the-rule astigmatism remained emmetropic in childhood whether their spherical equivalent was negative or positive. Although the findings of Gwiazda and colleagues[35] are of clinical interest, the children who were reported in the study did undergo treatment over the observed study period (and no information on progression by compliance is presented), so these data are confounded from a natural history perspective. It is unknown whether, if treatment were not undertaken, the same changes in refractive error which were reported would have occurred.

In addition to reporting cross-sectional non-cycloplegic refraction data from 1000 children aged 0–6 years, Gwiazda and colleagues[36] also

reported longitudinal changes in 48 children followed for 4 years from 6 months of age (the response rate to invitation letters was 10%). The general conclusion from the data was that much of the early astigmatism was either eliminated or reduced in amount over the follow-up period, with an indication of a shift in axis to with-the-rule. Of the 19 children without significant astigmatism in the first year, only one child acquired significant astigmatism (with-the-rule) by 4 years.

In two papers in the same journal issue, Abrahamsson and colleagues[37,38] reported a longitudinal study of a population-based sample of children with astigmatism. The first paper reported on refraction and amblyopia and the second on the changeability of anisometropia. The authors described progression and impact of astigmatism at 4 years in 310 children with astigmatism at 1 year (although children were treated at 3 years if astigmatism >1D, ametropia >3D or anisometropia ≥1D). Increasing or constant astigmatism was identified in only 30 of the 310 children at 4 years. A total of 58 children (19%) were found to have anisometropia at some point in the follow-up period, although the maximum observed prevalence was 34 at age 2 years, with 28 having anisometropia at age 4 years. A total of 30% (9/30) of children with increasing or unchanged astigmatism developed amblyopia, compared with 5% (14/280) of children with decreasing astigmatism. It should be noted that the study population investigated by Abrahamsson and colleagues[37,38] were not in the UK, and such observations cannot be assumed to occur in a UK cohort.

The studies identified inform us that changes in refractive error do occur over time (known as the emmetropisation process). This process has been shown to occur during the preschool years. Particular changes in astigmatism have been reported. The quality of the data in terms of a description of the natural history changes which occur in amblyopia in a representative sample of UK children is extremely limited.

Amblyopia and refractive error

Three papers were identified which considered the natural history changes which occur in cases of refractive error and amblyopia. In a longitudinal study, Dobson and Sebris[39] described clinical outcomes in terms of strabismus, hypermetropia, astigmatism and anisometropia at age 36 months. A cohort of 65 children who were initially examined at age 8 months were included in the study. Subjects were categorised as infantile esotropes; high hypermetropia (no strabismus, refractive error ≥4D); moderate hypermetropia (no strabismus, refractive error 3–3.75D); family history of strabismus or amblyopia; and a control group. Children were monitored at regular time intervals, at which they had VA measured in addition to stereopsis assessment. The authors reported no differences among the groups in absolute acuity scores or interocular acuity differences until the infants reached 30 and 36 months of age. At this point, VA was reported to be lower in the children with infantile esotropia. The authors do not clarify as to whether intervention was initiated once reduced VA or change in binocular status occurred. Surgery is included as an outcome at 36 months for the strabismic group, and so it is possible that other interventions may also have occurred in other groups. It is therefore difficult to draw any firm conclusions from this study as to whether the changes in VA which occurred in the children are truly representative of the natural history of amblyopia. The authors also reported on the observed changes in binocular status, refractive error and VA in children categorised as having high hypermetropia. It is of interest that some of the infants demonstrated reduction in their refractive error, others continued to show high hypermetropia and another demonstrated high hypermetropia in one eye and moderate hypermetropia in the other eye. However, intervention in terms of the prescription of glasses was initiated between the ages of 14 and 24 months. As this intervention occurred, the findings reported by Dobson and Sebris[39] cannot be deemed to be representative of natural history changes in refractive error.

Townshend and colleagues[40] cited previous studies that illustrate uncertainty about whether higher degrees of anisometropia are associated with more severe degrees of amblyopia. They stated that previous studies did not separate hypermetropia and myopia, and that hypermetropia and myopia influence amblyopia differently. They investigated the relationship between the depth of anisometropic amblyopia without strabismus and differences in refraction for hypermetropic and myopic individuals. A retrospective review of 303 charts identified 35 patients aged 7–70 years with untreated anisometropia amblyopia without strabismus (between 1991 and 1992). The authors reported a strong correlation between depth of amblyopia and differences in refraction for individuals with anisometropic amblyopia, with the correlation being greater for myopic patients (this result was unexpected, and may be due to the

selection of myopic patients with amblyopia). The implication of the findings of this study is that the identification of children with large differences in refractive error has the greatest potential for benefit.

Donahue[41] aimed to test whether amblyopia develops as a function of duration of anisometropia in preschool children by identifying whether young children have a lower prevalence and depth of amblyopia than those identified at a later age. VA results from children examined formally following referral from the Tennessee (USA) state-wide preschool photoscreening programme and found to have anisometropic refractive error (>1.0D) were examined. Anisometropic children with superimposed strabismus were classified as strabismic; thus all anisometropic individuals were orthotropic. This study found that amblyopia is rare in anisometropic children under the age of 2 years, affecting only 14% of such children. The prevalence of amblyopia rises rapidly, however, and by age 3 years nearly two-thirds of children having greater than 1.0D anisometropia have developed amblyopia. The prevalence of amblyopia increases only slightly after this. This finding is extremely important, because traditional screening cannot occur until at least age 3 years. This study suggests that by this age, amblyopia has already occurred in most children in whom it will develop. Although the prevalence of anisometropic amblyopia does not increase after age 3 years, the depth of amblyopia does.

To compare all the results by age, and rule out that an age-associated bias in acuity testing produced the observed results, the 562 patients who were referred from the Tennessee screening programme and found to have strabismus on formal examination were evaluated. Results from the 506 children referred with strabismus show that the prevalence of amblyopia was less related to age than it was for anisometropic children. In addition, although there was a trend for strabismic amblyopia to increase in severity in older children, the trend was not as apparent in patients with strabismus as it was for anisometropia. Hence anisometropia appears to be a more powerful amblyogenic factor than strabismus, and the duration of anisometropia also appears to be more important than the duration of strabismus with respect to the development and depth of amblyopia.

The main limitation to these data is that photoscreening has a high specificity when the published Tennessee referral criteria are used, which reduces sensitivity, particularly to detect low-magnitude refractive error. Therefore, many children with mild and moderate levels of anisometropia were probably not detected and hence not included in this study. In addition, the study population could not be deemed to be representative of the UK population.

The information obtained from the studies identified shows that identification of children with large differences in refractive error has the greatest potential for benefit. In terms of natural history of amblyopia prevalence and anisometopia, prevalence of amblyopia appears to increase with anisometropia greater than 1.0D. In addition, prevalence of anisometropic amblyopia does not appear to increase after age 3 years, but the depth of amblyopia does. Screening for either factor prior to the age of 3 years would therefore be inappropriate.

Refractive error and strabismus

In examining the emmetropisation process, Ingram and colleagues[42] identified children aged 6 months with refractive error of +5D, and described changes in hypermetropia by eye (not child) between 6 months and 3½ years, stratified by no strabismus, microtropia and strabismus. Separate tables presented patient-level data from the first and last cycloplegic retinoscopy in the fixing eye and the non-fixing eye, by diagnosis of microtropia or strabismus. The authors reported that children who eventually had either a convergent strabismus or microtropia were significantly less likely to have spontaneously reduced their hypermetropia. However, it should be noted that these children, once diagnosed with strabismus, and with clinically significant refractive error will have undergone interventions in terms of treatment. Once such intervention occurred, it is not possible to state whether any changes would have still occurred if intervention had not been initiated.

Refractive error, strabismus and amblyopia

Abrahamsson and Sjostrand[43] identified 20 children at age approximately 1 year with anisometropia (spherical equivalent) ≥3 and <5.5D. Refractive errors and VA were measured at 6-monthly intervals to age 10 years, at which point the children were categorised as:

A Ametropia and anisometropia increased at 10 years, all cases developed amblyopia (n = 6), 3 cases developed esotropia.

B Decreasing anisometropia, and developed either amblyopia (n = 6) or convergent strabismus (n = 1).
C Decreasing anisometropia, and no amblyopia nor convergent strabismus (n = 7).

Two children had no astigmatism; the others varied from 0.5 to 3D, and no obvious relation between the amount of astigmatism and amblyopia could be identified. The authors used these results to suggest that amblyopia may cause anisometropia, not vice versa. The paper stated that children were prescribed glasses that fully corrected the anisometropia at 2–3 years, which is likely to be a confounding factor on the observed results. It must be noted that the subject numbers included in the study were low.

An earlier paper by Ingram and colleagues[44] described the predictive value of refractive error identified at age 1 year on the prevalence of strabismus and amblyopia at age 3½ years. The authors also presented data describing the change in the distribution of amounts of astigmatism between these ages. The findings of the study suggested that anisometropia is associated with strabismus and/or amblyopia.

Conclusions

The papers identified following the literature search do not adequately inform the natural history of amblyopia, strabismus or amblyogenic factors. Although the emmetropisation process is known to occur during preschool years, intervention (in terms of prescribing of glasses) invalidates the findings of the some of the studies. The association of refractive error, amblyopia and/or strabismus development cannot be fully understood because of this. It would be unethical to observe changes in infants and fail to act once a condition (amblyopia or strabismus) had been diagnosed. It is therefore not surprising that much of what is known about vision and disease development in humans has been informed by animal studies, particularly primate models. Although this information is of great clinical value and importance, the inclusion of such studies in this appraisal cannot be justified.

Natural history of amblyopia in adulthood

The literature was reviewed to examine the impact of amblyopia in adulthood in terms of subsequent vision loss in the non-amblyopic eye. Papers were also examined to determine any changes in VA that occurred in response to vision loss in the amblyopic eye.

Subsequent vision loss in the non-amblyopic eye

Rahi and colleagues[45] investigated the risk, causes and outcomes of visual impairment attributable to loss of vision in the non-amblyopic eye. In 1997, the British Ophthalmologic Surveillance Unit (BOSU) established a national surveillance scheme for the study of rare ophthalmological disorders or events. All senior ophthalmologists received a notification card every month over a 2-year period (1997–9) to notify individuals with unilateral amblyopia with correct VA worse than 6/12 and newly acquired loss of vision in the non-amblyopic eye with VA worse than 6/12. Following notification, and again 1 year after notification, more detailed questionnaires were sent to reporting ophthalmologists. Based on modelling notification card return rates and a survey of respondents, it was estimated that around 70% of all eligible cases were observed. A total of 370 individuals were identified over a 2-year period; however, data collection was incomplete for all cases. The authors reported the age distribution for 368 individuals with loss of vision in the non-amblyopic eye (*Table 9*).

Table 10 describes the vision outcome at 1 year; in total, 19% of individuals had recovered sufficient vision to facilitate driving, with a further 22% experiencing VA of less than 6/18 (socially significant). Looking at other impacts of the binocular vision loss, 284 of the 370 had some treatment for their non-amblyopic eye, 129 had surgery, 52 laser treatment and 104 medical treatment and 93 were given optical correction or low vision aids. One year after presentation, 232 were under regular review of an ophthalmologist. Of 102 individuals in paid employment, 36 were able to continue their work, 50 could not and outcome was uncertain in 16.

Of the 370 cases identified, complete data were available for the 1-year follow-up point for 363 cases. Using these data, the authors report lifetime

TABLE 9 *Age distribution of 368 individuals with loss of vision in non-amblyopic eye*[45]

	15 years or younger	16–64 years	65 years or older
No. (%)	15 (4)	114 (31)	239 (65)

TABLE 10 *Outcome at 1 year [no. (%)] following loss of vision in healthy eye:[45] visual impairment categories based on WHO classification (socially significant, worse than 6/12; visual impairment, worse than 6/18; severe, worse than 6/60)*

At presentation	At 1 year				
	Recovered (able to drive)	Socially significant	Visual impairment	Severe or blindness	Total
Socially significant	38 (37)	47 (46)	14 (14)	4 (4)	103 (100)
Visual impairment	29 (17)	28 (16)	101 (58)	16 (9)	174 (100)
Severe or blindness	3 (3)	4 (5)	12 (14)	67 (78)	86 (100)
Total	70 (19)	79 (22)	127 (35)	87 (24)	363 (100)

risk (cumulative incidence) in three age categories: childhood (by 16 years), working-age adults (by 64 years) and older adults (by 95 years) per 100,000 of the total UK population. In addition, the annual rates of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye are reported in these categories (*Table 11*).

It can be seen that the lifetime risk of visual impairment or blindness increases substantially from age 15–64 and 95 years. This can be attributed to the increased prevalence of other ocular disorders (such as age-related macular degeneration) that occur with increasing age.

Excluding cases in which vision recovered to better than 6/18, *Table 12* presents the projected period risks and associated annual rates of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye in individuals with amblyopia. Three models are presented, each incorporating alternative estimates of the age-specific prevalence rates of unilateral amblyopia. Model 1 assumes a prevalence of amblyopia with VA less than 6/12 of 1% of all age groups, model 2 assumes a prevalence of amblyopia with VA less than 6/12 of 1% in those aged 15 years or younger and 2% in those 16 years or older and model 3 assumes a prevalence of amblyopia with VA less than 6/12 of 1% in those aged 15 years or

TABLE 11 *Total population risk and annual rate of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye[45]*

	Incidence per 100,000 total UK population (95% CI)
Lifetime risk (cumulative incidence)	
Childhood (by 16 years)	0.35 (0.07 to 0.64)
Working-age adults (by 64 years)	5.67 (4.33 to 7.01)
Older adults (by 95 years)	32.98 (29.06 to 36.89)
Annual rate (age-specific incidence)	
5–15 years	0.04 (0.01 to 0.06)
16–64 years	0.11 (0.09 to 0.13)
65–95 years	0.91 (0.79 to 1.03)

TABLE 12 *Incidence of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye[45]*

	Incidence per 100 people with unilateral amblyopia[a] (95% CI)		
	Model 1	Model 2	Model 3
Cumulative incidence			
Childhood (by 16 years)	0.04 (0.01 to 0.06)	0.04 (0.01 to 0.06)	0.04 (0.01 to 0.06)
Working-age adults (by 64 years)	0.57 (0.45 to 0.69)	0.30 (0.24 to 0.36)	0.30 (0.24 to 0.36)
Older adults (by 95 years)	3.29 (2.91 to 3.69)	1.67 (1.47 to 1.86)	1.21 (1.07 to 1.35)
Annual incidence			
5–15 years	0.004 (0.001 to 0.006)	0.004 (0.001 to 0.006)	0.004 (0.001 to 0.006)
16–64 years	0.011 (0.008 to 0.013)	0.005 (0.004 to 0.007)	0.005 (0.004 to 0.007)
65–95 years	0.091 (0.077 to 0.103)	0.046 (0.039 to 0.052)	0.030 (0.026 to 0.034)

[a] VA worse than 6/12.

younger, 2% in those aged 16–64 years and 3% in those aged 65 years or older.

Tommila and Tarkkanen[46] estimated the probability of loss of vision in the non-amblyopic eye in Finland. The denominator is estimated as

prevalent cases of amblyopia	=	annual birth rate (60,000) × amblyopia prevalence in 7-year-old children (1.8%) × 20 years
	=	21,600 (rounded up to 22,000 by Tommila and Tarkkanen[46])

The numerator was informed by the number of amblyopic patients who received pleoptic treatment for loss of vision in the healthy eye (23 patients) over a 20-year period at the Helsinki eye hospital. The number was uprated to 35 to account for the suspected catchment area of the hospital. The incidence of loss of vision in the healthy eye is estimated to be 1.75 ± 0.3 per 1000 individuals with amblyopia. The use of pleoptics as a management option for the treatment of amblyopia is no longer commonplace. Amblyopia treatment is discussed further in Chapter 5.

An analysis of blindness in England and Wales[47] between 1963 and 1968 estimated that in a cohort of 100,000 blind individuals, around 400 would have become blind due to unilateral vision loss in childhood [*sic*] from squint, and subsequent loss of vision in the remaining eye. Fifty-two such cases were registered over the 6-year period. The probability of loss of vision in the non-amblyopic eye could be estimated as

p (loss of healthy eye vision)	=	cases of amblyopia-led blindness (52)/[adult amblyopia prevalence (5%) × population estimate (48 million) × 6 years]
	=	0.004 per 1,000

Vereecken and Brabant[48] investigated spontaneous improvement in the amblyopic eye, following loss of vision in the non-amblyopic eye. They identified 203 cases in which vision was lost in the non-amblyopic eye, including 59 identified from the literature and 144 from a questionnaire sent to ophthalmologists in four European countries. The literature cases were presented separately as it is possible that cases were published to show that spontaneous improvement was possible. Of the literature cases, in the pre-pleoptic period (i.e. prior to the introduction of eye exercises) all published cases showed improvement. In the pleoptic period, 22 of 53 cases showed improvement, 21 of which were achieved with treatment.

The survey data (all in the pleoptic period) showed that 41 of 144 cases showed improvement, of which 16 were reported to be with treatment and 25 without treatment. *Tables 13* and *14* describe the results by the degree of improvement and by age of loss of vision in the non-amblyopic eye. The majority of those experiencing improvement gained significant vision, which age at beginning of treatment is interpreted (by the authors) as showing no relationship between age and outcome.

The major part of the improvement in VA always occurred during the first weeks after the loss of the good eye. Five patients had received treatment for the amblyopic eye prior to losing the good eye – three of these patients experienced improvement after loss of the good eye – some evidence that prior treatment even if unsuccessful at the time improves the likelihood of improvement after the loss of the good eye.

Rahi and colleagues[49] also looked at the likelihood, and factors predictive of, improved vision in the amblyopic eye after loss of vision in the non-amblyopic eye. *Table 15* presents the outcomes at 1 year for 254 individuals aged ⩾11 years with loss of vision in the non-amblyopic eye, which shows a significant minority do gain vision in the amblyopic eye. The findings are in

TABLE 13 *Degree of improvement in the amblyopic eye*[48]

	No. of improved cases	
	Literature (*n* = 59)	**Survey (*n* = 144)**
Excellent	7	10
Good	14	24
Fair	7	7
Total	28	41

TABLE 14 *Improvement rates by age at loss of vision in the non-amblyopic eye*[48]

Age (years)	No. of cases	No. of improved results
9–21	21	10
21–31	22	8
31–41	18	7
41–51	17	3
51–61	22	9
>61	27	4

TABLE 15 *Vision in amblyopic eye at 1 year*[49]

Outcome	No. (%)
Some increase in VA	48 (17)
⩾2 lines increase in VA	25 (9)
No change	185 (66)
VA worse	21 (8)

agreement with the theory of residual plasticity outside childhood in a few people with amblyopia, which could be subject to some competitive influence from the non-amblyopic eye.

Table 16 presents the results of a multivariate analysis on factors that may affect the probability of an improvement in VA in the amblyopic eye. All of the factors appear to have a significant effect. In addition, it was not possible to differentiate between alternative treatments, so it may be that more effective treatments have a greater effect.

Kandel and colleagues[50] compared the characteristics of dominant eyes (the fellow eyes of unilateral amblyopia) and normal eyes (normal binocular fixation), primarily in young adults. They found that normal eyes are more sensitive than dominant eyes during the later stages of dark adaptation. In addition to differences in foveal pre-eminence between normal and dominant eyes, there is a measurable acuity difference that favours normal eyes; dominant eyes also differ in their fixation and in their capacity to respond to moving targets. The authors were unable to determine if these differences were due to the binocular nature of the visual system or the treatment effect of occlusion.

Conclusions

It is not possible to determine accurately the impact of subsequent vision loss in the good eye in individuals with amblyopia. Studies reporting such numbers are clinically based, so consideration must be given to those who do not seek referral or examination. The figures relating to the prevalence of such cases are likely to be an underestimation of the true extent of the problem. The papers identified report that lifetime risk of visual impairment in this population increases with age. This is not surprising when the prevalence of conditions, such as age-related macular degeneration, is known to increase with age.

Changes in VA in the amblyopic eye following vision loss in the non-amblyopic eye are reported. There is some evidence to suggest that improvements in VA in the amblyopic eye can occur. It should be noted that some papers discuss the use of pleoptic treatment; the use of pleoptics as a management option for the treatment of amblyopia is no longer commonplace. Improvements in VA in the amblyopic eye suggest that a degree of plasticity in the visual system exists. However, the literature was not searched with the purpose of identifying amblyopia treatment in adulthood; it is accepted that clinical treatment of amblyopia should occur before the age of 7 years. The data presented serve to inform that a degree of vision improvement in the amblyopic eye following subsequent vision loss in the non-amblyopic eye may occur. The impacts of such an occurrence on QoL are discussed in Chapter 6.

Risk factors

The literature search identified only two papers relating to risk factors associated with amblyopia and/or strabismus. Neither of these papers identified adequately reported risk factors with respect to the general population.

TABLE 16 *Multivariate analysis for any improvement in VA*[49]

Predictive factor	Proportional odds ratio (95% CI)	*p*
Age (per increasing year)	0.98 (0.96 to 0.99)	0.027
New optical treatment for amblyopic eye		
Untreated (174)	Baseline	
Treated (80)	70.1 (11.97 to 410.7)	<0.0001
VA of non-amblyopic eye at presentation:		
6/24 or better (98)	Baseline	
6/36 or worse (156)	3.79 (0.96 to 15.01)	0.057
VA of amblyopic eye at presentation:		
6/36 or worse (169)	Baseline	
6/24 or better (85)	5.38 (1.53 to 18.97)	0.009

TABLE 17 *Grade of observed re-fixation pattern*[51]

Grade	Description
1	Previously deviating eye maintains fixation through a blink (alternates)
2	Previously deviating eye holds fixation up to a dissociating event (blink)
3	Previously deviating eye holds fixation for a few seconds but the preferred eye resumes fixation before a blink
4	Preferred eye resumes fixation immediately

TABLE 18 *Statistically significant risk factors for esotropia and exotropia*[52]

Risk factor	*p*
Ethnicity (for esotropia) (increased risk in whites vs blacks)	<0.0001
Low birth weight	<0.0001
Maternal smoking during pregnancy	<0.0001
Maternal age (for esotropia) (increased risk at older ages)	0.0005

Risk factors – amblyopia

Laws and colleagues[51] undertook a prospective study to compare the binocular fixation pattern and presence of amblyopia in strabismic children. Fifty-three children with manifest strabismus were examined with binocular fixation pattern and logMAR VA was measured. The authors used a modification of the Zipf[53] classification of re-fixation pattern. This classification uses dissociative events such as blinking or saccades to define intermediate re-fixation patterns (see *Table 17*).

When the authors interpreted the results of binocular fixation pattern, they found a significant trend towards amblyopia from grade 1 (alternation) to grade 4 (no uniocular fixation) ($\chi^2 = 24.78$), $p < 0.001$). That is, patients who had a freely alternating strabismus did not have amblyopia, and those with maintained or preferred fixation with a given eye did exhibit amblyopia in the non-preferred eye. This paper could be interpreted such that the presence of a strabismus with maintained or preferred fixation is a risk factor in the development of amblyopia.

Risk factors – strabismus

Chew and colleagues[52] identified risk factors associated with esotropia and exotropia in a cohort of children in the USA ($n = 39{,}227$) followed up from gestation to age 7 years. Potential risk factors were evaluated from the maternal, socio-economic, perinatal and neonatal characteristics. Statistically significant risk factors are detailed in *Table 18*.

Conclusions

The evidence of statistically significant risk factors associated with amblyopia and strabismus is weak, and the results are not able to inform the development or existence of a suitable screening programme. Screening for amblyopia or strabismus on the basis of ethnicity, low birth weight, maternal smoking during pregnancy or maternal age is neither practical nor appropriate. Children born with very low birth weight or systemic health problems are recognised to be at increased risk of developing amblyopia, strabismus and/or refractive error. However, such children are monitored within the healthcare system under the care of a paediatrician. To this end, it is assumed that any screening programme will be directed at the general population as a whole.

Chapter 4
Screening

This chapter describes data reported in 19 papers[54–72] that evaluated specific tests that can be used to screen children for amblyopia, strabismus and/or amblyogenic factors. Twelve papers[73–84] were identified that examined screening programmes. In addition, six papers[85–90] examining who should undertake the vision screening examination were identified. Finally, seven papers[91–97] were identified which report on the impact of screening programmes on treatment outcomes.

Vision tests

Simmers and colleagues[54] investigated the effectiveness of the single optotype Sheridan Gardiner vision test in the detection of amblyopia compared to the Glasgow Acuity Cards (log-based linear test). A total of 702 schoolchildren underwent VA testing in addition to an orthoptic assessment consisting of cover–uncover test, ocular motility, convergence, prism reflex test and stereoacuity testing. The authors reported a significant difference in the mean VA measured using the different vision tests ($p = 0.0001$). When using the 95% CIs for a significant interocular difference in VA as criteria for the detection of amblyopia, the Glasgow Acuity Cards were found to be most sensitive (100%) in identifying unilateral amblyopia, compared with a sensitivity of 74% using the Sheridan Gardiner test.

Newman and East,[55] assessed the negative predictive value of the Sheridan Gardiner test for amblyopia detection in a cohort study of 936 children in the UK. The presence of amblyopia among the children who had passed screening was determined using the Snellen acuity test as the reference test. None of the children who had previously passed preschool vision screening were found to be amblyopic, so the negative predictive value (NPV) of the screening programme was therefore 100% (95% CI 99.4 to 100%). However, when analysing the results using the Sheridan Gardiner vision test in isolation, the authors reported an NPV for amblyopia of 99.6% (95% CI 98.7 to 99.9%).

As part of the Vision in Preschoolers Study,[56] a multi-centre clinical study was designed to evaluate commonly used and/or commercially available preschool vision screening tests. The study cohort consisted of 2588 children aged 3–5 years. The first paper reported the sensitivity and specificity of 11 preschool vision screening tests, of which linear Lea Symbols and HOTV VA tests were assessed (*Table 19*). (The HOTV distance VA test is administered in the same manner as the Lea Symbols test, except that the optotypes are the letters H, O, T and V.) Children were categorised into three groups: those with conditions important to detect and treat early; those important to detect early; and those where detection is clinically useful. In addition, the authors also reported sensitivity by condition type (*Table 19*).

In a subsequent publication, the authors reported on the sensitivity of the tests when the overall specificity was set at 94% in detecting amblyopia,

TABLE 19 *Sensitivity by vision and condition type[a] with specificity set to 0.90 for tests without established failure criteria[56]*

Test	Any condition *n* = 346	Group 1 *n* = 139	Group 2 *n* = 108	Group 3 *n* = 99	Specificity *n* = 796
Lea Symbols	0.61	0.77	0.57	0.41	0.90
HOTV	0.54	0.72	0.41	0.44	0.89
Test	**Amblyopia *n* = 75**	**Reduced VA *n* = 132**	**Strabismus *n* = 48**	**Refractive error *n* = 240**	**Specificity *n* = 796**
Lea Symbols	0.76	0.58	0.56	0.70	0.90
HOTV	0.73	0.48	0.65	0.59	0.89

[a] May have more than one condition.

strabismus, refractive error or reduced VA.[57] The results are summarised in *Table 20*.

Cover–uncover test

Williams and colleagues,[58] as part of the Avon Longitudinal Study of Parents and Children (ALSPAC), were able to report on the efficacy of the cover–uncover test in detecting strabismus and/or amblyopia at 37 months. The authors reported data on children who had attended for intensive orthoptic screening at 8, 12, 18, 25, 31 and 37 months. A total of 848 children were included in the study. The sensitivity and specificity of the cover test for detecting strabismus at 37 months was calculated to be 75% (95% CI 0.577 to 0.899%) and 100%, respectively.

The Vision in Preschoolers (VIP) study[56] also assessed the cover–uncover test. The results by condition severity and condition type are presented in *Table 21*.

In a subsequent publication, the authors reported on the sensitivity of the tests when the overall specificity was set at 94% in detecting amblyopia, strabismus, refractive error or reduced VA.[57] The results are summarised in *Table 22*.

Polaroid suppression test

Pott and colleagues[59] assessed the effectiveness of the polaroid suppression test (PST) in detecting amblyogenic factors by screening for suppression in young children. A total of 201 children aged 5 years underwent testing with the PST and examination of VA, eye alignment (using the Hirschberg method) and photorefraction. Data were available for 196 children for both VA and PST. The authors reported specificity of PST for VA impairments of 91%, with a test sensitivity of 60%.

In a follow-up study, Pott and colleagues[60] further reported on the use of the PST in detecting amblyogenic factors. In this study, 604 children aged 3–15 years were examined. Additional orthoptic testing included measurement of eye alignment, motility and monocular VA testing, plus cycloplegic refraction. Amblyopia was present

TABLE 20 *Sensitivity of tests when specificity was set to 0.94*[57]

Test	Amblyopia sensitivity (95% CI)	Strabismus sensitivity (95% CI)	Refractive error sensitivity (95% CI)	Reduced VA sensitivity (95% CI)
Lea Symbols	0.65 (0.54 to 0.76)	0.48 (0.34 to 0.62)	0.58 (0.52 to 0.64)	0.48 (0.39 to 0.57)
HOTV	0.52 (0.41 to 0.63)	0.44 (0.30 to 0.58)	0.40 (0.34 to 0.46)	0.36 (0.28 to 0.44)

TABLE 21 *Sensitivity by vision and condition type*[a] *with specificity set to 0.90 for tests without established failure criteria*[56]

Test	Any condition *n* = 346	Group 1 *n* = 139	Group 2 *n* = 108	Group 3 *n* = 99	Specificity *n* = 796
Cover–uncover	0.16	0.24	0.13	0.06	0.98
	Amblyopia *n* = 75	**Reduced VA *n* = 132**	**Strabismus *n* = 48**	**Refractive error *n* = 240**	**Specificity *n* = 796**
Cover–uncover	0.27	0.06	0.60	0.16	0.98

[a] May have more than one condition.

TABLE 22 *Sensitivity of cover–uncover test when specificity was set to 0.94*[57]

Test	Amblyopia sensitivity (95% CI)	Strabismus sensitivity (95% CI)	Reflective error sensitivity (95% CI)	Reduced VA sensitivity (95% CI)
Cover–uncover	0.27 (0.17 to 0.37)	0.60 (0.46 to 0.74)	0.16 (0.11 to 0.21)	0.06 (0.02 to 0.10)

in 84 children, with abnormal eye alignment. In 79 of these the PST result was abnormal, and in five children the test could not be performed due to non-cooperation. None of the children with amblyopia had a normal PST result. Results are summarised in *Table 23*. The PST is not routinely used in screening programmes in the UK.

Worth-4-Shape test

Morale and colleagues[61] assessed the testability reliability of the Worth-4-Shape test. This is a modification of the Worth-4-Dot test used to detect suppression. Subjects were recruited from a variety of sources, including a school participating in preschool screening, a vision research laboratory and a paediatric ophthalmology clinic (131 patients and 123 normal subjects). The age range of participants was 2–8 years. The authors compared the results of the Worth-4-Dot and Worth-4-Shape tests with a gold standard of medical history, assessment of bifoveal fixation and stereoacuity. The results are shown in *Table 24*.

Stereotests

A number of stereotests are available for vision screening. Ruttum and Nelson[62] evaluated the Random Dot E stereotest on 3- and 4-year-old children who had been referred for a one-line difference in VA testing. The Random Dot E stereotest was administered at two distances. Approximately 3000 children were screened during the study period, and 76 were found to have a one-line difference in VA and were referred for a full examination. A total of 58 children were included in the study (76%). Thirteen of the 58 children were found to have an abnormal eye examination; six of these had passed the screening using the Random Dot E stereotest when tested at 1.5 m and seven had failed it. Forty-five children had a normal examination; 39 of these had passed the screening Random Dot E stereotest at 1.5 m and six had failed it. The results of the sensitivity and specificity were 54% and 87%, respectively.

The VIP Study Group[63] reported on the testability of three different stereotests used to screen for vision disorders. They assessed the Random Dot E, Stereo Smile and Randot Preschool stereotests on 118 children aged between 3 and 3½ years. A total of 117 children were tested using the Random Dot E and Randot Preschool tests and 118 children were tested on the Stereo Smile test. Each child underwent pretesting with each test to demonstrate they understood the task. Testability on the pretest was significantly greater for the Stereo Smile test than for the Random Dot E test ($p = 0.007$) or the Randot Preschool test ($p < 0.0001$) and greater for the Random Dot E test than for the Randot Preschool test ($p = 0.02$) (*Table 25*). The percentages of all children able to complete the gross stereo task are shown in *Table 26*. The authors concluded that the results suggest that the use of two-choice procedure stereotests (like those studied) increases the testability of young preschool children. There was no significant difference in the proportion of children able to complete the gross stereotask among those testable for each test ($p > 0.12$, for all comparisons).

Table 27 describes the findings of the VIP[56] analysis of the Random Dot E and Stereo Smile II tests with respect to sensitivity by vision and condition type.

In a subsequent publication, the VIP study reported sensitivity of the Random Dot E and Stereo Smile II stereotests when the overall specificity was set at 0.94.[57] The results are summarised in *Table 28*.

As part of a study investigating refractive error and preferential looking VA in infants, Kohl and Samek[64] reported the responses of infants to the

TABLE 23 *Assessment of the PST[60]*

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
96.2	41.1	62.8	91.3
PPV, positive predictive value.			

TABLE 24 *Assessment of the Worth-4-Dot and Worth-4-Shape tests[61]*

Test	Sensitivity (%)	Specificity (%)
Worth-4-Dot	91.6	96.3
Worth-4-Shape	88.7	96.6

TABLE 25 *Testability of children on non-stereotest tasks[63]*

Stereotest	*n/N*	Testable (%)
Random Dot E	95/117	81
Preschool Randot	83/117	71
Stereo Smile	107/118	91

TABLE 26 *Ability of children to complete gross disparity random dot stereotasks*[63]

Stereotest	No. among all children (%)	No. among children testable on non-stereotask (%)
Random Dot E	87/117 (74%)	87/95 (90%)
Preschool Randot	66/117 (56%)	66/83 (80%)
Stereo Smile	91/118 (77%)	91/107 (85%)

TABLE 27 *Sensitivity by vision and condition type*[a] *with specificity set to 0.90 for tests without established failure criteria*[56]

Test	Any condition *n* = 346	Group 1 *n* = 139	Group 2 *n* = 108	Group 3 *n* = 99	Specificity *n* = 796
Random Dot E	0.42	0.59	0.33	0.27	0.90
Year 2:	*n* = 409	*n* = 172	*n* = 121	*n* = 116	*n* = 1037
Stereo Smile II	0.44	0.72	0.30	0.20	0.91
	Amblyopia *n* = 75	**Reduced VA *n* = 132**	**Strabismus *n* = 48**	**Refractive error *n* = 240**	**Specificity *n* = 796**
Random Dot E	0.63	0.38	0.60	0.47	0.90
Year 2:	*n* = 88	*n* = 114	*n* = 62	*n* = 299	*n* = 1037
Stereo Smile II	0.77	0.30	0.68	0.51	0.91

[a] May have more than one condition.

TABLE 28 *Sensitivity of tests when specificity was set to 0.94*[57]

Test	Amblyopia sensitivity (95% CI)	Strabismus sensitivity (95% CI)	Refractive error sensitivity (95% CI)	Reduced VA sensitivity (95% CI)
Random Dot E	0.28 (0.18 to 0.38)	0.29 (0.16 to 0.42)	0.23 (0.18 to 0.23)	0.24 (0.17 to 0.31)
Stereo Smile II	0.61 (0.51 to 0.71)	0.58 (0.46 to 0.70)	0.37 (0.32 to 0.42)	0.20 (0.13 to 0.27)

Stereofly test. They observed an increase in positive Stereofly responses as a function of increasing age in their studied group of 18 infants. By 24 months, the cumulative percentage positive response to the test was reported as 87%. Particular limitations of this study include the low subject numbers and repeated testing over a 2-year period, which may show a learned response rather than a test positive response.

Non-cycloplegic retinoscopy

The VIP study[56] assessed non-cycloplegic retinoscopy. A summary of the results is presented in *Table 29*.

In a subsequent publication, the authors reported on the sensitivity of the test when the overall specificity was set at 94%.[57] The results are summarised in *Table 30*.

Photoscreening

The literature search identified many articles relating to the use of photoscreening in screening for amblyopia, strabismus and refractive errors in children. Due to the large number of identified studies, stricter exclusion criteria were established, including non-English language of the article, incorrect population studied (in terms of age and ethnicity), high-risk population studied, use of outdated equipment, and selected follow-up of subjects (i.e. only screening failures examined). Nine papers were kept for full review. A number of different photorefractors and/or autorefractors were described.

Otago photoscreener

Kennedy and colleagues[65] reported on the effectiveness of the Otago photoscreener in detecting amblyogenic factors in the general population. A total of 1245 children of

TABLE 29 *Sensitivity by vision and condition type[a] with specificity set to 0.90 for tests without established failure criteria[56]*

Any condition *n* = 346	**Group 1** *n* = 139	**Group 2** *n* = 108	**Group 3** *n* = 99	**Specificity** *n* = 796
0.61	0.90	0.63	0.29	0.90
Amblyopia *n* = 75	**Reduced VA** *n* = 132	**Strabismus** *n* = 48	**Refractive error** *n* = 240	**Specificity** *n* = 796
0.85	0.47	0.56	0.81	0.90

[a] May have more than one condition.

TABLE 30 *Sensitivity of non-cycloplegic retinoscopy when specificity was set to 0.94[57]*

Amblyopia sensitivity (95% CI)	**Strabismus sensitivity (95% CI)**	**Refractive error sensitivity (95% CI)**	**Reduced VA sensitivity (95% CI)**
0.88 (0.81 to 0.95)	0.50 (0.36 to 0.64)	0.74 (0.68 to 0.80)	0.38 (0.30 to 0.46)

kindergarten age were screened (exact age ranges not stated). Subjects with an abnormal result from the photoscreening, plus a random sample of 20% of those with negative screening results, underwent standard ophthalmological testing, including objective refraction (without cycloplegia). The results are summarised in *Table 31*.

MTI Photoscreener™

Ottar and colleagues[66] reported on the accuracy of the MTI Photoscreener to screen for amblyogenic factors in healthy children. A total of 1003 children underwent photoscreening with the MTI Photoscreener and 949 were included in the study, which included a full ophthalmic examination with cycloplegic refraction. It should be noted that the age range of the study population was 6–59 months, with an average age of 28.7 months. The ethnicity of the study population was 81.3% Caucasian, 7.8% African American, 5.8% Hispanic and 2.9% Asian. The sensitivity of the test was reported as 81.8%, with a specificity of 90.6%. The positive predictive values (PPVs) and NPVs were 68.9% and 95.2%, respectively. The authors reported that the MTI Photoscreener detected all cases of strabismus and media opacities.

TABLE 31 *Assessment of the Otago photoscreener[65]*

Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**False-negative rate (%)**
81	98	77	1.6

Using the same data set, Donahue and colleagues[67] reported on the sensitivity of the MTI Photoscreener to detect high-magnitude refractive error. Results are described with respect to sensitivity in detecting anisometropia, hypermetropia and astigmatism (*Tables 32*, *33* and *34*, respectively).

Hatch and colleagues[68] assessed the validity and reliability of the MTI Photoscreener in a cross-sectional field study. Children of migrant field workers were asked to participate in the study; they were aged from 2 years 9 months to 10 years 9 months (mean age 6 years 6 months, SD 1 year 8 months). The ethnicity of the study population was not representative of the UK population, with cultural background in order of frequency being Portuguese, Asian (primarily Cambodian), Italian, Haitian, other Hispanic, white and Native American. The specific percentages of the ethnic groups were not reported. A total of 161 children were included in the study, which compared the MTI Photoscreener with VA testing, gross external examination of the eyes, objective refraction, cover–uncover test and ophthalmoscopy. The authors reported results of sensitivity and specificity based on two referral screening test definitions that differed in their case criterion for referral. The results are shown in *Table 35*.

One fundamental disadvantage of the MTI Photoscreener is that it requires subjects to be photographed in a darkened room. This may not be feasible or appropriate for use in all screening situations.

TABLE 32 *Sensitivity to detect anisometropia*[67]

Amount (Sph)[a]	*N*	Passed	Referred	Sensitivity (%)[b]
+1.25	5	3	2	46
+1.50	12	10	2	48
+2.00	6	1	5	89
+2.50	1	0	1	100
+3.00	1	0	1	100
+3.50	1	0	1	100
Total	26	14	12	

[a] Inter-eye difference in refractive error in greatest meridian.
[b] Sensitivity to detect amblyogenic factor of this or greater magnitude.

TABLE 33 *Sensitivity to detect hypermetropia*[67]

Amount (D)	*N*	Passed	Referred	Sensitivity (%)
+3.75	2	1	1	53
+4.00	6	3	3	53
+4.25	1	1	0	54
+4.50	7	6	1	55
+5.00	3	1	2	70
+5.25	3	1	2	71
+5.5	8	4	4	71
+5.75	3	0	3	100
+6.00				
>6.00	3	0	3	100
Total	36	17	19	

TABLE 34 *Sensitivity to detect astigmatism*[67]

Amount (D)	*N*	Passed	Referred	Sensitivity (%)
+1.75	11	7	4	57
+2.00	13	7	6	63
+2.25	1	0	1	70
+2.50	14	5	9	69
+2.75	1	1	0	75
+3.00	3	1	2	82
+3.50	4	1	3	88
+4.00	1	0	1	100
+4.50	2	0	2	100
+6.00	1	0	1	100
Total	51	22	29	

TABLE 35 *Sensitivity and specificity of MTI Photoscreener™*

Study	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ottar *et al.*[66]	81.77	90.62	68.86	95.15
Hatch *et al.*[68]	54.0 53.0	87.0 91.0	52.0 45.0	

Nikon Retinomax

Cordonnier and Dramaix[69] assessed the reliability of the Retinomax in measuring astigmatism in children aged 9–36 months. A total of 1205 children underwent non-cycloplegic screening with the Retinomax, 299 (25%) had repeated non-cycloplegic measurements, 302 (25%) were refracted using cycloplegia with the Retinomax and 88 (7%) underwent retinoscopy or further examination with an on-Table refractor. Results are reported using three different thresholds of manifest astigmatism (≥1.5, ≥1.75, ≥2D). *Table 36* details the results with the Retinomax, where true-positive case was defined as showing astigmatism of ≥2D by retinoscopy or with a Table refractor.

Cordonnier and Kallay[70] acknowledged the selection bias of the study, and addressed this in a follow-up study published in 2001. This study contained 1218 children, of whom 239 were considered positive for the presence of refractive error (19.6%) and 979 (80.4%) were negative. Of the 1218 children, 302 (25%) underwent cycloplegic refraction using the same autorefractor. The authors then used prevalence rates from other published studies to modify their results to eliminate selection and verification bias (*Table 37*).

Barry and Konig[71] assessed the Retinomax in screening for amblyopia in a study of 427 3-year-old children. A gold standard examination which included two orthoptic examinations and an ophthalmological examination was obtained in 404 (95%) of the study group. The authors applied differing referral criteria in determining the effectiveness of screening for amblyopia using the Retinomax (*Table 38*).

The VIP study[56] reported the sensitivity of the Retinomax and other autorefractors by vision and condition type, the results of which are presented in *Table 39*. It should be noted that the referral criteria for refractive errors using the Retinomax differed from year 1 to year 2.

TABLE 36 *Performances of the non-cycloplegic screening for the Retinomax[69]*

Manifest cylinder	Positive test, *n* (%)	Negative test, *n* (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥2D						
Right eye	20 (23)	68 (77)	52	95	85	76
Left eye	25 (29)	62 (71)	65	90	76	87
≥1.75D						
Right eye	23 (26)	65 (74)	58	93	83	78
Left eye	35 (40)	52 (60)	83	81	69	90
≥1.5D						
Right eye	31 (35)	57 (65)	82	93	87	89
Left eye	40 (46)	47 (54)	89	76	65	94

TABLE 37 *Results of sensitivity and specificity rates reported by Cordonnier and Kallay[70]*

Absolute refractive anomaly	Expected prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hypermetropia >3.5D	7.5	46	97	55	96
Myopia >3D	0.5	87	99	33	100
Astigmatism ≥2D	6	37	99	69	96
Anisometropia ≥1.5D	2.5	66	93	19	99

TABLE 38 *Effectiveness of screening[71]*

Screening option	Sensitivity (%)	Specificity (%)
Spherical equivalent ≥–1 to +3D or >1.5 DC, or >1D anisometropia	80	58
Spherical equivalent ≥–3 to +1.5D or =2 DC, or =1.5D anisometropia	70	60

TABLE 39 *Sensitivity by vision and condition type[a] with specificity set to 0.90 for tests without established failure criteria[56]*

Test	Any condition *n* = 346	Group 1 *n* = 139	Group 2 *n* = 108	Group 3 *n* = 99	Specificity *n* = 796
Retinomax	0.63	0.87	0.632	0.30	0.90
Year 2:	*N* = 409	*N* = 172	*N* = 121	*N* = 116	*N* = 1037
Power Refractor II	0.54	0.72	0.43	0.39	0.90
iScreen Photoscreener	0.37	0.57	0.24	0.20	0.94
MTI Photoscreener	0.37	0.55	0.27	0.19	0.94
SureSight Vision Screener	0.63	0.81	0.68	0.29	0.90
Retinomax	0.64	0.88	0.55	0.37	0.90
	Amblyopia *n* = 75	**Reduced VA *n* = 132**	**Strabismus *n* = 48**	**Refractive error *n* = 240**	**Specificity *n* = 796**
Retinomax	0.85	0.50	0.65	0.78	0.90
Year 2:	*N* = 88	*N* = 114	*N* = 62	*N* = 299	*N* = 1037
Power Refractor II	0.80	0.43	0.55	0.61	0.90
iScreen Photoscreener	0.62	0.27	0.50	0.43	0.94
MTI Photoscreener	0.63	0.24	0.65	0.42	0.94
SureSight Vision Screener	0.89	0.43	0.59	0.75	0.90
Retinomax	0.85	0.45	0.69	0.76	0.90

[a] May have more than one condition.

In a subsequent publication, the authors reported on the sensitivity of the tests when the overall specificity was set at 94% in detecting amblyopia, strabismus, refractive error or reduced VA.[57] The results are summarised in *Table 40*.

Topcon PR2000 paediatric refractometer

Williams and colleagues[72] assessed the accuracy of the Topcon PR2000 in a preschool population in the UK. A total of 222 children were recruited into the study and underwent examination by an orthoptist (cover test only) and then measurement with the PR2000. A cycloplegic refraction was then undertaken by a paediatric optometrist. Complete results were obtained from 189 children; incomplete results were due to error readings from the PR2000 (n = 13), out-of-range readings (n = 10) and low confidence readings (n = 10).

The authors reported good agreement with the PR2000 and cycloplegic retinoscopy (*Table 41*).

The authors also examined the effect of age on the accuracy of the PR2000, the results of which are shown in *Table 42*.

The authors concluded that the PR2000 underestimated hypermetropic refractive errors, but was as reliable as other refractive error screening instruments in the detection of anisometropia.

Screening programmes

Twelve papers were identified in the literature search that described the use of screening programmes within a given population. These

TABLE 40 *Sensitivity of tests when specificity was set to 0.94[57]*

Test	Amblyopia sensitivity (95% CI)	Strabismus sensitivity (95% CI)	Refractive error sensitivity (95% CI)	Reduced VA sensitivity (95% CI)
Retinomax	0.77 (0.67 to 0.87)	0.54 (0.40 to 0.68)	0.66 (0.60 to 0.72)	0.39 (0.31 to 0.47)
Year 2:				
Power Refractor II	0.57 (0.47 to 0.67)	0.34 (0.22 to 0.46)	0.42 (0.36 to 0.48)	0.27 (0.19 to 0.35)
iScreen Photoscreener	0.62 (0.52 to 0.72)	0.50 (0.38 to 0.62)	0.43 (0.37 to 0.49)	0.27 (0.19 to 0.35)
MTI Photoscreener	0.63 (0.53 to 0.73)	0.65 (0.53 to 0.77)	0.42 (0.36 to 0.42)	0.24 (0.16 to 0.32)
SureSight Vision Screener	0.80 (0.72 to 0.88)	0.54 (0.42 to 0.66)	0.63 (0.58 to 0.68)	0.35 (0.26 to 0.44)
Retinomax	0.78 (0.69 to 0.87)	0.53 (0.41 to 0.65)	0.63 (0.58 to 0.68)	0.36 (0.27 to 0.45)

TABLE 41 *Differences between Topcon PR2000 and retinoscopy*[72]

Refractive error	Mean difference between PR2000 and retinoscopy (D)	*r* and r^2 values	*p*
Spherical refractive error	1.16 ± 1.52	0.67; 0.45	<0.001
Anisometropia	0.01 ± 0.83	0.53; 0.28	<0.001
Astigmatism	–0.1 ± 0.61	0.57; 0.33	<0.001

TABLE 42 *Effect of age on the accuracy of the PR2000, when specificity is at least 95%*[72] *(n = 189)*

Age group (months)	Target (D)	Prevalence of target error (%)	PR2000 referral level (D)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<36	Spherical error >3.75	8	2.00	57	97	57	97
(*n* = 83)	Anisometropia >1.00	4	1.25	25	99	50	96
	Astigmatism >1.25	7	1.25	67	95	50	98
36–59	Spherical error >3.75	24	2.00	54	95	75	85
(*n* = 45)	Anisometropia >1.00	15	1.25	63	96	71	94
	Astigmatism >1.25	22	1.00	50	100	100	88
>59	Spherical error >3.75	20	2.00	47	95	70	88
(*n* = 61)	Anisometropia >1.00	30	1.25	65	95	79	90
	Astigmatism >1.25	18	1.00	62	95	73	92

differed widely with respect to the personnel performing the screening, the age at which the child was screened, the tests undertaken and the referral criteria.

Allen[73] examined the efficacy of visual screening by comparing the number of true- and false-positive referrals between two health districts in the UK, one with a screening programme and the other without. The results are shown in *Table 43*. The author observed that the number of false-positive referrals is much lower in the screened cohort.

Jarvis and colleagues[74] compared the efficacy of three different screening programmes within an area of the UK. Three cohorts were described in the study, in which screening was performed by different personnel on children of differing ages. The details are shown in *Table 44*.

The authors reported performance characteristics of the screening programmes over an 18-month period, which included examinations of 7000 children. Analyses were performed on those with any target condition and those who had treated target conditions only (*Table 45*). The authors stated that the results demonstrate that screening performed by orthoptists at 35 months is superior to health visitor screening at 30 months. It cannot be assumed that the difference in PPV rates is due to differing healthcare personnel administering the screening. Differences in screening programme content must also be acknowledged.

In a UK study, Allen and Bose[75] audited a screening programme with respect to both uptake and the effectiveness of the screening itself. The screening programme consisted of VA testing at aged 3½ years by medical officers using the Stycar vision test. Results were compared with the vision test results recorded following school nurse examination of VA at age 6 years. A random sample of 599 records was selected, with data available for 531 children. The uptake of screening was poor (53.5%). Of the 284 children who attended testing, the sensitivity and specificity were calculated as 77% and 96%,

TABLE 43 *Referrals from two districts*[73]

Referrals	Screened district, *N* (%)	Non-screened district, *N* (%)
True-positive	275 (79%)	169 (57%)
False-positive	73 (21%)	129 (43%)

TABLE 44 *Timing and content of screening in the three areas*[74]

Area	Younger cohort	Older cohort	Personnel
Northumberland comparison	At 7–9 months: squint check	At 30–36 months: squint check	Health visitor, GP, clinical medical officer
Orthoptist[a]	At 5 months: cover–uncover test, ocular motility, prism reflex test, convergence	At 35 months: as at 5 months plus visual acuity	Orthoptist
Newcastle comparison	At 9 months: standard check, family history	At 30 months: standard check	Health visitor

[a] Superimposed on the Newcastle system (see comparison area).

TABLE 45 *Performance characteristics of screening programmes*[74]

	Sensitivity (treated target condition) (%)	Specificity (treated target condition) (%)	PPV (treated target condition) (%)
Younger cohorts			
Orthoptist area	25 (50)	99.7 (99.7)	33 (33)
Newcastle comparison area	17 (0)	99.7 (99.6)	20 (0)
Older cohorts			
Orthoptist area	100 (100)	98.3 (97.1)	74 (55)
Newcastle comparison area	43 (50)	100 (100)	100 (100)

respectively. The PPV of the described screening programme was 50%.

De Becker and colleagues[76] reported the NPV of a population-based preschool vision screening programme in Canada. A total of 11,734 preschoolers were screened within the study period and were classified into 'pass' and 'fail' groups. A geographically stratified random sample of 200 children who had passed the screening examination was identified for a gold standard examination. The screening examination was undertaken by community health nurses, and consisted of VA testing (HOTV chart) and stereoacuity testing (Randot). The gold standard examination included a full orthoptic examination and cycloplegic refraction and funduscopy. Of the 11,734 children screened, 10,932 (93.2%) passed and 802 (6.8%) failed. Of the 200 randomly chosen subjects selected for gold standard examination, 157 were actually examined (78.5%). In this group, 11 (7%) failed the gold standard. The PPV of the screening programme was 50% (95% CI 35 to 63%). The NPV was 93% (95% CI 89 to 97%).

Williamson and colleagues[77] reported on the efficiency of a preschool vision screening programme in Glasgow to detect amblyopia. The results for 712 patients who were considered to require referral were analysed, and the default rates were assessed in addition to the efficacy of treatment determined. Screening was administered by orthoptists and included VA (single Sheridan Gardiner); cover–uncover test; ocular motility; prism reflex test; and stereoacuity (Randot or TNO). Screening was administered to $3\frac{1}{2}$ to $4\frac{1}{2}$-year-old children. Diagnoses of the 712 children referred included no abnormality detected (n = 184, 26%); strabismus (n = 141, 20%); refractive error (n = 350, 49%); and other (n = 37, 5%). The false-positive rates with respect to the percentage of patients with abnormal screening test results who had amblyopia (when amblyopia was defined as having VA of less than 6/9) were recorded, and are summarised in *Table 46*.

McNamara and Duckworth[78] reported on the effect of removing vision testing from child surveillance programmes in a UK-based study.

TABLE 46 *Assessment of screening programme*[77]

Screening test	*N*	6/9 or better (false positives) (%)
VA worse than 6/6	566	92.2
VA worse than 6/9	566	62.3
Cover–uncover test	574	22.9
Stereopsis	510	19.2

They retrospectively examined a sample of letters of referral (n = 157) from health visitors requesting a child to be assessed for secondary orthoptic screening. They reported that three risk factors were most commonly stated as the reason for referral: positive family history; parental concern or failed VA or cover–uncover test; or a combination of factors. The results are shown in *Table 47*. The authors continued to report on the referral patterns of different healthcare professionals who assessed children at different ages over the same period. The authors observed fewer false-positives in the younger cohort.

Robinson and colleagues[79] assessed the validity of a preschool vision screening programme measured over a 3-year period to determine how well strabismus and refractive errors could be detected. In this Canadian study, screening was administered by public health nurses and consisted of VA (using Crowding Cards), ocular alignment (using the Hirschberg method) and stereoacuity (Titmus). The test for stereoacuity was introduced midway through the programme (year 2), so not every child enrolled in the study underwent assessment using this test. Every child who that failed the screening examination was referred for an ophthalmological assessment. For each child who failed screening, the next child who passed was also referred as a control. The results of the screening programme are shown in *Table 48*.

Mulley[80] compared two primary orthoptic screening regimes at two ages with respect to detection rates of strabismus and reduced vision undertaken in Keighley (UK). Children were screened by an orthoptist at 1½ or 3½ years. The 1½-year examination included cover–uncover test, ocular motility, convergence, prism reflex test, stereotest (Frisby or Lang) and photorefraction. The 3½-year assessment included VA testing (Sonkson Silver, Kays or single Sheridan Gardner), cover–uncover test, ocular motility, convergence, prism reflex test, stereoacuity (Frisby, Lang or TNO) and photorefraction. Children were referred if any strabismus or abnormality of ocular movements were detected, if VA was reduced from normal in either and if significant refractive error was detected on photorefraction. The referral criteria for photorefraction differed slightly for the two age groups. The results of the study are shown in *Table 49*. It should be noted that sensitivity and specificity values of screening at 1½ years cannot be calculated. This is due to the lack of false-negative and true-negative results available, as not all children received a second diagnostic test. An odds ratio (OR) was calculated to see whether there was a statistically significant difference between the false positive rates of the screening tests at 1½ and 3½ years old. The OR was found to be statistically significant ($p < 0.05$).

Eibschitz-Tsimhoni and colleagues[81] evaluated the efficacy of a mass screening programme for amblyopia and amblyogenic risk factors in Israel. They reported on two cohorts; a group who had undergone screening between ages 1 and 2½ years (n = 988, of whom 808 participated), and a group

TABLE 47 *Assessment of screening programme*[78]

	PPV when only factor for referral used (%)	PPV when combination of factors for referral used (%)
Family history	41.66	28.57
Failed tests	27.50	32.60
Family concern	16.66	29.23

TABLE 48 *Assessment of screening programme*[79]

	Year 1	Year 2	Year 3
Failures, no. (%)	339 (28.9)	385 (34.7)	293 (25.5)
Controls, no. (%)	312	297	240
PPV (%) (95% CI)	25.4 (20.2 to 30.5)	21.6 (17.1 to 26.2)	32.3 (26.2 to 38.4)
NPV (%) (95%CI)	93.6 (90.6 to 96.6)	95.3 (92.7 to 97.9)	92.6 (88.7 to 96.5)
Proportion of true positives newly diagnosed (%)	89	83	83.6
Sensitivity, (%)	61.9	70.9 (83.8[a])	60.4
Specificity, (%)	75.6	69.6 (64.6[a])	79.7

[a] With stereoacuity.

TABLE 49 *Results of vision screening programme*[80]

Age (years)	Attendance rate (%)	False positives (%)	PPV (%)
1½	59	25	75
3½	67	12.7	87

who had received no visual screening (n = 782). All children were examined at 8 years of age and the incidence of amblyopia was documented. The authors reported the prevalence of amblyopia in the screened population to be lower than in the non-screened population (p = 0.098). The prevalence of severe amblyopia was also lower in the screened population (p = 0.00026). The authors reported a sensitivity of the screening programme of 85.7%, with a specificity of 98.6%. The PPV was 62.1% and the NPV was 99.6%. It should be noted that the study involved a population which differs in ethnicity from the general population within the UK.

Juttmann,[82] on behalf of the Rotterdam Amblyopia Screening Effectiveness Study (RAMSES) steering committee, reported on the compliance with vision screening and the PPV of the screening tests used. In this programme children were screened during the first 2 years of life by healthcare physicians. Those with a positive screening result were advised to arrange for ophthalmological testing, and the results of these examinations were used as a reference for establishing the PPV. A total of 4072 children were examined, the results of which are shown in *Table 50*.

Barry and Konig[83] analysed the test characteristics of orthoptic screening in 1180 children aged 3 years in Germany. Orthoptic screening included the inspection of the anterior eye segment, full cover–uncover test and near and distance fixation, examination of ocular motility and head posture and VA testing using the Lea Single Symbols acuity test. Children were referred for gold standard examination if they failed the screening criteria. The gold standard examination included a repeat orthoptic examination some 3–6 months later. If the screening criteria were still not met, the child was referred for a full ophthalmological examination, including cycloplegic refraction. Results were analysed with respect to the 1093 children in whom the gold standard was obtained and who were not treated for amblyopia or amblyogenic risk factors before screening. Inconclusive results of screening items were excluded from analysis. A summary of the results is shown in *Table 51*.

Chui and colleagues[84] assessed a vision screening programme used in Nova Scotia for children aged 4½ and 5½ years. Public health nurses administered the screening, which consisted of VA testing (Linear Lea Symbols), stereoacuity testing (Frisby stereoplate) and external examination of the eye to assess for obvious strabismus or gross abnormalities of the eye or external adnexae. Results were compared with a gold standard examination which took place on the same day as the screening examination or no later than 3 months following screening. The gold standard examination consisted of VA testing (Linear Lea Symbols), stereoacuity testing (Titmus, Frisby and Worth-4-Dot tests), ocular examination (fusional vergence amplitudes, cover–uncover testing, ocular motility, convergence and bifoveal fixation), papillary examination, cycloplegic refraction and full fundus and media examination. A total of 141 patients were included in the study and analysed with respect to children aged under 41 months and those aged 41 months or older. The results are shown in *Table 52*. Higher reproducibility occurred between screening and clinically significant gold standard examinations for the older age group (p < 0.001). Differences in

TABLE 50 *Results of the PPV at different ages*[82]

Test	No. evaluated by ophthalmologist	Visual disorder not amblyopia	Probably amblyopia	PPV all visual disorders	PPV amblyopia
At 9 months	41	7	15	0.54	0.37
At 14 months	36	9	12	0.58	0.34
At 24 months	24	6	15	0.88	0.62
Total	101	22	42	0.63	0.42

TABLE 51 *Results of orthoptic screening*[83]

Test	Inconclusive results, *N* (%)	Positive results, *N* (%)	No. of conclusive results	Proportion of detected gold standard positive cases[a]	Sensitivity (%)	Specificity (%)
Inspection	0 (0.0)	2 (0.2)	1093	1/26	3.8	99.9
Ocular motility	47 (4.3)	12 (1.1)	1046	3/25	12.0	99.1
Cover–uncover testing	51 (4.7)	13 (1.2)	1042	4/25	16.0	99.1
VA	118 (10.8)	63 (5.8)	975	19/22	86.4	95.4
Cumulated	118 (10.8)	79 (7.2)	975	20/22	90.9	93.8

[a] Proportion of detected cases with positive gold standard among all cases with positive gold standard in children with conclusive result for the screening item (equal to sensitivity).

TABLE 52 *Results of screening and clinically significant gold standard examinations*[84]

	Positive (failure)		Negative (pass)	
	<41 months	⩾41 months	<41 months	⩾41 months
Positive screen (failed)	9	3	13	4
Negative screen (passed)	3	3	28	78
Sensitivity (%)	–	–	75	50
Specificity (%)	–	–	68	65
False-positive rate (%)	–	–	32	5
PPV (%)	–	–	41	43
NPV (%)	–	–	90	96

specificity ($p < 0.001$) and sensitivity ($p = 0.004$) values were significant.

Who should screen for amblyopia and strabismus?

Current UK screening programmes vary widely, despite recommendations by the Hall Report.[98] The Child Health Sub-Group evaluated vision screening against the National Screening Committee[3] criteria and produced a document which recommended that all children should be screened for visual impairment by orthoptists or by professionals trained and supported by orthoptists.[99]

Hall and Stewart-Brown[100] discussed the advantages of using orthoptists as primary screeners. They noted that referral and failure of treatment of cosmetically unacceptable strabismus are not due to lack of identification. The detection of small angle strabismus or microtropia, however, does require expert examination, yet often presents with amblyopia. The authors state that it is desirable for vision screening to be performed by orthoptists, due to acceptable sensitivity and specificity studies published in the literature. However, in order to directly compare the sensitivity and specificity of screening programmes carried out by orthoptists and other healthcare professionals, the screening programmes should include identical assessment methods. In many studies, this is not the case. Additional tests are performed by orthoptists to aid detection and/or diagnosis, which could account for increased sensitivity and specificity rates published.

Rosner and Rosner[85] investigated whether parents were accurate screeners in identifying whether their child had strabismus. A total of 536 children were included in the study, ranging in age from 3 to 71 months. They reported that parents are not always able to detect strabismus in their children, but when they do detect it their observations are likely to be correct. Sensitivity of parents as screeners was 65% (having identified 55 of the 84 strabismic children). Specificity was 99%, having correctly identified 448 of the 452 non-strabismic children. The accuracy of positive identification (predictive value of positive tests) was 93% (judging 59 children to be strabismic when 55 were).

Although parents may be able to detect the presence of strabismus, clinicians would argue that parents are unable to detect the presence of reduced VA. Paysse and colleagues[86] evaluated the accuracy of parent-administered VA tests in a prospective, experimental study. Children had their VA first tested by the parent or guardian using an electronic VA tester, and then re-tested by a technician. The authors were therefore able to determine the reliability of the parent-administered visual acuity test. Results showed that reliability of parent-determined VA scores was high (r = 0.91 and 0.81 for right and left eyes, respectively), with 93% of right eye parent scores and 85% of left eye parent scores within 0.11 logMAR units of the technician score. The results of this American study have obvious limitations when considering healthcare and screening programmes within the UK. The authors argue that the parents could use such equipment in waiting rooms to increase office efficiency, an option that would not be deemed acceptable within current NHS guidelines. What the results do demonstrate, however, is that electronic VA testing equipment can be used reliably by lay persons.

The concept of using lay screeners was examined by the VIP Study Group in another American-based study.[87] This multi-centre, multi-disciplinary, phased study to evaluate vision screening tests for identifying preschool children, who would benefit from a comprehensive eye examination, compared the performance of nurse screeners with that of lay screeners in administering the screening tests. The screening tests comprised autorefraction (using two different autorefractors), VA measurement (using linear optotypes) and stereoacuity measurement. The results of screening were compared with a gold standard eye examination performed by optometrists and ophthalmologists. The authors found that nurse screeners achieved slightly higher sensitivities using the autorefractors and stereoacuity tests than the lay screeners, but that these differences were small and not statistically significant. However, nurse screeners did achieve significantly higher sensitivity when measuring VA using linear optotypes (0.49 versus 0.37; p = 0.0004). The results are shown in *Table 53*. It should be noted that Single Lea Symbols were performed by lay screeners only. Results were then analysed with respect to condition type (*Table 54*).

The authors do not make any recommendations as to who should perform the screening examinations; however, it can be implied that personnel with training are more accurate than lay persons in detecting deficits in VA.

TABLE 53 *Sensitivity of screening tests by vision with specificity set to 0.90*[87]

Test	Any condition *n* = 462	Group 1 *n* = 210	Group 2 *n* = 144	Group 3 *n* = 108	Specificity *n* = 990
Linear Lea Symbols					
Nurse screener	0.49	0.60	0.38	0.42	0.90
Lay screener	0.37	0.50	0.19	0.35	
Difference	0.12	0.10	0.19	0.07	
95% CI	0.05 to 0.19	–0.01 to 0.19	0.08 to 0.29	–0.06 to 0.20	
Single Lea Symbols					
Lay screener	0.61	0.78	0.51	0.40	0.91
Retinomax					
Nurse screener	0.68	0.88	0.59	0.39	0.90
Lay screener	0.62	0.85	0.49	0.36	0.90
Difference	0.06	0.03	0.10	0.03	
95% CI	0.02 to 0.09	–0.01 to 0.07	0.04 to 0.17	–0.06 to 0.12	
SureSight Vision Screener					
Nurse screener	0.64	0.83	0.57	0.34	0.90
Lay screener	0.61	0.82	0.51	0.34	0.90
Difference	0.03	0.01	0.06	0.00	
95% CI	–0.01 to 0.06	–0.02 to 0.05	0.00 to 0.12	–0.10 to 0.10	
Stereo Smile II					
Nurse screener	0.45	0.58	0.37	0.30	0.90
Lay screener	0.40	0.56	0.31	0.23	
Difference	0.05	0.02	0.06	0.07	
95% CI	0.00 to 0.09	–0.05 to 0.09	–0.02 to 0.14	–0.04 to 0.15	

Due to the existence of different screening programmes and regimes within the UK, Edwards and colleagues[88] were able to investigate the appropriateness of different healthcare professionals in undertaking visual screening. They compared the results of a community programme of screening for visual defects in 3½–4-year-olds by orthoptists with those of a dual system of health visitor screening and GP referral. Orthoptists were found to be more accurate in performing screening with a lower false-positive referral rate (1%, two of 198 referrals) compared with health visitors (67%, 54 of 81 referrals). Although the visual screening assessment was the same for both programmes, the level of training was very different in the two groups. The health visitors described in the study had received a half-day seminar on methods of assessment. It could be deemed that such a level of training is inappropriate, and that if healthcare professionals other than orthoptists are to perform visual screening then high false-positive referral rates can be expected.

Bolger and colleagues[89] reported similar findings when comparing the detection rates and false positive referral rates of orthoptists and clinical medical officers (CMOs). The authors found that detection rates for amblyopia were higher with orthoptists performing the screening (relative detection rate 2.4; 95% CI of 1.4 to 4.1). Detection rates for strabismus were also higher (relative detection rate 3.9; 95% CI 1.9 to 15.3). The number of false-positive referrals which occurred when orthoptists were primary screeners was also lower, with 1.8 times more false-positive referrals from the CMO cohort (95% CI 1.4 to 2.0). The authors therefore concluded that orthoptists are more effective than CMOs in screening for visual abnormalities.

Bray and colleagues[90] reported on the differences in referral patterns in visual screening programmes. They compared referral rates in three cohorts: those who received vision screening performed by orthoptists at a local clinic; those who received vision screening performed by health visitors at a home visit; and those who received screening by GPs, CMOs or health visitors (HVs) at a local clinic. Their findings demonstrated that orthoptic screening identified children with amblyopia and refractive errors at an earlier age, compared with children screened by GPs, CMOs or HVs. The authors reasoned that if diagnosis, and therefore implementation of treatment, occur promptly, then a successful outcome in terms of final VA levels is more likely. The authors stated that early correction of refractive errors and

TABLE 54 *Sensitivity of Linear Lea Symbols and Single Lea Symbols by condition type with specificity set to 0.90*[87]

Test	Amblyopia sensitivity *n* = 101	Reduced VA sensitivity *n* = 117	Strabismus sensitivity *n* = 47	Refractive error sensitivity *n* = 387
Linear Lea				
Nurse screener	0.69	0.53	0.53	0.51
Lay screener	0.56	0.48	0.39	0.37
Difference	0.13	0.05	0.14	0.15
95% CI	0.00 to 0.27	–0.08 to 0.18	–0.05 to 0.31	0.07 to 0.22
Single Lea				
Lay screener	0.87	0.61	0.79	0.64
Retinomax				
Nurse screener	0.87	0.48	0.62	0.78
Lay screener	0.81	0.46	0.60	0.71
Difference	0.06	0.02	0.02	0.06
95% CI	0.00 to 0.12	–0.06 to 0.09	–0.10 to 0.15	0.03 to 0.10
SureSight Vision Screener				
Nurse screener	0.82	0.52	0.53	0.70
Lay screener	0.79	0.53	0.49	0.69
Difference	0.03	–0.01	0.04	0.01
95% CI	–0.03 to 0.09	–0.08 to 0.08	–0.06 to 0.14	–0.02 to 0.05
Stereo Smile II				
Nurse screener	0.64	0.43	0.64	0.47
Lay screener	0.61	0.37	0.72	0.42
Difference	0.03	0.06	–0.08	0.05
95% CI	–0.07 to 0.13	–0.04 to 0.14	–0.21 to 0.04	0.0 to 0.10

treatment of amblyopia in the orthoptic screened cohort yielded excellent results, particularly as this group was found to have a greater number of children with 'straight-eyed' amblyopia. The authors observed that the prevalence of amblyopia between the three cohorts at age 7 years was similar for all groups. This could not be fully explained, but may have resulted from small sample sizes.

The location of the screening programme is likely to affect uptake. Screening at GP surgeries, nurseries or schools all have their advantages and disadvantages in terms of suitability of testing environment and accessibility to the population to be screened.

Effect of screening programmes on disease prevalence and treatment outcomes

Seven papers were identified that reported the impact or effect of preschool visual screening on treatment outcomes. It should be noted that such papers cannot be used to inform appropriateness of screening, or the prevalence of amblyopia and/or strabismus in the general population.

Kohler and Stigmar[91] analysed the number of visual disorders in 7-year-old children, some of whom had received previous vision screening, to determine whether the screening had any effect on disease prevalence. In this Swedish study, some children received screening at age 4 years. All children underwent screening of VA by school nurses at age 7 years. Children who failed screening at age 7 years were referred for full ophthalmological examination. Of the 2178 children screened at age 7 years, 310 (14.2%) were referred for further examination. About 49% of the referred children had 'significant eye disorders' that required treatment. Results were analysed to demonstrate that the number of newly detected eye disorders was greater in children who had not received previous screening (*Table 55*). The results demonstrated that the risk of detecting a significant eye disorder at age 7 years was six times greater in children who had not received previous visual screening.

Edwards and colleagues[92] assessed the outcome of preschool vision screening performed on children aged between 3½ and 4½ years who were referred for treatment in this UK study. A total of 198 referrals were made, and the records of 128 who had completed treatment were available. Late referrals who had not received preschool visual screening were also examined. The authors reported that more surgery was performed in the screened group compared with the late referral group and that this was of statistical significance ($p < 0.01$). Of the children initially diagnosed with abnormal VA, more patients in the late referral group failed to achieve 6/9 or better in the worse eye ($p < 0.05$). Of the 131 children who had received vision screening, 75 (57.2%) completed treatment, achieving VA of 6.6 or better, compared with only 34 (30.4%) in the late referral group. The authors stated that the screened group appeared more likely to achieve an excellent, rather than acceptable, VA in the worse eye ($p < 0.01$).

In a UK study, Newman and colleagues[93] assessed the outcome of children referred following orthoptic preschool screening at age 3½ years. The main outcome measures were the diagnosis of children referred following screening and the visual outcome after completion of treatment. The authors reported a PPV of screening of 79.9%, with 243 cases of 304 referred found to have a visual problem. Analysis demonstrated that of the children referred with amblyopia, VA of 6/9 or better was achieved in most (*Table 56*). The efficacy of amblyopia treatment could be determined only for 47 of the 91 children with amblyopia. Improvement of two Snellen lines or more was achieved by 62% of the children (29/47 cases).

Harrad and colleagues,[94] as part of the ALSPAC study, reported on VA levels at age 7 years following orthoptic screening at different ages. They hypothesised that preschool vision screening improves visual outcome in children with amblyopia. An RCT compared intensive orthoptic

TABLE 55 *Newly detected significant eye disorders in 7-year-old children with and without screening at 4 years of age*[91]

	No. of newly detected significant eye disorders (%)
Previously screened at 4 years of age	11 (0.7)
Previously not screened	29 (4.5)
Total	40 (1.8)

TABLE 56 *Visual acuity achieved in the amblyopic eye*[93]

VA	No. (%) of children with amblyopia
6/6 or better	41 (46.0)
6/9	27 (30.0)
6/12	13 (15.0)
6/18	3 (3.0%)
6/24	4 (4.0%)
6/36	1 (1.0%)

screening, performed at 8, 12, 18, 25, 31 and 37 months with intermediate-level orthoptic screening performed at 37 months with no orthoptic screening. The outcome was assessed at age 7 years. The authors reported that the prevalence of amblyopia differed between the three groups (*Table 57*), which supported their original hypothesis.

Williams and colleagues[95] assessed the effectiveness of early treatment for amblyopia in children following screening before or at age 3 years as part of the ALSPAC study. Intensive orthoptic screening was compared with children who were screened only at 37 months (control group), and the prevalence of amblyopia and VA of the worse-seeing eye at age 7½ years were used as outcome measures. Results were also analysed using two definitions of amblyopia: definition A, where the interocular difference in acuity was 0.2 logMAR or more; or definition B, where the vision in the amblyopic eye was worse than 0.3 logMAR. A total of 3490 children participated in the trial, with final outcome data available for 1929. Of these, 15 were excluded from further analysis due to other ocular pathology or developmental delay, leaving the results for 1914 children to be analysed. Of these, 1088 had received intensive screening and 826 were in the control group. The prevalence of amblyopia at 7½ years is shown in *Table 58*. It can be seen that the prevalence was lower in the group which had received intensive orthoptic screening. This was statistically significant for amblyopia definition B ($p = 0.02$) and approaching significance for definition A ($p = 0.06$). VA in the amblyopic eye was found to be significantly better in treated children in the intensive orthoptic screening group compared with the control group ($p < 0.001$). As with the previous paper, the authors concluded that the results confirmed the hypothesis that early treatment for amblyopia leads to a better visual outcome, and that this may be achieved with improved detection from screening programmes.

In a subsequent paper, Williams and colleagues,[96] as part of the ALSPAC study, reported on amblyopia treatment outcomes after preschool vision screening versus school entry screening. Outcome was measured at 7½ years by orthoptists. The results for 6081 children were reported, of whom 1516 had been offered preschool vision screening and 1019 had received it. The authors reported a lower prevalence of amblyopia in those who had received preschool screening, even when the results were analysed following different applications of amblyopia criteria. The results were adjusted for sex, highest level of maternal education, birth weight, family history of strabismus or amblyopia and duration of breastfeeding (*Table 59*). (These factors were found

TABLE 57 *Prevalence of amblyopia across intensive, intermediate and no-screening groups*[94]

	Intensive group	Intermediate group	No screen group
Prevalence of amblyopia (%)	0.6	1.8	1.2
Likelihood of persistent amblyopia after treatment [odds ratio: (95% CI)], comparison with intensive group	–	4.1 (1.1 to 16.6)	7.0 (1.3 to 38.6)
Median acuities (logMAR)	0.12	0.19	0.27

TABLE 58 *Prevalence of amblyopia at age 7½ years*[95]

Amblyopia definition	Prevalence (95% CI) (%)	
	Intensive screening	Screening at 37 months
A	1.45 (0.89 to 2.35)	2.66 (1.76 to 4.00)
B	0.63 (0.30 to 1.32)	1.81 (1.10 to 2.98)

TABLE 59 *Prevalence of amblyopia at 7½ years in children who did or did not receive preschool vision screening (n = 6081)*[96]

Definition of amblyopia	Prevalence of children who had preschool screening (*n* = 1019) No (%)	Prevalence in children who did not have preschool screening (*n* = 5062) No (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
0.2+ logMAR or more between best acuity of each eye	11 (1.1)	100 (2.0)	0.53 (0.27 to 1.03) $p = 0.052$	0.63 (0.32 to 1.23) $p = 0.237$
Worse eye sees worse than 0.3 logMAR	7 (0.7)	65 (1.3)	0.53 (0.22 to 1.20) $p = 0.108$	0.72 (0.32 to 1.60) $p = 0.550$
Worse eye seen 0.18 or worse	19 (1.9)	171 (3.4)	0.54 (0.32 to 0.88) $p = 0.011$	0.65 (0.38 to 1.10) $p = 0.161$

to be significantly associated with VA in the worse-seeing eye in a multi-variable analysis.) Williams and colleagues[96] also found that the result of occlusion treatment was different in the two groups. Children who had received preschool screening had better VA than those who had not ($p < 0.001$).

Bui and Donahue[97] presented long-term follow-up data on preschool patients who had been initially identified as having amblyogenic risk factors following photoscreening. They reviewed 50 charts from a series of 400 patients. Of the 50 patients, 18 (36%) were diagnosed with some form of amblyopia and were treated with glasses and/or occlusion therapy. Of these amblyopic patients, 10 (56%) achieved ≥20/40 (0.3 logMAR equivalent) vision and six (33%) demonstrated at least two lines of improvement in acuity. The authors concluded that these results demonstrate that a significant number of children identified by photoscreening do have amblyopia, and that a significant number of these experience an improvement in vision following treatment. However, the authors do not disclose the age at which screening took place, or the ethnicity of population studied. It is therefore difficult to draw conclusions as to whether the results of this American study can be applied to a UK vision screening programme.

The Hall Report[98]

The fourth edition of *Health for All Children* (Hall 4)[98] was published in 2002. It provides guidance as to when screening programmes should be administered and by whom. A summary document produced by the Department of Health, Social Services and Public Safety entitled *Health for all children: guidance and principles of practice for professional staff*[101] summarises the implementation and recommendations of Hall 4. The document advocates visual assessment at the school entry age (i.e. 4–5 years). Referral criteria to orthoptic led services is reported as VA of worse than 6/9 Snellen, or a minimum line difference in either eye or 0.2 logMAR. The recommendations of the Hall Report advocating visual assessment at school entry could be reasoned to provide a greater uptake of screening in terms of the numbers of children tested (compared with screening at GP surgeries or health centres). The children will be available for testing, and it does not rely on parents/guardians bringing a child for an assessment. The suitability of the environment with respect to testing conditions could continue to be an issue (as with screening conducted at other locations).

Conclusions

The use of any test to detect amblyopia, strabismus and/or refractive error must be age appropriate, and to that end some of the published results should be treated with caution. The existence of age-related changes in both VA and refractive error are known to exist in both normal and screened populations. This can be attributed to concentration and cooperation, in addition to changing complexities of the screening test(s) used.

Stewart[102] reviewed the literature on the use of logMAR acuity tests in children and adults, and

TABLE 60 *LogMAR visual acuity norms for children*[102]

Reference	Age group (years)	Test	Mean VA ± SD	Normal range (logMAR)
Jones *et al.*[103]	3–5	Crowded Keeler	0.04	–0.125 to 0.3
		Kays linear	–0.04	–0.100 to 0.225
Stewart[104]	4–6	Crowded Keeler	0.087 ± 0.10	0.000 to 0.400
		Uncrowded (single) Keeler	–0.010 ± 0.10	0.100 to 0.300
Shea and Gaccon[105]	3	Crowded Keeler	0.200 ± 0.09	0.025 to 0.375
	4	Crowded Keeler	0.142 ± 0.08	–0.025 to 0.300

summarised VA data available for norms. The author identified three studies which reported both mean VA and normal range, the results of which are shown in *Table 60*.

The significance of such findings relates directly to the acknowledgement of age-related norms in VA. The current referral criteria as recommended by the NSC[99] is a VA measure of 0.2 logMAR or less in either eye. If this is adhered to, then it can be seen that there is a likelihood of false referrals, particularly in a younger screened population.

Published data informed by UK studies regarding the type of tests which may be employed as part of a screening programme for amblyopia and strabismus are scarce. The introduction of log-based VA tests within clinical practice invalidates a number of studies, as the use of single optotypes without crowding or standardised progression is not recommended.[106] The evidence in the literature is highly supportive of the use of gold standard logMAR-based VA tests. These have been shown to be more sensitive in the detection of amblyopia.[104] This is in agreement with the Royal College of Ophthalmologists' statement on the assessment of children.[106]

Following the publication of Hall 4[98] and the subsequent recommendations of the NSC,[99] there still remains a need for high-quality UK-based studies assessing the effectiveness of screening programmes in the detection of amblyopia, strabismus and/or refractive error. The recommendations have yet to be implemented in many Primary Care Trusts (PCTs) and, until audit and assessment of such services exist, the uncertainty surrounding vision screening cannot wholly be answered.

The use of photoscreening across the UK is varied, with a range of photoscreening equipment available. Published data regarding the sensitivity and specificity of such equipment in a study population similar to that of the UK general population have not been widely identified. It should be noted that the studies describing the use of photoscreeners were mainly conducted in the USA, where the population demographics differ from those in the UK. The inclusion of stereotests within a screening programme could also be questioned.

Caution must also be exercised when considering the assessment and/or referral of patients who demonstrated abnormal ocular movements. The full assessment of ocular movements ought to include testing of the systems which encompass ocular reflexes, smooth pursuit, saccades and convergence. In a screening situation, what is often tested are smooth pursuit movements and convergence. The studies which refer to ocular movements are often not specific in identifying exactly what was assessed; however, it is likely that smooth pursuit movements will have been included in the screening assessment. Additional testing is often not appropriate in this age group.

Evidence to demonstrate the impact of screening programmes was identified. Papers describing such programmes differ widely in the content of the screening programme itself, the population group examined and the personnel administering the screening. Published data regarding which healthcare professionals should administer visual screening is supportive of orthoptist-led programmes. This is in agreement with published guidelines from professional bodies such as the Royal College of Ophthalmologists.[106]

Chapter 5

Treatment for amblyopia and strabismus

A total of 35 papers[107–141] were identified in the literature search relating to the treatment of amblyopia, strabismus and refractive error. Twenty-nine papers[107–135] were identified that reported on treatment of amblyopia. These are discussed with respect to the severity of amblyopia present and the type of amblyopia therapy. Factors affecting visual outcome in the treatment of amblyopia are also discussed, in addition to treatment compliance. Three papers[136–138] were identified that reported on treatment for strabismus, the results of which are summarised. Treatment of refractive errors, strabismus and amblyopia with the use of paediatric refractive surgery is summarised, with three papers[139–141] identified in the literature search.

Treatment of amblyopia

The sensitive period for strabismic amblyopia in humans was explored by Epelbaum and colleagues.[107] They retrospectively analysed the data from patients with strabismic amblyopia (n = 407). In this study, amblyopia was defined by a difference in VA between the two eyes of at least 0.3 (when the Snellen acuity is expressed as a decimal). Amblyopia was purely strabismic in 336 patients (83%); the age at beginning of therapy averaged 27 months (range from 21 days to 107 months). The authors defined occlusion efficacy as the reduction ratio of interocular acuity difference at the start and end of treatment. The results showed that the efficacy of occlusion therapy depended on the age of initial treatment, with progressively deteriorating efficacy with increasing age. Treatment efficacy was found to be virtually nil at the age of 12 years.

Few studies exist that document effective treatment outcomes for amblyopia within a randomised clinical trial. Variables such as severity of amblyopia, age of subject when commencing treatment, compliance and differing treatment modalities mean that comparisons cannot easily be made between papers. Literature searches elicited treatment papers which can be considered under the categories of refractive adaptation and amblyopia therapy. The latter are further considered in terms of the severity of amblyopia (moderate or severe).

Refractive adaptation

The treatment of amblyopia in the presence of refractive error (with or without the presence of strabismus) has been investigated over recent years. There has been increasing evidence to suggest that prescription of glasses alone can improve VA to the extent that amblyopia therapy is not required, or that the amount of amblyopia therapy prescribed may be reduced. As part of the Monitored Occlusion Treatment for Amblyopia Study (MOTAS), Stewart and colleagues[108] reported changes in visual function following refractive adaptation, describing improvement in both VA and contrast sensitivity. Ninety-four subjects were included in the study (mean age 5.1 ± 1.4 years), where amblyopia was associated with strabismus (n = 34), anisometropia (n = 23) and with both anisometropia and strabismus (n = 37). Eighty-six of the participants required some form of refractive correction and underwent a period of refractive adaptation (18 weeks of glasses wear). As a result of refractive adaptation alone, 13 of the 86 subjects requiring refractive correction did not require amblyopia therapy (15%). The authors reported a mean VA in the amblyopic eyes at the start of refractive adaptation of 0.69 ± 0.38 logMAR. The mean VA in the amblyopic eyes at the end of the refractive period was 0.44 ± 0.42 logMAR.

Stewart and colleagues[109] described the visual response to refractive adaptation for children with unilateral amblyopia as a function of age, type of amblyopia and category of refractive error. Data were collected from 65 children with previously untreated amblyopia and significant refractive error (mean age 5.1 ± 1.4 years). Amblyopia was associated with anisometropia (n = 18), strabismus (n = 16) and both anisometropia and strabismus (n = 31). The mean (SD) VA in the amblyopic eyes at recruitment was 0.77 (0.41) and ranged from 0.1 to 1.6 logMAR. Following a period of 18 weeks of refractive adaptation, amblyopic eye mean (SD) VA improved significantly from 0.67 (0.40) to 0.43 (0.37), and was statistically significant ($p < 0.001$). This represents a mean improvement of 0.24

(0.18), range 0.00 to 0.60 log units. The results showed that the change in mean (SD) logMAR VA (from the start of refractive adaptation to the best VA measurement) did not differ significantly by amblyopia type [anisometropia, 0.29 (0.17); mixed, 0.19 (0.15); strabismus, 0.30 (0.24) ($p = 0.29$)]. Similarly, the change in mean (SD) logMAR VA (from the start of refractive adaptation to the best VA measurement) did not differ significantly by age [under 4 years ($n = 19$), 0.23 (0.18); 4–6 years ($n = 29$), 0.24 (0.20); over 6 years ($n = 17$) 0.16 (0.23) ($p = 0.38$)]. The mean number of weeks taken to achieve best VA of the amblyopic eye did not differ significantly between amblyopia groups ($p = 0.52$) or with age ($p = 0.63$). The authors reported that during the refractive adaptation process, 14 study participants (22%) achieved improvement in VA such that they did not require occlusion therapy and concluded that refractive adaptation is a distinct component of amblyopia treatment.

Amblyopia therapy

Over recent years, multi-centre studies in the USA have contributed to existing clinical practice within the UK. The Paediatric Eye Disease Investigator Group (PEDIG) has reported on outcomes for amblyopia therapy using a variety of treatment interventions.

Treatment of moderate amblyopia – conventional occlusion

PEDIG[110] compared 2 hours versus 6 hours of daily patching as treatment for moderate amblyopia in children younger than 7 years old. The authors defined moderate amblyopia as vision of 20/40 to 20/80 in the amblyopic eye or an interocular VA difference of three or more logMAR lines. A total of 189 subjects were recruited into the trial, where 95 were assigned 2 hours of patching and 94 were assigned 6 hours of patching, with both groups undertaking 1 hour of near visual activities while patching. All subjects were monitored at 5 and 17 weeks. The authors reported substantial improvement in VA in both groups at both 5 weeks and 4 months. At 4 months, 79% of subjects in the 2-hour patching group and 76% of subjects in the 6-hour patching group had an improvement in VA by two or more lines from baseline. VA had improved from baseline by an average of 2.40 logMAR lines in each group, with a mean difference in logMAR acuity between the groups of 0.001 (95% CI –0.040 to 0.042). There was no statistical evidence for an interaction between treatment group and either patient age ($p = 0.76$), cause of amblyopia ($p = 0.85$) or baseline VA of the amblyopic eye ($p = 0.96$). The authors therefore concluded that either treatment method produces improvements in VA of similar magnitude.

The amount of patching therapy prescribed is often at the discretion of the treating physician. No clinical guidelines are available to determine the amount of occlusion required for a given level of amblyopia at presentation. Elliott[111] reported that the prevalence of written guidelines for occlusion therapy was low, and significant variations exist within the amount of occlusion prescribed across the UK. However, studies describing the response to occlusion therapy can be used to inform decision-making in the clinical setting. PEDIG[112] assessed the response of patching treatment in moderate amblyopia (20/40 to 20/100) in children who were allocated into groups receiving occlusion for 6 hours daily, or occlusion up to all waking hours, at the investigator's discretion. A total of 209 children participated in the study, aged from 3 to 7 years. The authors assessed the response to treatment at 5 weeks, 16 weeks and 6 months following the commencement of therapy. Results at 5 weeks demonstrated an improvement in VA from baseline by a mean of 2.2 lines. Patients with a baseline acuity of 20/80 or 20/100 showed a positive association between the number of hours patched and improvement in acuity ($p = 0.05$). This association was not present when the baseline acuity was 20/40 to 20/60 ($p = 0.57$). The results at 6 months showed an improved VA from baseline by a mean of 3.1 lines. Of the group of patients with baseline acuity of 20/80 to 20/100, 20% had a 6-month VA of 20/25 or better compared with 56% in patients with a baseline VA of 20/40 to 20/60. This was found to be statistically significant ($p < 0.001$). At 6 months, the number of lines of improvement in acuity from baseline was greater when the baseline acuity was 20/80 to 20/100 than when 20/40 to 20/60 (mean lines of improvement 3.6 versus 2.8; $p < 0.001$). The authors concluded that at 6 months the amount of improvement appears to be similar, irrespective of whether 6 hours of daily patching are initially prescribed or a greater number of hours. However, a greater number of hours of occlusion initially may improve VA faster, particularly when the baseline acuity is 20/80 to 20/100. Similar improvements in VA were seen for both strabismic and anisometropic amblyopia.

Treatment of moderate amblyopia – pharmacological penalisation

The treatment of amblyopia does not always include conventional occlusion therapy.

Pharmacological penalisation is an alternative that involves the instillation of a long-acting topical cycloplegic agent into the good eye (such as atropine). The cycloplegia prevents accommodation, resulting in a blurred image from the good eye at near fixation. Atropine may be used in conjunction with optical penalisation (adjusting spectacle correction to further enhance the blurred image from the good eye) or in isolation.

PEDIG[113] compared the effect of conventional occlusion and atropine for children with moderate amblyopia (VA in the range 20/40 to 20/100). In this randomised clinical trial, patients were subjected to a patching regime of a minimum of 6 hours daily for 6 months unless the criteria for successful treatment were met (amblyopic eye improved to 20/30 or better, or improved by three or more lines from baseline). If criteria for successful treatment were met, the patching time was reduced to a minimum of 7 hours per week; if the acuity became equal, patching was discontinued. Patients assigned to the atropine regime were prescribed daily atropine, until the vision in the amblyopic eye met criteria for successful treatment. At this point, the frequency of atropine could be reduced (at the clinician's discretion). A total of 419 patients participated in the study (215 in the patching group and 204 in the atropine group) and were examined at 5, 16 and 26 weeks and 6 months following commencement of treatment. The authors reported that although a substantial improvement in visual acuity from baseline to 6 months occurred in both groups, VA in the amblyopic eye showed a greater improvement initially with patching than with atropine. At 5 weeks, VA had improved from baseline by a mean of 2.22 lines in the patching group and 1.37 lines in the atropine group (mean difference in logMAR VA between groups, 0.087; 95% CI 0.060 to 0.113). However, at 6 months the mean difference in logMAR VA between the two treatment groups was 0.034 (95% CI 0.0005 to 0.0064). This is of no clinical significance, and the authors concluded that either treatment modality is appropriate in the treatment of moderate amblyopia. There was no statistically significant interaction between the cause of amblyopia, age and baseline amblyopic eye acuity and outcome acuity in the amblyopic eye ($p = 0.68$, 0.84 and 0.59, respectively).

The effect of different atropine regimens in the treatment of moderate amblyopia (20/40 to 20/80) has also been reported. PEDIG[114] compared the effect of daily atropine with weekend atropine in children younger than 7 years. The cycloplegic effect of atropine is known to last for several days. This study addressed the clinical question of how often atropine needs to be administered. A total 168 children were enrolled in the study, 83 being prescribed daily atropine instillation and 85 weekend atropine. The authors reported similar amounts of improvement in the amblyopic eye from baseline to 4 months in both groups, with a similar course of VA improvement. The improvement in VA in the amblyopic eye averaged 2.3 lines in each group (mean difference in VA between groups, 0.00 logMAR; 95% CI –0.04 to 0.04). There was no evidence for an interaction between treatment group and gender ($p = 0.57$), age ($p = 0.72$), iris colour ($p = 0.11$), baseline amblyopic eye acuity ($p = 0.59$), prior amblyopic treatment ($p = 0.65$) or sound eye refractive error ($p = 0.11$). Patients who started with worse amblyopic eye acuity at baseline improved more on average than patients who started with better acuity (2.0 mean line difference in patients with baseline acuity of 20/40 to 20/50 compared with 2.5 line difference in patients with baseline acuity of 20/63 to 20/80; $p < 0.001$). The authors concluded that weekend atropine provides an improvement in VA of a magnitude similar to that seen with daily atropine instillation.

Treatment of severe amblyopia – conventional occlusion

Treatment of severe amblyopia has been reported. In a randomised trial of patching regimes, PEDIG[115] compared the effect of full-time patching (all hours or all but 1 hour per day) with 6 hours of patching treatment. A total of 175 children were included in the study, with a range of amblyopia from 20/100 to 20/400 (85 children in the 6-hour group and 90 in the full-time group). Substantial improvements in VA occurred from baseline to 4 months in both groups and the course of VA improvement appeared similar in both treatment groups. At 4 months' follow-up there was no statistical evidence for interaction between treatment group and baseline amblyopic acuity ($p = 0.24$), cause of amblyopia ($p = 0.34$) or age ($p = 0.94$). However, the change in amblyopic eye acuity from baseline to 4-months showed greater variability in the 6-hour group than the full-time group ($p = 0.04$). Patients with a worse amblyopic eye at baseline improved more than those who started with better VA at baseline (5.9 lines of improvement in patients with VA of 20/200 to 20/400 versus 4.1 lines of improvement in patients with baseline VA of 20/100 to 20/160), which was statistically significant ($p < 0.001$). Younger patients were also found to show more

improvement than older patients (5.5 lines of improvement in patients aged <5 years versus 3.8 lines of improvement in patients aged 5 years or older), which was also statistically significant ($p < 0.001$). The authors concluded that each treatment method was as effective in improving VA in the amblyopic eye.

The use of atropine in the treatment of severe amblyopia was investigated by Foley-Nolan and colleagues.[116] They compared the efficacy of atropine with conventional occlusion as a primary treatment for amblyopia. Within this small study ($n = 36$), patients were allocated into treatment regimens on an alternate basis, resulting in equal subject numbers in each group. The atropine group were prescribed daily instillation and the patching group were prescribed occlusion, the amount of which was based upon the age of the child and the amount of amblyopia present. Both groups had initial VA ranging from 6/18 to 6/120, with a geometric mean of 6/50 and 6/60 in the atropine and patching groups, respectively. Both groups were shown to have statistically significant improvements in VA in the amblyopic eye following treatment ($p < 0.001$). Acuities in the amblyopic eye in the atropine group after treatment ranged from 6/6 to 6/60, with a geometric mean of 6/11. Acuities in the amblyopic eye in the patching group after treatment ranged from 6/6 to 6/120, with a geometric mean of 6/19.

Dose–response relationship in occlusion therapy

In the absence of guidelines for the treatment of amblyopia, Stewart and colleagues[117] attempted to determine the dose–response relationship in occlusion therapy. Other studies reporting outcome of occlusion treatment discuss findings in terms of hours of patching prescribed. Clinicians have long recognised that the amount of treatment prescribed and the amount of treatment carried out may differ. Objective measurement of the amount of occlusion worn has been made possible with the introduction of the occlusion dose monitor.

Four MOTAS papers[117–120] were identified that described the dose–response relationship in occlusion therapy. This prospective study involved three phases: baseline, refractive adaptation and occlusion. Children who required spectacle correction entered the refractive adaptation phase, which lasted 18 weeks. Those children who did not require spectacle correction, or following refractive adaptation still had amblyopia, were entered into the occlusion phase. Occlusion was prescribed for 6 hours daily and was monitored objectively. During the occlusion phase, visual function was recorded at regular intervals.

Stewart and colleagues[117] obtained data from 57 children with amblyopia (mean age 5.1 ± 1.4 years) with amblyopia associated with strabismus ($n = 22$), anisometropia ($n = 15$) and both anisometropia and strabismus ($n = 20$). Forty-eight subjects required refractive correction and underwent a period of refractive adaptation prior to the commencement of occlusion therapy of patching for 6 hours daily. The authors reported a change in VA, with approximately 85% of the improvement occurring in the first 6 weeks of the occlusion phase. Children aged 5 years and younger were reported to have a statistically significant greater improvement in VA than those aged over 5 years (a change of VA of 0.39 versus 0.12 log units) ($p < 0.01$). The authors reported that the relationship between the gain in VA and the total occlusion dose was described by a monotonic function, which appears to be linear up to 160 hours of the total recorded dose.

Stewart and colleagues[118] further described the dose–response relationship of amblyopia in a larger group of subjects ($n = 94$). The mean age of participants was 5.2 ± 1.4 years. Amblyopia was associated with anisometropia in 23 participants, strabismus in 34 and mixed anisometropia with strabismus in 37. In total, 64 participants (75%) underwent refractive adaptation before entering the occlusion phase. Within the refractive adaptation phase, the mean ± SD (range) VA for amblyopic eyes improved from 0.65 ± 0.41 (1.6 to 0.14) to 0.43 ± 0.37 (1.3 to –0.08) logMAR, a mean ± SD (range) improvement of 0.22 ± 0.18 (0 to –0.6 log units). VA change was not significantly different for each type of amblyopia ($p = 0.29$), nor were there significant differences for age ($p = 0.38$). Seventy-two participants entered the occlusion phase of the study. The mean ± SD (range) VA in the amblyopic eye improved from 0.50 ± 0.36 (1.6 to 0.0) to 0.15 ± 0.25 (1.02 to –0.15) logMAR, a change of 0.35 ± 0.19 (0.0 to 0.12) log units. With the exception of only three participants, all improvement took place in the first 4 weeks. The mean ± SD improvement in VA increased significantly with decreasing age ($p = 0.0014$). Once the authors had accounted for age, analysis revealed that the mean ± SD change in VA was not significantly different for each type of amblyopia ($p = 0.03$). The authors also reported that the total occlusion dose required in order to achieve the observed

gains in logMAR VA was described by a monotonic function. All categories of amblyopia appeared to be linear with an approximate dose–response rate of 0.1 log unit improvement per 120 hours of occlusion. The overall response did not differ significantly for each amblyopia type ($p > 0.1$). Although dose rates of 2 hours daily and over could be seen to have a similar impact on outcome, the greater doses were seen to reduce the length of treatment time to achieve the best VA.

In a randomised study, Stewart and colleagues[119] compared changes in visual function occurring in response to two prescribed occlusion dose rates: substantial (6 hours daily) and maximal (12 hours daily). Forty-two participants entered the study, with amblyopia associated with strabismus ($n = 11$), anisometropia ($n = 19$) and both anisometropia and strabismus ($n = 11$). Of the 42 subjects, 41 undertook a period of refractive adaptation prior to randomisation to receive either 6 hours ($n = 22$) or 12 hours ($n = 20$) of occlusion daily. The authors reported that changes in VA for the 6-hour group were not significantly different from those for the 12-hour group ($p = 0.56$). The mean total dose worn and dose rate to achieve the best VA were also not significantly different ($p = 0.20$ and 0.08, respectively). The authors then analysed the results according to dose rates of occlusion actually worn: 0–3 hours ($n = 13$), >3–6 hours ($n = 17$) and >6–12 hours ($n = 11$). Significant differences were found between the 0–3-hour group and the >6–12-hour group ($p = 0.009$). The authors concluded that children who comply with considerable doses of occlusion demonstrate significantly more improvement than those receiving minimal amounts of patching.

Stewart and colleagues[120] also reported dose responses to occlusion in treatment outcomes for amblyopia. They demonstrated statistically significant differences in observed changes in VA in the three groups of actual worn rates of occlusion (0–3, >3–6 and >6–12 hours daily; ($p = 0.04$). Significant differences were also found in residual amblyopia ($p = 0.004$) and proportional improvement in VA ($p < 0.0001$) between the groups. The results indicate that children complying with more occlusion treatment show significantly more improvement than those wearing lower doses. The authors recommended that in order to achieve acceptable levels of occlusion wear, clinicians should prescribe approximately 6 hours of occlusion daily (on the evidence that the actual dose worn is lower than this).

Randomised controlled trial of treatment of unilateral amblyopia

One paper was identified in the literature search which was an RCT of unilateral visual impairment detected at preschool vision screening. Clarke and colleagues[121] examined the efficacy of three treatment modalities: full treatment with glasses and patching; glasses only; and no treatment. A total of 177 children aged 3–5 years were included in this multi-centre, UK-based study. Follow-up data were available for 164 children at 54 weeks. The results demonstrated that children who received full treatment or glasses treatment alone demonstrated better VA at follow-up than children who had received no treatment. The overall treatment effect was small. The data were then analysed comparing the initial level of VA at the start of treatment. The authors reported that children with moderate levels of amblyopia (6/18 to 6/36 at presentation) demonstrated better improvements in VA, particularly in the group who received full treatment. Full treatment showed a substantial effect in the moderate acuity group, and no significant effect in the mild acuity group ($p = 0.006$). At the end of the trial, all children were subjected to treatment. Follow-up data at 6 months revealed that there were no significant VA differences between the groups. This finding led the authors to conclude that delaying treatment until the age of 5 years did not appear to influence treatment effectiveness.

Factors influencing visual outcome

A number of clinical factors may be attributable to the success of amblyopia treatment, occlusion dose being one. Stewart and colleagues[142] sought to identify other such factors as part of the MOTAS study. As with previous published results, this study consisted of three distinct phases: baseline, refractive adaptation and occlusion. The study included 85 participants with unilateral amblyopia due to strabismus ($n = 32$), anisometropia ($n = 20$) or both anisometropia and strabismus ($n = 33$). The authors reported an overall improvement (including both refractive adaptation and occlusion phases) of VA, which increased significantly with decreasing age [under 4 years ($n = 23$), 0.57 ± 0.32 (95% CI 0.05 to 1.475); 4–6 years ($n = 34$), 0.44 ± 0.34 (95% CI 0 to 1.55); older than 6 years ($n = 28$), 0.24 ± 0.18 (95% CI 0 to 92); $p < 0.0001$)]. Once age had been accounted for, the change in VA was not significantly different for amblyopia associated with each amblyopia type ($p = 0.03$). The severity

of the amblyopic deficit was also cited as a significant factor affecting visual outcome. Participants were sub-categorised according to the severity of their initial amblyopic deficit (mild, moderate and severe). The authors reported that residual amblyopia differed significantly ($p < 0.001$) between the mild and severe group and the moderate and severe group. Other factors reported to affect outcome were binocular vision status and fixation of the amblyopic eye. Non-binocular participants (i.e. subjects with strabismus) had significantly greater residual amblyopia ($p = 0.0001$) than binocular participants. Similarly, participants with eccentric fixation (where the subject fixes an object with a point on the retina other than the fovea) had significantly greater residual amblyopia ($p < 0.0001$) than those with central fixation.

Levartovsky and colleagues[122] assessed the effect of initial VA and type of amblyopia on the long-term results of successfully treated amblyopia. They continued to monitor patients after the best VA in the amblyopic eye was achieved, and when necessary reintroduced occlusion if the vision in the amblyopic eye deteriorated. In total, 94 children were monitored up to the age of at least 9 years. Results were reported in two categories: those with initial VA of 20/60 to 20/100 ($n = 45$) and those with initial VA of 20/200 or worse ($n = 49$), and type of amblyopia, strabismic ($n = 56$), anisometropic ($n = 14$) and both anisometropia and strabismus ($n = 24$). VA score at the long-term follow-up examination was compared with that attained by the participant upon termination of occlusion therapy. The difference between them was classed as the deterioration score. The authors reported that 44 (47%) of participants maintained VA, whereas in 50 (53%) the VA had deteriorated. In both initial VA groups, deterioration of VA was evident at the follow-up examination, and the authors deemed this difference to be statistically significant (although no details are given). They reported that the amount of deterioration seen was significantly higher in children who had started treatment with a VA of 20/100 or worse in the amblyopic eye. Deterioration was also evident when participants were categorised according to type of amblyopia. The percentage of patients showing deterioration in VA was significantly higher in the mixed amblyopia group than in the other two groups ($p < 0.01$). The amount of deterioration seen at the long-term follow-up examination was also significantly higher in the mixed amblyopia group than the strabismic group ($p < 0.01$).

Woodruff and colleagues[123] examined possible factors which could affect the visual outcome when treating children with amblyopia. In a retrospective review of case records, they examined the outcome in terms of different types of amblyopia, final VA and initial VA levels, and hours of patching and final VA. Data were collected on 961 patients at seven centres within the UK who were prescribed occlusion therapy for anisometropia, strabismic or mixed amblyopia. The authors reported a statistically significantly better visual outcome for anisometropic patients ($p < 0.0001$) and described a significant relationship between the difference in spherical equivalent between the two eyes and final VA amongst those with amblyopia ($p < 0.0001$ for pure anisometropia and $p < 0.0001$ for mixed amblyopia) with worse final VA associated with higher degrees of anisometropia. The authors reported no association with age at the start of treatment and final outcome for all types of amblyopia ($p = 0.08$) or considering each group separately (anisometropic $p = 0.48$; strabismic $p = 0.10$; mixed $p = 0.64$). The level of VA at referral and level of final VA were correlated, and proved to be statistically significant for all types of amblyopia ($p < 0.0001$). A statistically significant relationship was also found between the hours of patching prescribed in the first 3 months of treatment and the final VA for all types of amblyopia ($p = 0.0001$).

Long-term follow-up specific to hypermetropic anisometropic patients was reported by Levartovsky and colleagues.[124] They reported results from 86 patients who had been treated by occlusion for unilateral amblyopia, with a follow-up regime similar to that of the above study. Results were reported in terms of the amount of anisometropia present: anisometropia of $\leqslant$1.50D ($n = 74$) and anisometropia $\geqslant$1.75D ($n = 12$). The authors found that deterioration was evident in both groups but the difference between the groups was not significant. However, the amount of deterioration in VA at the long-term examination was significantly higher in the group with the larger amount of anisometropia ($p < 0.05$). The overall improvement was significantly better in the group with the small amount of anisometropia ($p < 0.05$).

Maintenance of improvement for anisometropia was investigated by Fitzgerald and Krumholtz.[125] They retrospectively reviewed records of children who had undergone different treatment modalities ($n = 23$); spectacle correction alone ($n = 6$); spectacle correction and occlusion ($n = 10$); and spectacle correction, occlusion and vision therapy

(n = 7), in terms of treatment to improve binocular status. Maintenance gains of VA were evident in all groups, with statistically more maintenance of VA seen in patients treated with glasses, occlusion and vision therapy ($p < 0.1$). The authors reported that all subjects retained at least their initial pretreatment VA, irrespective of treatment outcomes. In those where VA did deteriorate, such deterioration lost treatment-related acuity gains only. The retention or regression of post-treatment VA was not influenced by post-treatment acuity gains. No statistical difference was found in retention of VA gains based on the initial depth of amblyopia.

PEDIG[126] examined maintenance of VA following treatment for amblyopia in children who had undergone occlusion or atropine therapy for unilateral amblyopia. A total of 145 children who had been successfully treated for anisometropic or strabismic amblyopia were followed without treatment to assess for any recurrence of amblyopia. At the time of enrolment into the study, 112 recruits (77%) had stopped occlusion and 33 (23%) had stopped atropine. The mean VA at enrolment was 0.13 in the amblyopic eye. A recurrence of amblyopia occurred in 30 (21%) patients (95% CI 14 to 28%) by the 52-week follow-up point. A recurrence of amblyopia occurred in 28 (25%) of the patients who had stopped patching treatment (95% CI 17 to 34%) and in seven (21%) of the patients who had stopped atropine treatment (95% CI 9 to 39%). Of the subjects who had undergone patching treatment, fewer hours of patching stopped at enrolment were associated with a lower recurrence risk ($p = 0.008$). The authors also reported a suggestion of a similar relationship between fewer hours of maximal patching treatment and a lower recurrence risk ($p = 0.18$). The results suggested that patients who had stopped daily atropine had a higher recurrence risk than those who had stopped less than daily atropine ($p = 0.16$).

Awan and colleagues[127] investigated compliance with the occlusion dose monitor (ODM) and assessed the dose–effect relationship in amblyopia. In a study of 52 patients with strabismic and mixed amblyopia, children were randomly allocated different treatment for 12 weeks. One group were given no patching (n = 18), one group were prescribed 3 hours of daily occlusion (n = 17) and the final group were prescribed 6 hours of daily occlusion (n = 17). The authors reported a wide spread of patching times in both the 3- and 6-hour groups, and reported no significant difference between the groups for compliance with patching ($p = 0.33$). Neither age ($p = 0.22$) nor gender ($p = 0.30$) had a significant influence on compliance. However, the initial level of amblyopia present was a significant factor, in that children with worse VA at the start of treatment were less likely to comply with occlusion ($p = 0.03$).

Hussein and colleagues[128] reported on factors which might predict the lack of improvement in patients who had undergone treatment for anisometropic amblyopia. They retrospectively examined the records of 104 children (aged 3–8 years) who were treated with either atropine or patching. Data analysed included the age at which treatment was initiated, gender, initial and final VA, initial cycloplegic refraction, the presence of manifest strabismus, treatment modality and treatment compliance (by parental report) at the first follow-up examination. Results were presented as ORs for each characteristic. Failure risk factors were found to be age 6 years at the onset of treatment (adjusted OR = 4.69, 95% CI 1.55 to 14.2), the presence of astigmatism of more than 1.50D in the amblyopic eye (adjusted OR = 5.78, 95% CI 1.27 to 26.5), poor compliance with treatment (adjusted OR = 5.47, 95% CI 1.70 to 17.6) and initial VA in the amblyopic eye of 20/200 (6/60 Snellen equivalent) or worse (adjusted OR = 3.79, 95% CI 1.28 to 11.2). Strabismus was not found to be a significant risk factor, nor the type or amount of anisometropia present.

Scott and colleagues[129] retrospectively reviewed patients (n = 600) with unilateral amblyopia who were treated with full-time occlusion, to determine the effectiveness and side-effects associated with such a treatment regime. A total of 439 subjects had strabismic amblyopia, 56 anisometropic amblyopia and 105 a combination of strabismic and anisometropic amblyopia. The authors reported that the duration of occlusion (time taken to reach end-point) was statistically significantly related to the type of amblyopia, the age at initial treatment, and the initial VA ($p < 0.0001$). They reported that patients with strabismic amblyopia required a shorter duration of occlusion to reach their end-point than anisometropic patients or those with combination amblyopia ($p < 0.0001$). Older patients and those with worse initial VA required a longer duration of occlusion ($p < 0.0001$). Initial VA also correlated with VA outcome ($p < 0.0001$). VA outcome was statistically significantly related to age at the initiation of treatment ($p < 0.0001$). The authors reported the presence of occlusion amblyopia in

some patients (n = 155, 25.8%), a factor which should be considered when prescribing occlusion therapy.

Levartovsky and colleagues[130] also examined factors affecting long-term results of successfully treated amblyopia, specifically the age at which treatment began and the age at which monitoring of VA ceased. The paper reported on 104 patients who were previously treated for amblyopia, and were analysed in three age groups according to the age at which treatment started (2–5.5, 5.5–8 and older than 8 years). Deterioration in VA following cessation of treatment occurred in all groups. The long-term results were better in the youngest group compared with children aged 5.5 years and over; however, this was not statistically significant. The study demonstrated that the age at which treatment for amblyopia was started does not affect the final visual outcome after cessation of treatment, provided that monitoring of the VA was continued until after the age of 9 years.

Cobb and colleagues[131] retrospectively analysed data from 112 children in the UK with anisometropic amblyopia to identify factors that influence the final visual acuity. Analysis revealed no correlation between the age of presentation and final VA in amblyopic eye (p = 0.804). There was a strong trend correlating refractive error and degree of anisometropia with the final VA (p > 0.001 and p = 0.001, respectively). Mean final VA was significantly worse in strabismic than non-strabismic children (p < 0.001). The authors surmised that children with poorer VA and higher degrees of anisometropia at presentation should be treated 'more aggressively' and that children with anisometropic amblyopia should be treated regardless of age.

Treatment compliance

As described in the previous section, compliance with treatment for amblyopia is an important predictor of treatment success. Four papers were identified in the literature review that solely examined compliance with treatment for amblyopia. Smith and colleagues[132] reported factors that affect treatment compliance in children. The definition of compliance was attendance of all their prescribed appointments within the first year of treatment. In this multi-centre study of 961 patients, the authors reported no statistically significant difference in compliance between types of amblyopia (strabismic, anisometropic and mixed) (p = 0.04). Compliance was not significantly related to sex (p = 0.43), VA at the start of treatment (p = 0.14), difference in refractive error between the two eyes (p = 0.6) or ethnic group (p = 0.11). However, as the authors acknowledged, the above factors are not accurate measures of treatment compliance. A child's attendance at a clinical appointment is driven by the parent's desire to attend the appointment, and is therefore not representative of treatment compliance. Treatment compliance to patching therapy can now be monitored with devices such as the ODM, although at present these are used solely for research purposes.

Newsham[133] examined parental understanding of the disease and treatment (including occlusion therapy, critical period and prognosis) to discover the parent's perceptions with respect to treatment compliance. Parental knowledge was assessed in the form of a questionnaire and compliance to treatment was measured by a diary of occlusion time (completed by the parent). Results showed a lack of parental understanding in key areas, particularly the critical period, with parents reporting a wish to delay treatment until the child was older (to gain cooperation and understanding).

In a follow-up study, Newsham[134] examined whether the use of educational material (in the form of a leaflet) would improve parental understanding of amblyopia and occlusion therapy, and subsequently increase concordance to treatment in an RCT. Parental knowledge and adherence to treatment were assessed as before. The author reported that the group which received the leaflet demonstrated better knowledge than the control group (p < 0.001). Non-concordance was significantly higher in the control group (p < 0.005) (0.23, 95% CI 0.13 to 0.35 compared with 0.54, 95% CI 0.41 to 0.67). The author therefore concluded that written information is a 'highly effective' method of increasing concordance.

Dixon-Woods and colleagues,[135] in a qualitative study, examined the reasons why occlusion therapy for amblyopia can be so difficult. Following a series of semi-structured questionnaires, the authors reported problems with occlusion therapy experienced by some families and strategies that they used to support the treatment. Respondents acknowledged that patching is a difficult experience, which resulted in strained relationships with their child. Analysis revealed six main strategies that were adopted by parents to support the patching regime: explanation, normalisation, rewards, customising the patch,

establishing a routine and enlisting the help of others. The authors acknowledged that the study did not examine whether such strategies did improve treatment compliance, although they stated that guidance in the form of literature might be useful for parents, care-givers and teachers.

Treatment of strabismus

Few papers were identified that satisfied the search criteria detailed. The literature search resulted in just three papers relating to the treatment of strabismus. Each paper is specific to a particular type of strabismus.

Spencer and colleagues[136] reported on the use of botulinum toxin in the management of childhood intermittent exotropia. The case-controlled study of 32 patients, aged between 3 and 144 months (mean age 41.2 ± 5.8 months), examined the effect of bilateral injections of botulinum toxin into the lateral rectus muscles for the treatment of intermittent exotropia (minimum distance deviation of 15 prism dioptres). Patients were observed for 12–44 months after initial injection, and satisfactory outcome was considered to be a stable alignment of the eyes to an orthophoric range of ±10 prism dioptres. The authors reported that 12 (37.5%) of patients required two or more bilateral injections to achieve stable orthophoria. Overall, male patients ($n = 4$) required fewer injections (1.3 ± 0.1) than female patients (2.2 ± 0.4) at a statistically significant level ($p < 0.05$). Differences in the number of injections also appeared to be related to the age of the patient at the time of initial injection. Patients aged between 24 and 56 months required only a single bilateral injection to achieve orthophoria. Patients younger than 24 months or older than 56 months required more frequent injections. The authors concluded that this treatment option had good efficacy (68% of patients achieving orthophoria), and stated that this outcome is comparable to previous literature reporting surgical outcome success.

In a paper describing the clinical course of accommodative esotropia, Rutstein and Marsh-Tootle[137] examined 39 patients who had previously undergone treatment for accommodative esotropia earlier in childhood. A shift in refractive error was seen from initial evaluation (+2.77DS) to recall examination (+1.95DS), a mean refractive shift of –0.08DS per year. In terms of ocular alignment, the authors reported that only five of the 39 patients did not produce a manifest strabismus when viewing an accommodative target without glasses prescription. The persistence of accommodative esotropia into adolescence resulted in the authors recommending careful monitoring during this period to ensure that changes in refractive error do not affect binocular status.

Ing and Okino[138] studied the effect of duration of misalignment in congenital esotropia using stereopsis as an outcome measure. Ninety patients were included in the study, and data were collected on age of onset and age at which alignment was achieved (to within 10 prism dioptres). Patients were divided into subgroups based on the age of alignment or duration of alignment. Stereopsis levels were analysed for each subgroup. The authors reported that the percentage of patients with stereopsis (80%) was identical for patients aligned at 0–6 and 7–12 months. Patients achieving alignment by 13–24 months had a lower rate of stereopsis (58%). The difference between the groups was statistically significant ($p < 0.5$). The quality of the stereopsis achieved was similar in patients aligned by 6 or 12 months ($p > 0.05$). However, if duration of misalignment was greater than 12 months a decrease in quality of stereopsis was evident ($p < 0.001$).

Refractive surgery

Three papers were identified in the literature review which addressed the use of refractive surgery in children.[139–141] Two papers are reviews of previous literature describing the role of paediatric refractive surgery[140,141] and one paper reports the use of photorefractive keratectomy (PRK).[139]

Although the practice of paediatric refractive surgery is not known to occur widely within the NHS, the above articles have been included in the review. The results of the studies are summarised below.

Photorefractive keratectomy

Paysse[139] assessed the safety and efficacy of PRK in children with anisometropic amblyopia. Eleven children were treated with PRK in this retrospective study, with a mean age of 6.1 years (range 2–11 years). Both myopic ($n = 8$) and hypermetropic ($n = 3$) children were included in the study. Of the 11 patients treated, nine were able to perform quantitative VA measurements pre- and postoperatively. Improvements in VA

were evident in seven of nine eyes by a minimum of two or more Snellen lines. The author reported that compliance with amblyopia therapy did not improve postoperatively in any patient.

Review articles

Drack and Nucci[140] discussed the advantages of paediatric refractive surgery in reducing anisometropia, and hence a major risk factor for amblyopia. The authors acknowledged the benefits in terms of the possibility of discarding any spectacle correction and possible increased compliance with amblyopia treatment. However, the risks and unpredictability of refractive surgery in children were noted, and the authors suggested that a conservative approach to its use following the age of visual maturation may be more appropriate.

Hutchinson[141] reviewed the literature surrounding paediatric refractive surgery from 1995 to 2003. The author acknowledged that although studies have reported the use of this treatment method, there are no studies which demonstrate that refractive surgery improves amblyopia treatment outcomes. The author summarised the findings of a few studies in which refractive surgery was used to treat accommodative esotropia. These studies were rejected from this systematic review due to the age at which treatment was initiated (adulthood).

Conclusions

The purpose of this review is not to dictate clinical practice in terms of treatment recommendations. Clinical management must be made following careful consideration on a case-per-case basis, taking into account factors such as age, level of VA and personal circumstances, to name but a few. The review does demonstrate the existence of literature which reports on treatment effectiveness in the management of amblyopia and/or strabismus. As is understood within clinical practice, the success of treatment appears to be linked to treatment compliance and adherence.

Successful treatment of amblyopia is reported using a variety of treatment modalities. Conventional occlusion has been demonstrated to improve VA. The amount of occlusion prescribed appears to affect the rate of VA improvement rather than the final VA outcome. That is, a successful VA outcome may be achieved with few hours of occlusion prescribed over a long treatment period compared with increased hours of occlusion prescribed over a short treatment period. Atropine has also been demonstrated to be an appropriate treatment method, with weekend use shown to be as effective as daily atropine in the treatment of moderate amblyopia. Age at start of amblyopia therapy is a factor in treatment outcome; overall improvement in VA appears to increase significantly with decreasing age. Maintenance and regression of acuity following cessation of treatment have been shown to exist in all types of amblyopia, and following all types of treatment modalities.

The lack of evidence supporting the treatment of strabismus is unsurprising. The outcome measures for strabismus treatment could include restoration of binocularity or improvement in cosmetic appearance. As the presence of strabismus is an amblyogenic factor, treatment could also be considered in terms of reducing amblyopia development. The most appropriate outcome measure may differ depending on a clinician or parent/guardian perspective. Parents/guardians may rank cosmetic appearance as a greater priority than binocular status.

RCTs into the efficacy, effectiveness and efficiency of strabismus treatment are unlikely to be feasible. Ethical considerations in study design prevent complete abstention of treatment, and decisions regarding treatment are often overridden by clinical need.

Chapter 6

Quality of life

Many studies have indicated that impaired vision of any kind can affect HRQoL. This may be in terms of ability to perform daily living tasks, mobility or psychological well-being. This chapter reports on the impact of amblyopia and strabismus on QoL. This is discussed in terms of the presence of the condition itself and the impact of treatment for the given condition. Twelve papers[143–154] were identified which were related to QoL, 10[143–152] with respect to amblyopia and two[153,154] with respect to strabismus.

Impact of amblyopia on quality of life

The literature search produced 10 papers which related to the impact of amblyopia on QoL. These are reviewed in terms of measures used to assess the impact of amblyopia on QoL, the effect of treatment of amblyopia on QoL and bullying.

Measures used to assess the impact of amblyopia on quality of life

Very little evidence could be found in the literature to quantify the impact of the condition amblyopia in terms of HRQoL. Two papers were identified in the literature search.[143,144]

Packwood and colleagues[143] tried to assess the psychosocial effects of growing up with and living with amblyopia. They issued a 20-question survey to 45 subjects (aged 15–64 years; mean age 30.2 years), which focused on medical background, education, self-image, history and treatment of amblyopia and the effects of amblyopia on work, school, friendships and self-esteem. Subjects were also asked to complete the Hopkins Symptoms Checklist (HSC). This is a 58-item psychological self-report inventory that evaluates somatisation, obsession–compulsion, interpersonal sensitivity, depression and anxiety. The results were directly compared with a control group of subjects which included people with strabismus, psychoses and control subjects. The authors reported that subjects with amblyopia experience more distress in the areas of somatisation, obsession–compulsion, interpersonal sensitivity, anxiety and depression when compared with the control subjects. These difficulties can affect individuals' self-image, work, school and friendships. The authors argued that as amblyopia does have a "significant effect on psychosocial functioning", screening and treatment of amblyopia is warranted. The study has a number of notable flaws, the first being the study population. Of the 45 subjects who were issued the survey, 15 (60%) expressed concern as a result of being teased or ridiculed. It is not clear as to why this may have been the case, although it could be assumed that any teasing or ridicule is centred on the treatment of amblyopia (glasses and/or patching). A diagnosis of amblyopia without noticeable strabismus (as defined in the inclusion criteria for the study) or treatment that could be seen by others could not lead to ridicule, as there would be no physical evidence of amblyopia. The results of the study could be deemed to document the impact of amblyopia treatment on QoL, rather than the impact of amblyopia on QoL.

Van de Graaf and colleagues[144] designed and validated a questionnaire to assess the decrease in QoL in patients with amblyopia and strabismus. The Amblyopia and Strabismus Questionnaire (A&SQ) was compared with the National Eye Institute Visual Function Questionnaire-25 (VFQ-25), and the Short Form with 12 Items (SF-12) health survey to healthy cohorts (n = 53), patients (n = 67) and a cohort of subjects who had previously undergone treatment for amblyopia and strabismus (n = 172). The A&SQ consists of five domains: fear of loss of the better eye, distance estimation, visual disorientation, diplopia and problems with social contact and cosmetic problems. Results concluded that QoL was best in healthy controls, and worst in the current patient cohort. This was found on the VFQ-25 and SF-12, in addition to the A&SQ measure. The authors stated that this demonstrates that the A&SQ is an acceptable measure compared with the VFQ-25 and SF-12, and confirms its validity.

Effect of treatment of amblyopia on QoL

An alternative approach has been to consider QoL issues relating to the treatment of amblyopia. Van de Graaf and colleagues[144] (as described previously) reported that QoL appeared to be most deleteriously affected in subjects currently

undergoing treatment for amblyopia and strabismus (patients). This was observed using the VFQ-25, SF-12 and A&SQ measures.

In a prospective study, Parkes[145] examined changes in children's behaviour as a result of occlusion therapy for amblyopia. The study examined these changes and found that differences in the way in which children behaved appeared to vary according to the density of amblyopia present. Questionnaires were issued to 79 parents of children undergoing amblyopia treatment. The questionnaire included a list of possible behaviour patterns that children may exhibit during occlusion, the list being based on past clinical experience of comments that parents have made about their problems with occlusion therapy. Fifty-nine questionnaires were available for analysis. The author confirmed that children with mild amblyopia appeared to be more tolerant of treatment than those with moderate or dense amblyopia, and as such compliance with treatment in children with dense or moderate amblyopia was negatively affected.

Treatment compliance and clinical outcome are related to both density of amblyopia and parental beliefs. Parents and carers often report on the difficulties of amblyopia treatment and the stresses associated with treatment. Searle and colleagues[146] also reported on the psychosocial and clinical variables that influence compliance with occlusion therapy, but in terms of parental compliance with treatment. Children (n = 151) receiving occlusion therapy were recruited from five clinics in Bristol (UK). Parents completed a questionnaire based on the main components of Protection Motivation Theory (PMT). This included the severity of visual impairment, vulnerability (future implications of amblyopia), response costs (barriers to treatment of occlusion), response efficacy (perceived effectiveness of eye patching), self-efficacy (parents' belief in ability to patch child) and protection motivation (intention to patch child). Clinical and socio-demographic data were also collected and analysed. The results demonstrated that self-reported treatment compliance was 54%. The authors found that two variables were significant predictors of compliance with occlusion therapy. The first, "self-efficacy" (the belief in the ability to patch a child), was positively associated with compliance. Parental belief that occlusion therapy prohibits the child's activities was negatively associated with treatment compliance.

Choong and colleagues[147] used the Perceived Stress Index (PSI) and the Perceived Psychosocial Questionnaire (PPQ) to measure a carer's perception of stress and psychosocial well-being of the child prior to and following commencement of treatment for amblyopia. This prospective study included carers of two groups: occluded (n = 31) and non-occluded (n = 28). The purpose of the study was to evaluate the carer's perception of their personal stress level, psychosocial impact of occlusion therapy on the child and carer–child relationship, which were evaluated prior to and following treatment for amblyopia. The authors found no significant difference in carer's stress and child's psychosocial well-being between the two groups ($p > 0.5$). Within the occluded group, the carer's stress and child's psychosocial well-being did not differ significantly before and following the start of treatment ($p > 0.5$). However, carers felt more negative towards their child following the onset of glasses therapy ($p < 0.01$) and became more positive when occlusion was introduced in the subsequent follow-up visit ($p < 0.01$). Although this temporary negative feeling towards the child was evident due to the introduction of glasses, the authors concluded that there was no significant evidence to indicate that occlusion therapy has a negative psychosocial impact on carers and children alike.

Bullying and amblyopia

Bullying and peer victimisation in children are often cited by parents and carers as reasons why a child is reluctant to comply with amblyopia treatment, both in terms of glasses wear and/or occlusion therapy. Horwood and colleagues[148] investigated whether glasses wear or history of occlusion therapy predisposed children to being victimised more frequently at school. Children from the ALSPAC cohort were asked if they had received or used any forms of bullying. A total of 7599 children participated in this aspect of the study. Results were reported in terms of both overt victimisation (belongings stolen, name calling, physical abuse, etc.) and relational victimisation (other children not wanting to play with them, withdrawing friendship, telling tales on them, etc.). The study differs from previous studies as responses were directly obtained from the children (as opposed to proxy reporting from parents/carers). A summary of results is shown in *Table 61*. The authors summarised the findings by stating that children who "currently wear glasses or have a history of wearing eye patches were 35% to 37% more likely to be victims of physical or verbal bullying".

Due to the maturing nature of the visual system, it is important for amblyopia treatment to be

TABLE 61 *Prevalence (%) of victimisation groups within categories of vision defects (unadjusted for social class)*[148]

	None (*n* = 3356)	Overt only (*n* = 1279)	Relational only (*n* = 313)	Both (*n* = 559)	Total (*n* = 5507)
Wears glasses:			$p = 0.010$[a]		
Frequently	53.9 (187)	31.7 (110)	5.8 (20)	8.6 (30)	347
Occasionally	57.9 (66)	27.2 (31)	4.4 (5)	10.5 (12)	114
Never	61.5 (3103)	22.6 (1138)	5.7 (288)	10.2 (517)	5046
Strabismus:			$p = 0.145$[a]		
Large >20Δ	51.4 (19)	27.0 (10)	10.8 (4)	10.8 (4)	37
Small <20Δ	61.4 (35)	33.3 (19)	3.5 (2)	1.8 (1)	57
None	61.0 (3302)	23.1 (1250)	5.7 (307)	10.2 (554)	5413
Ever worn patch:			$p = 0.085$[a]		
Yes	52.9 (90)	30.6 (52)	7.1 (12)	9.4 (16)	170
No	61.2 (3266)	23.0 (1227)	5.6 (301)	10.2 (543)	5337
Number of defects:			$p = 0.003$[a]		
2 or more	53.7 (79)	29.9 (44)	7.5 (11)	8.8 (13)	147
1	55.6 (213)	30.8 (118)	4.4 (17)	9.1 (35)	383
None	61.6 (3064)	22.4 (1117)	5.7 (285)	10.3 (511)	4977

[a] Probabilities derived by the Pearson χ^2 statistic.

completed by approximately 8 years of age. If detection of the condition is to occur at approximately 4–5 years of age, then the window of opportunity for treatment is approximately 3–4 years. Clinicians, parents and carers acknowledge that this is an important period within a child's physical, emotional and psychological well-being. The timing of amblyopia treatment and its impact on a child's well-being was examined by Williams and colleagues,[149] using ALSPAC data. In this prospective study, the authors examined data for two groups of children: those who had been offered state-provided preschool screening and those who had not. They calculated the risk of reporting a history of having been bullied for children who had been treated by occlusion therapy in each group. For comparison, they also calculated the same risk for children who had been prescribed glasses at any time. The authors hypothesised that glasses wear usually continues once started and, as such, preschool screening would be unlikely to reduce any risk of bullying associated with wearing of glasses. Data were available for 4473 children. Results are summarised in *Table 62*. Findings of the study confirmed that preschool screening for amblyopia may be associated with less bullying for children that require occlusion treatment. There was an almost 50% reduction in children who reported having been bullied in the group that had been offered preschool screening compared to those who had not.

Rahi and colleagues[150] examined the impact of amblyopia on educational, health and social outcomes, including bullying. They compared people with normal vision with people with amblyopia from a 1958 British birth cohort study, with respect to subsequent health and social functioning; 8861 subjects were included in the study. The authors reported that children with amblyopia did as well as their peers in educational attainment and employment, and were no more likely to have significant behavioural problems. The authors stated that, when measured by the Rutter scale at age 7 or 11 years (a measure of dimensions of behaviour in children), children with amblyopia were no more likely to be bullied (when adjusted for sex, social class and ever having had a strabismus) (*Table 63*). Additionally, they found no evidence to suggest an association between amblyopia and participation in social activities in either childhood or adult life. No functionally or clinically significant differences existed between people with and without amblyopia in general or mental health and mortality or paid employment.

Consequences of amblyopia

Previous literature regarding the consequences of amblyopia refers to the risk of blindness to the healthy eye as a result of injury or disease. Other papers reflect on the impact of amblyopia on

TABLE 62 *Prevalence and odds ratios (95% CI) for reporting being bullied, according to whether or not the child was offered preschool screening*[149]

Group	No. (%) bullied in preschool screening group	No. (%) bullied in no screening group	*p* (χ^2)	OR (95% CI)	Adjusted OR[a] (95% CI) *p*-value
All children (n = 4473)	375 (33.8)	1200 (35.7)	0.26	0.92 (0.80 to 1.06)	0.92[b] (0.80 to 1.06) p = 0.257
Children who were patched (n = 122)	9 (25.7)	41 (47.1)	0.03	0.39 (0.16 to 0.92)	0.39[b] (0.16 to 0.92) p = 0.033
Children with glasses (n = 364)	29 (35.4)	118 (41.8)	0.293	0.76 (0.44 to 1.24)	0.74 (0.46 to 1.27) p = 0.252

[a] Adjusted for sex, paternal socio-economic class, highest level of maternal education, type of housing.
[b] In these analyses, none of the factors was significantly associated with the outcome ($p < 0.1$).

TABLE 63 *Associations between mild or moderate/severe amblyopia and bullying*[150]

Age (years)	Level of amblyopia	OR (95% CI)	*p*-Value
7	Mild	1.09 (0.59 to 2.00)	0.781
7	Moderate/severe	1.51 (0.63 to 3.61)	0.354
11	Mild	0.75 (0.36 to 1.60)	0.462
11	Moderate/severe	0.62 (0.32 to 1.89)	0.404

QoL, either in terms of having the condition itself or as a result of treatment therapies. Chua and Mitchell[151] examined the consequences of amblyopia on education, occupation and long-term vision loss. Amblyopia (defined as best corrected VA of ⩽6/9 and not attributable to any underlying structural abnormality of the eye or visual pathway) was detected in 118 of the 3654 participants of the Blue Mountains Eyes Study (a population-based survey of people aged 49 years or over, in two postcode areas of the Blue Mountains, Australia). The authors reported that amblyopia was not significantly associated with lifetime occupational class ($p = 0.5$); however, it was observed that fewer people with amblyopia completed higher university degrees ($p = 0.05$).

Hrisos and colleagues[152] assessed the impact of unilateral visual impairment and neuro-developmental performance in preschool children. The authors examined children in terms of a visual sensory assessment (VA and stereoacuity measurement), and neuro-developmental assessment (to assess visual-motor integration, fine and gross visuo-motor skills and visuo-spatial processing). Thirty children with unilateral visual impairment (amblyopia) were recruited to the study with a median VA of the impaired eye of 6/12 (range 6/6 to 6/60). Twenty children with normal vision in both eyes were recruited into the study, two of whom were found to have slightly reduced vision in one eye. The results demonstrated that unilateral visual impairment was moderately correlated with reduced stereoacuity (Pearson's coefficient $r = 0.525$, $p < 0.001$). However, there was no correlation with the score of the neuro-developmental assessment. Reduced stereoacuity did, however, show moderate correlations of statistical significance ($r = 0.417$, $p = 0.002$). It can therefore be concluded that impaired VA does not significantly predict performance on neuro-development tasks, but that stereoacuity does. This paper is the first of its kind to investigate the impact of unilateral visual impairment on neuro-development function. The authors acknowledged that the numbers of participants, particularly in terms of the range of unilateral visual impairment present, are low and that the impact of deficiency in stereoacuity may be greater than that reported.

Impact of strabismus on quality of life

The psychosocial implications of strabismus are more accepted and recognised. Two papers were identified in the literature search which report on the impact of socially noticeable strabismus on QoL in children. Satterfield and colleagues[153] designed a questionnaire which was used in a prospective study to assess the implications of growing up with and living with socially noticeable strabismus. The questionnaire was used in conjunction with the HSC, a self-report inventory which evaluates five variables (somatisation, obsession–compulsion, interpersonal sensitivity, depression and anxiety). Forty-three subjects who had a history of childhood strabismus that was uncorrected or incompletely corrected completed the study. The authors reported no differences in the responses of subjects with esotropia or exotropia. Subjects reported that the presence of strabismus affected friendships, relationships and interpersonal interactions, in addition to having a negative effect on self-image. Responses given to the HSC indicated that subjects had generalised higher levels of distress than the normal populations ($p < 0.01$).

Improvement in QoL after strabismus surgery is well documented in adults; however, its effect on children is not as extensively researched. Archer and colleagues[154] studied the impact of strabismus surgery on QoL in children from an emotional and social perspective. A modified version of the RAND Health Insurance Study questionnaire was used, with the addition of five questions that specifically addressed eye alignment concerns, parent–child interactions and clumsiness. Questionnaires were completed by parents or guardians of children with strabismus and were conducted before and 2 months after corrective surgery. Ninety-eight children with a mean age of 4.5 ± 3.3 years were studied. The authors compared the results of the questionnaires before and after surgery, and cited statistically significant improvements in a number of QoL dimensions following strabismus surgery, including functional limitations, anxiety, social relations, general health perceptions and developmental satisfaction (*Table 64*). The study implied that strabismus surgery can contribute to an improvement in QoL.

Conclusions

Published literature which investigated the impact of amblyopia therapy on family life does exist. However, none of these studies have adequately addressed the effect of treatment on HRQoL from the child's perspective. Parental reports may provide a substitute for children's HRQoL, but large differences have been shown to exist in proxy agreement at the child–parent level.[155]

The literature suggests that surgical intervention for strabismus leads to improvements in QoL. As with amblyopia, no studies could be found that have appropriately addressed the effect of treatment of strabismus on HRQoL from the child's perspective.

The presence of amblyopia and/or strabismus in terms of QoL can be considered in their impact on the immediate (i.e. during childhood) or long term (i.e. during adulthood) future. The data on either condition pertaining to their impact during childhood are weak. Future studies are required to quantify the effects during this period. The impact

TABLE 64 *Effect of surgery on quality of life dimensions*[154]

Subscale	Difference between pre- and postoperative dimension scores	*p*-Value
Functional limitations	0.22	0.01
Anxiety	0.14	0.01
Depression	0.19	<0.01
Positive well-being	0.01	0.85
Social relations	0.20	<0.01
General health perceptions:	0.23	<0.01
Current health	0.18	0.01
Resistance/susceptibility	0.35	<0.01
Prior health	0.15	0.11
Satisfaction with development	0.22	<0.01
Eye alignment concerns	0.70	<0.01
Parent–child closeness	0.04	0.06

of amblyopia and/or strabismus during adulthood can be considered in terms of risk of losing the healthy eye to disease or injury, any long-term psychosocial implications (e.g. confidence, self-esteem) and other implications such as limitations in career choice due to VA. Although clinical recall may identify patients where the loss of a healthy eye resulted in great visual handicap, case studies which describe such events need to be put into context. Consideration must be made taking into account subjects who have amblyopia and/or strabismus (treated or otherwise), and neither condition has had a detrimental impact on their HRQoL. However, there remains a need for paediatric disease-specific HRQoL measures to assess the impact of amblyopia and/or strabismus and their respective treatment. This could evaluate the immediate impact of the condition itself, and monitor the effect of treatment on HRQoL. Longitudinal studies are required to ascertain whether any detriment to HRQoL remains into adulthood.

Chapter 7

Screening, diagnosis and treatment pathways

Introduction

This chapter defines the pathways and resources required to implement a screening programme for amblyopia, in addition to defining pathways and resource use involved in the diagnosis and treatment of amblyogenic factors and amblyopia. Unit costs are combined with the defined pathways to estimate cost parameters that are used to populate the cost-effectiveness model that is described in the following chapter. The chapter is organised into three main sections that describe the pathways and costs for screening, diagnosis and treatment.

Each section includes estimates of the unit costs for staff time for various types of staff, including administration and clerical staff, orthoptists, optometrists and consultant ophthalmologists. *Table 65* presents the estimated unit costs per hour spent with patients (excluding administration staff). The unit costs for consultant ophthalmologists were uprated to 2006 values from the Unit Costs for Health and Social Care 2005[156] using the Department of Health's Pay and Prices Index. These costs include all relevant additional staff costs, including on-costs, qualifications, overheads, capital overheads and travel. Similar staff unit costs for the other relevant staff were not published by Curtis and Netten.[156]

Mean salary levels for senior I/II orthoptists at pay point 2/3 and to optometrists grade B at pay point 16 were identified. To incorporate relevant additional costs, the relative contribution of non-salary costs to salary costs for hospital physiotherapists[156] was applied to the respective salary costs for orthoptists and optometrists to estimate full cost impacts of these staff. To estimate the unit cost per hour spent with patients, it was assumed that orthoptists and optometrists spend 60% of their time in clinics and 40% on non-clinical activity (based on ratio for occupational and speech and language therapists, which was informed by consultation with NHS Trusts[156]). Only salary on-costs and overheads were added to the salary level for administration and clerical staff (based on a salary level informed by grade 4/5, pay point 23).

TABLE 65 *Staff unit costs*

Staff type	Cost per hour spent with patients[a] (£)
Consultant ophthalmologist	110.56
Orthoptist	46.47
Optometrist	55.94
Administration and clerical	19.75

[a] Apart from administration staff.

Screening pathways and costs

Cost estimates for screening are presented as the cost per screen, and comprise the following components: administration costs, orthoptist time to conduct the tests, equipment costs and room rental costs (*Table 66*).

Administration costs include the costs of inviting parents to attend for screening with their children

TABLE 66 *Screening programme costs*

	Cost per test (range) (£)	
Cost parameter	**With autorefraction**	**Without autorefraction**
Screening invitation	2 (1–3)	2 (1–3)
Orthoptist time	10 (5–15)	6.67 (3.33–10)
Autorefractor cost	0.11 (0.07–0.19)	0
Room rental	50 (0–100)	50 (0–100)
Data entry	0.2	0.2
Total (95% CI)	12.90 (8.38 to 18.38)	9.26 (6.14 to 12.79)

and recording the screen results. No empirical estimates of these costs were identified, although previous studies have estimated invitation costs to be between £1 and £3 per individual invited to screening.[157,158] It was estimated that a data entry clerk could enter the results of 100 screening tests in 1 hour, and so the cost per test is £0.20.

If autorefraction is included as part of the screening test (in addition to VA tests and a cover test), a mean of 10 minutes per test was estimated for the time required to screen children, with a range of 5–15 minutes. If autorefraction is not included, the test time is assumed to be reduced by one-third. The time costs per test were estimated to be £7.75 and £5.17 with and without autorefraction, respectively.

Equipment costs include only the cost of the portable autorefractor machine. Prices obtained from a UK distributor included one for the Retinomax 2 autorefractor. As this is similar to the autorefractor used to inform sensitivity and specificity rates, the quoted cost of £6350 was defined. Applying a useful duration of use of 10 years, a 3.5% annual discount factor and 100% depreciation over that time period (i.e. a zero resale value), the annuitised cost was estimated to be £763. This figure was divided by the number of tests undertaken in 1 year, based on 10 sessions per week for 48 weeks.

Room rental was assumed to be £50 per 3-hour session, which was divided by the number of children per session (mean 10 children) to estimate a cost per screening of £2.78. Sensitivity analyses were undertaken in which the room rental cost was set at zero.

In the reference case, compliance was set at 100%, although in the sensitivity analyses lower rates of compliance were tested.

Diagnosis pathways and costs

Once referral has been made to the hospital eye services, patients are assumed to receive an appointment for diagnostic tests. Within the UK, variation exists between the lengths of time from initial referral to diagnostic visit and, in addition, the tests performed at the diagnostic visit, and the personnel who administer such tests. For the purpose of the model, the assumptions were made that at the diagnostic visit, each patient will undergo:

- orthoptic testing
- cycloplegic refraction
- fundus and media examination.

Orthoptic testing is required to diagnose the presence of amblyopia and/or strabismus. A number of diagnostic tests may be performed to investigate the binocular function of the patient. The number and type of tests carried out on this occasion are determined by a variety of factors, including suspected diagnosis, age of patient and cooperation, at the discretion of the orthoptist. Cycloplegic refraction is necessary to diagnose the presence/absence of refractive error. This test may be performed by an optometrist or ophthalmologist. A fundus and media examination is also required to exclude any underlying pathology. This test may also be performed by an optometrist or ophthalmologist. For the basis of the model, the scenarios described in *Table 67* were applied.

The length of time allotted for tests also varies across the UK. The times presented in *Table 68* were assumed.

The staff scenarios were combined with the estimated time required to undertake each diagnostic test to produce cost estimates for

TABLE 67 *Possible screening scenarios*

Scenario	Test	Orthoptist	Optometrist	Ophthalmologist
1	Orthoptic testing	Y	N	N
	Cycloplegic refraction	N	Y	N
	Fundus and media examination	N	N	Y
2	Orthoptic testing	Y	N	N
	Cycloplegic refraction	N	Y	N
	Fundus and media examination	N	Y	N
3	Orthoptic testing	Y	N	N
	Cycloplegic refraction	N	N	Y
	Fundus and media examination	N	N	Y

TABLE 68 *Times allotted for screening tests*

Test	Appointment time (range) (minutes)
Orthoptic testing	30 (15–40)
Cycloplegic refraction	15 (10–20)
Fundus and media examination	15 (10–20)

TABLE 69 *Estimates of staff costs per screening scenario*

Diagnostic scenario	Cost (range) (£)
1	65 (52–75)
2	51 (41–59)
3	79 (64–90)

diagnosis. The resulting estimates are presented in *Table 69*. As the midpoint estimate, diagnostic scenario 1 was used in the reference case analysis.

Treatment pathways and costs

Treatment pathways have been established for alternative diagnostic outcomes, including presence of refractive error alone, strabismus alone and amblyopia due to refractive error or strabismus. There will be patients in whom two or more pathways apply, and in such instances the amblyopia pathway is assumed. It is also assumed that each patient will be discharged to the care of an optician and that no subsequent treatment costs for amblyopia are incurred.

The treatment pathways represent the resource use associated with a 'standard' clinical case, which provides an estimate of the mean expected treatment costs. The pathways were estimated in consultation with orthoptists and ophthalmologists involved in the provision of screening and treatment of children with amblyopia or related risk factors. Uncertainty around the defined pathways was handled by estimating ranges around key input parameters, which informed probability distributions around the mean cost estimates. *Tables 70* and *72* describe the assumed treatment pathways, and *Table 75* summarises the cost estimates, and ranges for each treatment pathway.

Length of treatment pathway

In the treatment pathways, patients are discharged once treatment is complete or when treatment has

TABLE 70 *Refractive error pathway undertaken 6 weeks after diagnostic visit*

Frequency of orthoptic appointments	Frequency of cycloplegic refraction	Suitable for discharge
6 weeks then 6 months	Not applicable	Two consecutive visits with normal VA

TABLE 71 *Manifest strabismus pathway undertaken 6 weeks after diagnostic visit*[a]

Treatment option	Frequency of orthoptic appointments	Frequency of cycloplegic refraction	Frequency of ophthalmologist appointments	Suitable for discharge
Surgery	3 months	–[b]	6 months with additional appointments required immediately pre- and post-surgery	12 months following surgery with two stable consecutive orthoptist appointments
Observation only	6 months	–[b]	Not applicable	Two stable consecutive orthoptist appointments
Other treatment (e.g. exercises)	6 weeks	–[b]	Not applicable	6 months after completion of treatment with two stable consecutive orthoptist appointments

[a] It is assumed that of all patients diagnosed with strabismus, 40% will require surgery, 58% will require observation only and 2% will undergo other treatment. The cost of strabismus surgery was informed by the NHS Reference costs, Health-related Group B06 (Other Ophthalmic Procedures – Category 3), the mean cost of which was £995 after uprating to 2006 prices.
[b] Appointment based on clinical need, i.e. suspicion of development of refractive error.

TABLE 72 *Amblyopia pathway undertaken 6 weeks after diagnostic visit*

Treatment option	Frequency of orthoptic appointments	Frequency of cycloplegic refraction	Frequency of ophthalmologist appointments	Suitable for discharge
Refractive amblyopia:				
Moderate	6 weeks	–[a]	Only if not responding to treatment (i.e. three orthoptic visits with static, abnormal VA)	Two consecutive visits with normal VA or residual amblyopia (non-responder to treatment as confirmed by orthoptist and ophthalmologist)
Severe	4 weeks until VA improves to moderate level, then follow moderate pathway	–[a]	Only if not responding to treatment (i.e. three orthoptic visits with static, abnormal VA)	Two consecutive visits with normal VA or residual amblyopia (non-responder to treatment as confirmed by orthoptist and ophthalmologist)
Strabismic amblyopia:				
Moderate	6 weeks	–[a]	6 months with additional appointments required immediately pre- and post-surgery for strabismus or if not responding to amblyopia treatment (i.e. three orthoptic visits with static, abnormal VA)	Two consecutive visits with normal VA or residual amblyopia (non-responder to treatment as confirmed by orthoptist and ophthalmologist)
Severe	4 weeks until VA improves to moderate level, then follow moderate pathway	–[a]	6 months with additional appointments required immediately pre- and post-surgery for strabismus or if not responding to amblyopia treatment (i.e. three orthoptic visits with static, abnormal VA)	Two consecutive visits with normal VA or residual amblyopia (non-responder to treatment as confirmed by orthoptist and ophthalmologist)

[a] Appointment based on clinical need, i.e. suspicion of development of refractive error or change in refractive error status.

failed. Due to the maturing nature of the visual system, it is assumed that treatment must be complete prior to 7 years. Some clinicians may argue that during this development period, patients should remain under review to ensure no regression of treatment or development of new condition. The model does not take this approach, for the following reason: a child would not be referred following screening if refractive error, strabismus or an amblyogenic factor were not present. Therefore, if these factors are not evident while the child is under review under the hospital eye service, it can be argued that the child should be discharged. Each child is discharged to the care of their own optician, and it must be assumed that if amblyopia or strabismus were to develop or regress then the child would be re-referred to the hospital eye service. Additional post-discharge costs are estimated and include the costs of vouchers towards the provision of glasses and annual sight test fees. *Table 73* presents the proportions of children with differential diagnoses that are assumed to receive alternative forms of glasses and the associated costs of these glasses to the NHS. The present value of the costs of glasses over a 10-year time horizon from the point of diagnosis, discounted at 3.5% annually, is also presented. A 10-year time horizon is specified as voucher payments are assumed to reduce significantly from the late teens onwards. It is assumed that due to breakages, the mean annual number of pairs of glasses prescribed is 1.25.

This approach requires a period of treatment to be set for each condition. It is assumed that if a child is referred with refractive error alone then their length of treatment will be a total of 38 weeks (diagnostic visit, orthoptic appointment 6 weeks following diagnostic visit, repeat orthoptic appointment after 6 weeks, repeat orthoptic visit after 6 months, discharge) (*Table 74*).

If strabismus requiring treatment, and/or amblyopia, is present then it is assumed that the

TABLE 73 *Proportion of children requiring different types of glasses by diagnosis and 10-year costs*

Glasses type	Cost per pair of glasses (£)	Diagnosis[a]		
		Strabismic amblyopia	Non-strabismic amblyopia	Refractive error alone
Single vision				
Sphere: plano – 6.00; Cyl: 0.25–2.00	34.6	0.73 (£420.81)	0.83 (£479.25)	0.74 (£426.00)
Sphere: 6.25–9.75; Cyl: 2.25–6.00	52.6	0.22 (£168.76)	0.17 (£128.13)	0.19 (£142.37)
Sphere: 10.00–14.00; Cyl: 2.25–6.00	76.9	0.02 (£25.13)	0.00 (£0.00)	0.04 (£38.16)
Sphere: over 14.00; Cyl: over 6.00	173.7	0.00 (£0.00)	0.00 (£0.00)	0.00 (£0.00)
Bifocals				
Sphere: plano – 6.00; Cyl: 0.25–2.00	59.8	0.02 (£20.64)	0.00 (£0.00)	0.04 (£31.34)
Sphere: 6.25–9.75; Cyl: 2.25–6.00	76.0	0.00 (£0.00)	0.00 (£0.00)	0.00 (£0.00)
Sphere: 10.00–14.00; Cyl: 2.25–6.00	98.5	0.00 (£0.00)	0.00 (£0.00)	0.00 (£0.00)
Sphere: over 14.00; Cyl: over 6.00	190.9	0.00 (£0.00)	0.00 (£0.00)	0.00 (£0.00)
Mean cost (£)		635.33	607.38	637.87

[a] 10-year costs in parentheses; sight test fees (1 April 2006–7): £18.85

TABLE 74 *Treatment pathways: treatment duration summaries*

Condition	Length of treatment pathway
Refractive error alone	38 weeks
Strabismus	
Requiring treatment	18 months (78 weeks)
Not requiring treatment	38 weeks
Amblyopia	18 months (78 weeks)

total length of treatment time will not exceed 18 months (78 weeks) (*Table 74*). During this time, within the amblyopia pathway, patients will have undergone amblyopia treatment, a period of maintenance therapy and cessation of treatment prior to discharge. Patients with strabismus alone will have undergone orthoptic review prior to surgery (if required) and/or other treatment, with a period of review following cessation of treatment prior to discharge. Patients with strabismus not requiring surgery or other treatment will be discharged at 38 weeks following diagnosis (diagnostic visit, orthoptic appointment 6 weeks following diagnostic visit, repeat orthoptic

TABLE 75 *Treatment pathways: cost summaries*

Treatment pathway	Cost (£)		
	Mean	Lower 95% CI	Upper 95% CI
Failed moderate non-strabismus amblyopia	874	817	930
Failed severe non-strabismus amblyopia	909	852	965
Success moderate non-strabismus amblyopia	853	796	911
Success severe non-strabismus amblyopia	911	849	974
Failed moderate strabismus amblyopia	1253	1093	1416
Failed severe strabismus amblyopia	1280	1120	1443
Success moderate strabismus amblyopia	1319	1147	1485
Success severe strabismus amblyopia	1362	1190	1528
Success refractive error	736	716	755
Success treated strabismus	567	397	736
Failed refractive error, no subsequent amblyopia	763	740	787
Failed strabismus, no subsequent amblyopia	595	423	765
Failed refractive error, subsequent failed amblyopia	999	942	1057
Failed strabismus, subsequent failed amblyopia	1378	1217	1542
Failed refractive error, subsequent success amblyopia	979	920	1038
Failed strabismus, subsequent success amblyopia	1460	1287	1627

appointment after 6 weeks, repeat orthoptic visit after 6 months, discharge).

The above pathways were combined with the staff unit costs and the estimated cost of strabismus surgery to define aggregate treatment costs for the different diagnostic categories. Uncertainty in the cost estimates was represented by undertaking a probabilistic assessment of the cost pathways that incorporated uncertainty around the duration of the consultations described in the treatment pathways, unit costs of procedures (as informed by the NHS reference costs), and the proportions of children with strabismus receiving the different defined interventions. The resulting mean estimates and ranges are presented in *Table 75*, which were represented as log-normal distributions in the main probabilistic analysis.

Chapter 8

Model development and population

Introduction

This chapter describes the development process for two related models, the amblyopia screening model and the post-screening lifetime model. The combined analysis of these models informs the estimation of the incremental cost per QALY gained of various screening options for amblyopia. The perspective of the evaluation covers costs incurred by the NHS and other government departments. The time horizon follows individuals to death or a maximum age of 100 years. All cost estimates are presented as 2006 values, and both costs and QALYs are discounted at 3.5% per annum.

In addition to the treatment costs covered in the previous chapter, this chapter presents the estimation of the remaining model parameters, including the process of model calibration. The first section describes the findings from a review of the economic evaluation literature, including a description of how previous analyses informed the development of the current model framework. The following sections present the two main stages of the iterative process of the development of the screening model. Each stage includes a section describing the model structure and the relationships between the variables included in the structure and a section describing the planned population of the screening model. The final sections describe the development and population of the lifetime model that extrapolates the end-points of the screening model to estimate lifetime costs and QALYs.

Review of previous economic analyses of screening for amblyopia

Published economic analyses of screening programmes for amblyopia are dominated by German researchers. Of 11 identified economic papers, seven were published by the same German research team, seemingly led by Konig and Barry.[159–165] Two other separate German studies were identified,[166,167] and also two US-based studies.[168;169]

The earliest English language paper published by Konig and Barry's group[159] used a decision tree to estimate the cost per case detected from screening children at age 3 years (with re-screening 1 year later for non-compliant children). The analysis was based on a seemingly subjective estimate of the point prevalence of the target conditions, a high estimate of screening test sensitivity (95%) and assumed rates of compliance. A subsequent empirical economic analysis was published that populated the same decision tree model with data from 1180 screens undertaken in 121 German kindergardens.[162] The reference case analysis was based solely on the observed pathways of the children. A range of sensitivity analyses were reported that appear to be similar to the analyses presented in the first paper,[159] with only a tenuous link to the empirical study. The next paper made better use of the empirical data to estimate the majority of the parameters included in the same screening model, including prevalence and separate sensitivity rates for different screening tests.[163]

Probability distributions were specified for all input parameters and a PSA was undertaken. Konig and Barry[165] also presented an extensive set of one-way sensitivity analyses that identified the prevalence estimates, probability of treatment success at older ages and the probability of clinical presentation as important input parameters. However, by far the most important parameter was shown to be the assumed utility effects of unilateral visual impairment; the reference case incremental cost-effectiveness ratio (ICER) of €7397 per QALY gained (based on a utility decrement of 0.04) increased to €1.9 million when no utility decrement was assumed.

Gandjour and colleagues[166] evaluated screening for amblyopia at two separate ages: up to 12 months and between 3 and 4 years. The evaluation was conducted over a 1-year time horizon and the outcome measure was true positive cases detected. Thus, the model was subject to the same limitations as the earlier Konig and Barry studies.[159,162,163]

Another German evaluation estimated the cost per QALY gained from amblyopia screening based on

a very simple formula, where QALYs gained were estimated as the product of the test sensitivity, treatment effectiveness and a utility decrement (of 0.08) over the remainder of affected children's lives (60 years).[167]

Joish[168] evaluated screening children at 6–18 months, 3–4 years or 7–8 years. A decision tree described progression through this programme to describe true and false negatives, and true and false positives. The model was populated using observed referral rates for children at the different age ranges, to which test sensitivity and specificity rates were applied to estimate the PPVs and NPVs. The methodology is difficult to follow, but it appears that Joish[168] assumed that 99.9% of true-positive cases are treatable (and presumably cured), although this study does not incorporate non-screening clinical presentation (i.e. no screen negatives are treated). Prevalence rates for amblyogenic conditions at the three ages are described (25, 8–18 and 5%, respectively). It is unclear how the different prevalence rates were incorporated within the analysis to define similar underlying rates of amblyopia across the analyses of the different age groups.

Joish[168] described benefits in monetary terms, based on the whole person impairment (WPI) index, where 0% represents no impairment and 95–100% represents a state approaching death. VA of 20/200 or less is referenced as having a WPI of 19%, whereas binocular visual loss has a WPI of 85%. The cost of monocular visual loss is estimated as

> cost of monocular visual loss = cost of legal blindness × (0.19/0.85) = $3487 per year

The presented PSA is almost meaningless as the ranges tested are so wide, for example, referral rates of between 1 and 100%.

Discussion of economic studies

The main limitation of the early Konig and Barry papers,[159,162,163] and the other German studies,[166,167] is that they do not facilitate the evaluation of screening programmes based at alternative ages. Moreover, they do not describe the effects of identifying the target conditions for the screening programmes. Issues around the detection of a case of amblyopia include whether it can be effectively treated or whether it would have been detected in the absence of screening. Similarly, can an amblyogenic factor be effectively treated, would it have progressed to amblyopia in the absence of treatment and/or would it have been detected in the absence of screening?

The more recent Konig and Barry papers contained considerable developments in the methodology employed.[161] The decision tree model was extended to incorporate the probability of treatment effectiveness, in addition to attaching a lifetime horizon Markov model to describe the probability and timing of loss of vision in the non-amblyopic eye. Utility decrements were attached to individuals with either unilateral visual impairment (0.04) or bilateral visual impairment (0.22). An important assumption is that all children in the target group at age 3 years would be affected by a lasting unilateral visual impairment if untreated. The target group were defined as children in the empirical study who were newly administered patching therapy, or for whom spectacle therapy did not improve VA (either corrected VA was ≤20/50 in either eye, or difference in VA between eyes was ≥3 lines). Children in the target group that were not detected by screening at age 3 years were assumed to have an increasing annual probability of clinical detection up to age 10 years, with decreasing probabilities of treatment success.

There remain some limitations to the final Konig and Barry analysis.[165] First, the model only facilitated the analysis of screening at age 3 years; extending the model to incorporate alternative screening ages requires prevalence estimates at all relevant ages. Other limitations include the assumption of a single set of screening test parameters for all of the target conditions, which may be unrealistic as screening may be more likely to detect established cases of amblyopia, rather than cases with amblyogenic factors. The use of a single specificity rate is also problematic given the definition of a single target group, as the children outside the target group include non-affected children and also children with refractive errors who were successfully treated in the empirical study. Without defining the distribution of both the target and non-target groups, it is difficult to assign specific treatment costs to the true-positive and false-positive groups. Finally, the outputs are not calibrated or validated; a primary area of concern is the rate of clinical presentation, which is based on estimated age-specific ophthalmic visits, which are assumed to be independent of the presence of amblyopia (which will likely underestimate clinical presentation rates).

The study by Joish[168] did not explicitly describe the progression of amblyogenic factors, so it is not

clear how children with amblyogenic factors but without amblyopia at screen detection are accounted for, that is, is it assumed that all successfully treated amblyogenic factors would have progressed to amblyopia? Indeed, none of the previous economic studies addressed the key issue of the progression of amblyogenic risk factors satisfactorily, that is, describing the incidence of amblyopia in children with refractive errors and/or strabismus. This aspect is essential in order to estimate the impact of detecting such children via screening.

The amblyopia screening model

The amblyopia screening model describes the incidence and progression of amblyogenic factors and amblyopia in children to the age of 7 years. It was developed via an iterative process, involving discussions with clinical experts, reviewing the literature and analysing available data. The following sections summarise the two main stages in the process of defining the final model structure.

The complex screening model

The initially developed model structure described the progression of five 'eye variables': eye 1 astigmatism, eye 1 hypermetropia/myopia, eye 2 astigmatism, eye 2 hypermetropia/myopia and strabismus. The eye variables incorporated no, moderate and severe myopia, hypermetropia and astigmatism. Progression probabilities for each eye variable would be influenced by the state of each of the other eye variables, for example the probability and timing of progression of 'eye 2 astigmatism' could be defined as a function of the existing state of the 'eye 1 astigmatism' variable (and vice versa).

Parallel to the vision variables pathway, a clinical pathway describes the prevalence of anisometropia and the vision status of children at each year of life. Anisometropia would be sampled as a function of the vision variables and age each year. VA (in eye 1 and eye 2) would be sampled as a function of anisometropia, the vision variables, and age each year.

The clinical pathway was used to describe clinical presentation rates, and also to facilitate the evaluation of alternative screening programmes. The pathway described the referral of children at each year of age, which may occur as a result of incidental detection or screen detection. Given a combination of vision variable values (including anisometropia) and VA levels (for eye 1 and eye 2), children had a probability of incidental detection at each age and a probability of screen detection (if screening is undertaken at each age).

Table 76 describes the input parameters, incorporating the levels assigned to each of the five vision variables. This proposed model structure resulted in 784 vision variable combinations (excluding strabismus, i.e. even if strabismus is defined as a yes/no variable, the number of vision variable combinations would be doubled to 1568). However, the number of states was not the primary factor leading to the simplification of the model structure, as the proposed approach could have been handled efficiently as a discrete event simulation model if required.

Populating the complex model

Full details of the reviewed natural history literature are presented in Chapter 3. Few relevant data to inform the direct estimation of the model's parameters were identified from the natural history literature. The majority of the reviewed literature focused on the progression of refractive errors (primarily astigmatism) in the very early years of life, following children identified as having a refractive error within the first year of life to the age of 3–4 years. Although some studies did not control for treatment between follow-up times, a consistent message from the data is that a large proportion of astigmatism identified in the first year of life spontaneously resolves.

Potential uses for the data from the literature were considered in the context of the other available data, primarily data from ALSPAC. ALSPAC collected a large quantity of data from a series of detailed assessments undertaken in a cohort of children from their first year of life, at 6-monthly intervals to the age of 3½ years. One further follow-up point at approximately 7 years of age was also available. Data collected included birth characteristics (gestation period, birth weight, sex, single or multiple birth and systemic or developmental problems such as cerebral palsy, Down's syndrome and learning difficulties) and measures of spherical error, astigmatism, strabismus and VA in each eye.

The model was intended to represent the natural history of the alternative vision variables spherical error, astigmatism, and strabismus, in addition to VA, but the ALSPAC cohort were treated upon detection of an abnormality. Unfortunately, the timing of any treatment was not recorded, other than parents being asked at the 7-year visit

TABLE 76 *Initially defined vision variables for the amblyopia screening model*

Eye 1 astigmatism status at 12 months
Eye 1 hyperopia myopia status at 12 months
Eye 2 astigmatism status at 12 months
Eye 2 hyperopia myopia status at 12 months
Strabismus status at 12 months

Probability of progression and timing of:
No astigmatism → min. astigmatism
No astigmatism → mod. astigmatism
No astigmatism → high astigmatism
Min. astigmatism → mod. astigmatism
Min. astigmatism → high astigmatism
Mod. astigmatism → high astigmatism
No hyperopia/myopia → min. myopia
No hyperopia/myopia → mod. myopia
No hyperopia/myopia → high myopia
No hyperopia/myopia → min. hyperopia
No hyperopia/myopia → mod. hyperopia
No hyperopia/myopia → high hyperopia
Min. myopia → no hyperopia/myopia
Min. myopia → mod. myopia
Min. myopia → high myopia
Min. myopia → min. hyperopia
Min. myopia → mod. hyperopia
Min. myopia → high hyperopia
Mod. myopia → no hyperopia/myopia
Mod. myopia → min. myopia
Mod. myopia → high myopia
Mod. myopia → min. hyperopia
Mod. myopia → mod. hyperopia
Mod. myopia → high hyperopia
High myopia → no hyperopia/myopia
High myopia → min. myopia
High myopia → mod. myopia
High myopia → min. hyperopia
High myopia → mod. hyperopia
High myopia → high hyperopia
Min. hyperopia → no hyperopia/myopia
Min. hyperopia → mod. hyperopia
Min. hyperopia → high hyperopia
Min. hyperopia → min. myopia
Min. hyperopia → mod. myopia
Min. hyperopia → high myopia
Mod. hyperopia → no hyperopia/myopia
Mod. hyperopia → min. hyperopia
Mod. hyperopia → high hyperopia
Mod. hyperopia → min. myopia
Mod. hyperopia → mod. myopia
Mod. hyperopia → high myopia
High hyperopia → no hyperopia/myopia
High hyperopia → min. hyperopia
High hyperopia → mod. hyperopia
High hyperopia → min. myopia
High hyperopia → mod myopia
High hyperopia → high myopia
No strabismus → strabismus

Controlling for the status of the other four vision variables (if appropriate, i.e. dependent on the regression analyses informing the probabilities and timing of progression), and age

whether their children had been patched or currently or previously wore glasses. This meant that it was not possible to determine whether infeasible refractive error patterns (from a natural history perspective) were due to treatment effects, incorrect data entry, erroneous readings from the autorefractor or spontaneous manipulation of accommodation from the infant.

The simplified model

Due to limitations in the data available to populate the initially defined model, a simpler

modelling framework was developed. The final model structure included a more aggregated representation of variables describing amblyogenic factors, defining only the presence or absence of spherical error, astigmatism and/or clinically significantly strabismus. The presence of a refractive error (either spherical error or astigmatism) was defined as an abnormality of at least 2D. The presence of strabismus was defined as clinically significant strabismus, which included all cases of manifest strabismus, plus a proportion of latent strabismus cases.

Table 77 presents the 20 possible combinations of the three amblyogenic factor states that were defined, representing the presence or absence of the conditions in one or both eyes.

The 20 amblyogenic factor variables were combined with six variables describing different combinations of VA in children's two eyes (*Table 78*). VA was categorised into normal (logMAR VA $\leq$0.2), moderately affected (logMAR VA >0.2 and <0.5 and severely affected (logMAR VA $\geq$0.5). These categories were chosen on the basis of evidence in the literature.[113,114] These studies classified moderate amblyopia as 20/40 (0.3 logMAR) to 20/80 (0.6 logMAR). If we take vision of less than 20/40 (0.3 logMAR) to be 'normal', this would give a VA of 0.2 logMAR. Similarly, if we assume vision worse than 20/80 (0.6 logMAR) to be 'severe', this would give a VA of 0.5 logMAR. That is, a child with VA of $\leq$0.2 logMAR could be categorised as having normal vision and a child with VA $\geq$0.5 logMAR has severely affected vision.

Thus, a total number of 120 health states were defined. The amblyopia screening model was implemented as a cohort Markov model, which describes the transition of a cohort of individuals between health states over a defined time horizon. The time horizon is split into a finite number of cycles of equal duration; during each cycle, a proportion of the cohorts in each state transit to a corresponding state, based on the probability of transition between the different states. Transition matrices describe the probability of transition between each of a model's states within a defined period, so in a 120-state model, the corresponding transition matrix represents 14,400 potential transition probabilities.

The main limiting factor of a cohort Markov model is the Markovian assumption, which states that the probability of moving from the current state is dependent only on the current state and not the pathway taken to reach that state. In the context of the limited evidence available to populate the amblyopia screening model, the Markovian assumption is not considered to be overly onerous.

The starting point for the model was the distribution of individuals across the 20 amblyogenic factor states as described in *Table 76* at age 2 years. A starting age of 2 years provided a

TABLE 77 *Amblyogenic factor states*

No.	Amblyogenic factor state
1	No refractive error, without clinically significant strabismus
2	Spherical error in 1 eye, no astigmatism, without clinically significant strabismus
3	Astigmatism in 1 eye, no spherical error, without clinically significant strabismus
4	Spherical error and astigmatism in 1 eye (same eye), without clinically significant strabismus
5	Spherical error and astigmatism in 1 eye (different eyes), without clinically significant strabismus
6	Spherical error in both eyes, no astigmatism, without clinically significant strabismus
7	Astigmatism in both eyes, no spherical error, without clinically significant strabismus
8	Spherical error in both eyes, astigmatism in 1 eye, without clinically significant strabismus
9	Astigmatism in both eyes, spherical error in 1 eye, without clinically significant strabismus
10	Spherical error and astigmatism in both eyes, without clinically significant strabismus
11	No refractive error, with clinically significant strabismus
12	Spherical error in 1 eye, no astigmatism, with clinically significant strabismus
13	Astigmatism in 1 eye, no spherical error, with clinically significant strabismus
14	Spherical error and astigmatism in 1 eye (same eye), with clinically significant strabismus
15	Spherical error and astigmatism in 1 eye (different eyes), with clinically significant strabismus
16	Spherical error in both eyes, no astigmatism, with clinically significant strabismus
17	Astigmatism in both eyes, no spherical error, with clinically significant strabismus
18	Spherical error in both eyes, astigmatism in 1 eye, with clinically significant strabismus
19	Astigmatism in both eyes, spherical error in 1 eye, with clinically significant strabismus
20	Spherical error and astigmatism in both eyes, with clinically significant strabismus

TABLE 78 *Visual acuity states*

No.	VA state[a]
1	Normal in both eyes
2	Normal in one eye, moderately affected in the fellow eye
3	Normal in one eye, severely affected in the fellow eye
4	Moderately affected in both eyes
5	Moderately affected in one eye, severely affected in the fellow eye
6	Severely affected in both eyes

[a] Normal VA, logMAR ⩽0.2; moderately affected VA, logMAR >0.2 and <0.5; severely affected VA, logMAR ⩾0.5.

suitable age from which to model progression under the assumption that no children would be treated prior to this age. *Figure 1* describes the subsequent stages of development of the screening model. The first phase of the model was restricted to 6-monthly transitions between the amblyogenic factor states from age 2 years to age 3½ years, and so was developed as a 20-state Markov model. At age 3½ years, the children in each of the 20 amblyogenic factor states were distributed between the six VA states, expanding the size of the model to 120 states.

The stepped expansion approach to developing the model was chosen as data on the distribution of aggregate incidence of amblyogenic factors at age 3½ years were available, against which the 20-state model could be calibrated. Data on VA prior to 3½ years were not available and there was no advantage to estimating it at earlier ages as screening was not considered before 3½ years.

From age 3½ years, the model described 6-monthly transitions between the 120-combined amblyogenic factors/VA states in the absence of treatment using a 120-state transition matrix. The screening model followed children to age 7 years, after which it was assumed that no new cases of amblyopia occur, and no cases of treatable

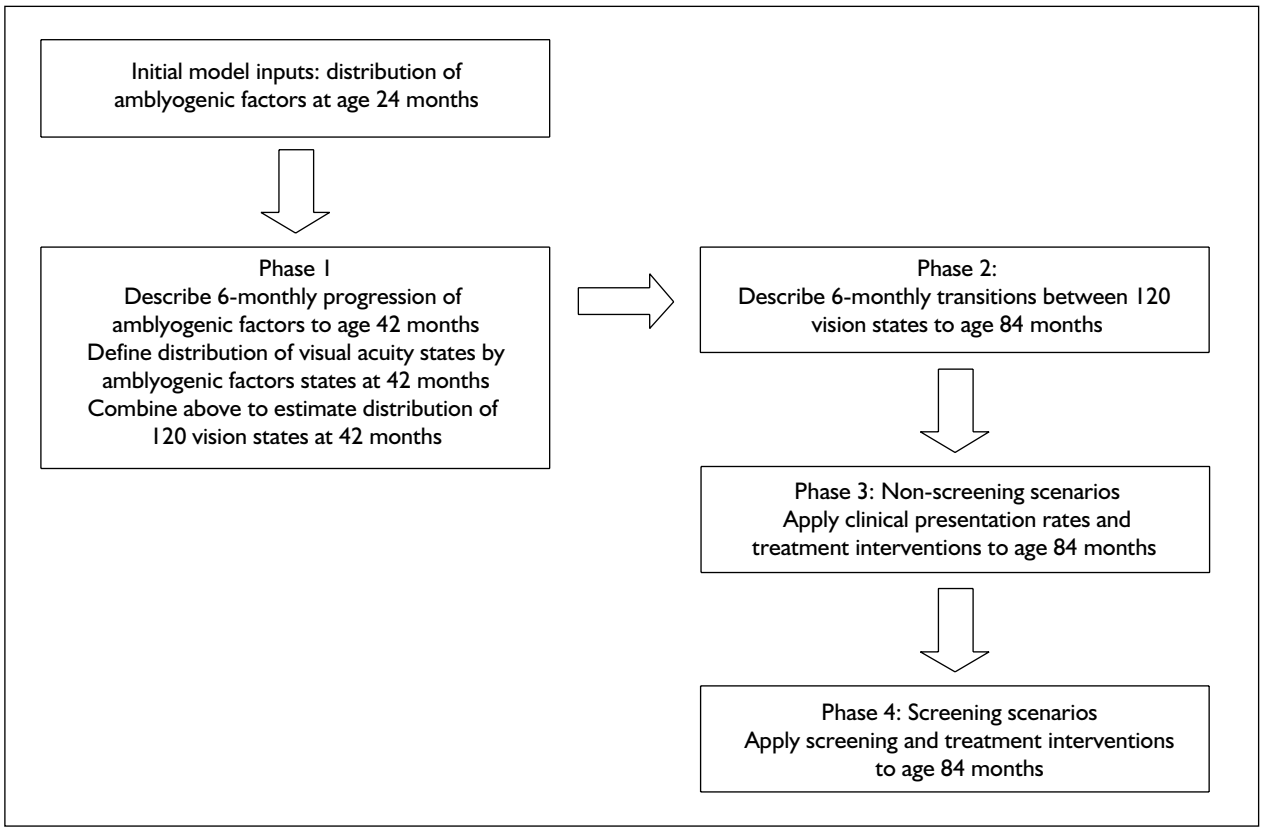

FIGURE 1 *Screening model development phases*

amblyopia present clinically, that is, it was assumed that all cases of treatable amblyopia present by the age of 7 years.

It was assumed that a proportion of affected children would be diagnosed via clinical presentation in the absence of screening. This might occur as a result of symptoms in the child or as a result of ophthalmological contact for an unrelated condition. The third modelling phase incorporated the likelihood of clinical presentation and treatment in the absence of screening. Children may present at any age up to 7 years, and with any combination of amblyogenic factor variables. Upon presentation, the model represented the potential impact of treatment on the natural course of the disease, that is, children may have amblyogenic factors removed as risk factors for amblyopia, or amblyopia itself may be successfully treated. The costs and effects associated with this non-screening scenario informed the baseline comparator for the amblyopia screening options.

Finally, screening interventions were overlaid on top of the baseline scenario to estimate the cost and health impacts of alternative screening options. Costs were applied to resource use associated with screening, and treatment of both amblyogenic factors and amblyopia. The main health outcome of the screening model was the remaining number of cases of amblyopia (either unsuccessfully treated or undiagnosed) in the population of 7-year-old children.

Populating the simplified model

Tables 104–111 describing all of the input data are presented in Appendix 8. The population of the screening model is described in stages that relate to the process described above and in *Figure 1*. The first stage describes the population of the 20-state amblyogenic factors model from the age of 2 to 3½ years, followed by the extended natural history model that also incorporated visual acuity to age 7 years. Clinical presentation rates (in the absence of screening), screening programme effectiveness parameters and treatment effectiveness parameters are subsequently described.

The initial distribution of children across the 20 amblyogenic factor states at age 2 years was subjectively estimated based on the limited prevalence data identified as part of the literature review reported in Chapter 3. Separate transition matrices were defined to describe transitions between the 20 amblyogenic factor states for the three 6-month Markov cycles between the ages of 2 and 3½ years.

A pragmatic approach to populating the amblyogenic factor transition matrices was adopted due to the lack of primary data. A range of aggregate probabilities for developing an amblyogenic factor were informed by the data identified from the literature review presented in Chapter 3. The type and/or combination of amblyogenic factors experienced was proportionately distributed between the 19 abnormal states, with some increased weighting applied to states that appeared to be more common from the literature review.

For transitions from the 19 amblyogenic factor states, aggregate estimates were specified of the probabilities of children remaining in the same state, experiencing spontaneous resolution of refractive errors (strabismus was assumed not to spontaneously resolve) or moving to an alternative abnormal state. As informed by the literature review, the analysis allowed for a slight decrease in the rate of spontaneous resolution of refractive errors with increasing age, in addition to differentiating between resolution in children with refractive error alone and children with refractive error and strabismus. The matrices also allowed for differences over time in the proportion of children moving to a strabismus state from a refractive error alone state.

The mean expectation was that half of the children without spontaneous resolution of refractive errors stayed in the same vision state, with the remainder distributed across the other abnormal states. Children with a refractive error but without strabismus were assigned a probability of developing strabismus, whereas children with strabismus were evenly distributed across the other strabismus states.

The transition matrices describe numbers of children moving between states, rather than probabilities. This is because the model calibration process sampled probabilities of each transition from Dirichlet distributions that were informed by the numbers in each cell of the transition matrices. Much larger numbers of children are in the cells describing transitions from the 'no amblyogenic factors' state, representing the increased certainty in the incidence of amblyogenic factors as opposed to the uncertainty around the transitions from the amblyogenic factors states.

The distribution of children across the 20 amblyogenic factor states at age 3½ years (as informed by the 20-state amblyogenic factor Markov model) was recorded as an input to the main model that combined these outputs with six VA states to define a 120-state model. The numbers of children estimated to be in each VA state were tabulated for each of the 20 amblyogenic states, which were again based on a subjective interpretation of the limited evidence identified in the literature review. Again, larger numbers are included in the 'no amblyogenic factor' state, representing the increased certainty that most children in this state will have normal acuity.

Finally, a transition matrix was defined that described the movement between seven VA states at 6-monthly intervals. Seven VA states were defined because the single 'normal VA' state was split into two states representing 'normal VA and no refractive error or strabismus' and 'normal VA and some form of refractive error or strabismus'.

Each sampled transition matrix for the post-3½-year amblyogenic factor states and the seven VA states were combined in the form of a 'grand matrix' that described the transitions between the full set of 120 states.

This pragmatic process for estimating values for the natural history input parameters was considered reasonable as the estimated parameter values were only inputs to the probabilistic calibration process that was intended to identify combinations of input parameter values that most accurately predicted observed outputs of the screening model. Therefore, the main purpose of the initial parameter estimation process is to identify relevant ranges for each input parameter.

Other parameters estimated for the screening model included screening parameters (individual test sensitivity and specificity rates), clinical presentation rates and treatment effectiveness parameters (for amblyopia and amblyogenic factors). The defined sensitivity and specificity rates were assumed to incorporate test compliance and so no additional compliance parameters were explicitly defined.

The screening and amblyopia treatment effectiveness parameters were informed by the reviewed literature, which was described in Chapter 4. The screening data required some adaptation due to the need to estimate separate screening parameters for individuals with moderate and severe VA abnormalities. Data describing the effectiveness of screening tests for VA and refractive error abnormalities were obtained from the same study, undertaken as part of the VIP study in the USA.[56] Sensitivity and specificity rates for autorefraction were informed by data describing the nurse-led use of the Retinomax Autorefractor. The single LEA symbols VA test (5 ft) was assumed to be the most relevant test from a UK perspective, although results were only presented for this test when undertaken by lay screeners. To reflect a potential increase in effectiveness when performed by orthoptists, the reported detection rates were increased by 5%. The single LEA symbols VA test was chosen as sensitivity and specificity data were available. It is a crowded log-based VA test, which has been reasoned to be a necessary component in detecting amblyopia.

The effectiveness of screening for the detection of strabismus was informed by data reported by ALSPAC[58] on the effectiveness of the cover test in detecting 28 cases of strabismus in 878 children. Screening test parameters were sampled from beta distributions that were informed by the numbers of children included in the VIP study[56] and ALSPAC[58] studies, respectively. To define separate sensitivity and specificity rates for the moderate and severe VA groups, separate rates were sampled for the any reduced VA group (n = 117 of 1452), the very important to detect early group (n = 210 of 1452) and the important to detect early group (n = 144 of 1452). Two sets of separate rates were then estimated by fitting the weighted ratio of the moderate to severe sensitivity rates to the observed ratio of the important to very important to detect early groups.

Treatment effectiveness rates for the treatment of different types and severities of amblyopia were based on a study of factors influencing visual outcome following treatment of unilateral amblyopia.[142] Stewart and colleagues presented the mean and standard deviation (SD) of the residual difference in VA between the two eyes of children who had received treatment for amblyopia.[142] These data were presented by type of amblyopia (anisometropic or strabismic), age at treatment (<4, 4–6, >6 years) and severity of amblyopia [mild (0 to <0.3), moderate (>0.3 to 0.6) and severe (>0.6)]. The range of final 'difference in acuities' scores were represented as log-normal distributions, and the cumulative probability that the final acuity difference score was under 0.2 was estimated for each subgroup. Using the sample sizes in each subgroup and the

respective cumulative probabilities, beta distributions were specified to represent the uncertainty around each effectiveness estimate. The estimates of effectiveness for the combined subgroups (as required to populate the model) were estimated as the mean effectiveness of the relevant component subgroups. The resulting means and 95% CIs are presented in *Table 79*.

No empirical data were available to inform treatment effectiveness for the amblyogenic factors refractive error and strabismus. Based on expert opinion of the clinically based authors, the model assumed that if refractive error (in the absence of amblyopia) is corrected, the amblyogenic factor is removed and the child is no longer at risk of amblyopia, that is, a 100% treatment success rate. Treatment for strabismus is less successful, and the model samples a random percentage between 0 and 30% as the success rate for removing strabismus as an amblyogenic factor.

No empirical data informed the rate of clinical presentation and so wide subjective prior probability distributions were defined. *Table 80* describes the ranges of the percentage of children with different amblyogenic factors and/or amblyopia that were assumed to present clinically in the absence of screening.

The post-screening vision loss model

The post-screening model estimates the long-term effects of childhood amblyopia, describing a cohort of amblyopic individuals as being in either a unilateral or bilateral vision loss state, or death state, over a 93-year time horizon (to a maximum age of 100 years). The model only describes the incidence of bilateral vision loss in amblyopic cases, that is, it was assumed that the non-amblyopes do not become blind. This is a minor assumption as the rates of binocular vision loss in the non-amblyopic population are likely to be negligible until older ages (e.g. at least 60 years), at which ages discounting reduces the impact of the assumption from an economic perspective. It is also a conservative assumption that favours more effective screening programmes. Cost and utility weights were applied to the unilateral and bilateral vision loss states, and summed across the model's time horizon to estimate the cost consequences of amblyopia.

Data extracted from the literature review were the only source informing the population of the post-screening model. These data described the incidence of fellow eye vision loss in the amblyopic population, in addition to describing the potential

TABLE 79 *Success rates for the cure of amblyopia by amblyopia type and severity and patient age*[a]

Type and severity of amblyopia	Age at treatment (years)			
	3	4	5	6
Moderate strabismic amblyopia	0.64 (0.46 to 0.80)	0.58 (0.41 to 0.73)	0.58 (0.41 to 0.73)	0.57 (0.39 to 0.73)
Severe strabismic amblyopia	0.52 (0.34 to 0.68)	0.45 (0.29 to 0.62)	0.45 (0.29 to 0.62)	0.44 (0.28 to 0.62)
Moderate non-strabismic amblyopia	0.68 (0.48 to 0.84)	0.61 (0.43 to 0.77)	0.61 (0.43 to 0.77)	0.60 (0.42 to 0.77)
Severe non-strabismic amblyopia	0.55 (0.37 to 0.73)	0.49 (0.32 to 0.66)	0.49 (0.32 to 0.66)	0.48 (0.30 to 0.66)

[a] Reported as mean (95% CI).

TABLE 80 *Annual clinical presentation ranges*

Category	Range (%)
Spherical error	0–20
Astigmatism	0–20
Strabismus	0–25
Normal in one eye, moderately affected in the fellow eye	0–10
Normal in one eye, severely affected in the fellow eye	0–20
Moderately affected in both eyes	0–40
Moderately affected in one eye, severely affected in the fellow eye	0–40
Severely affected in both eyes	30–80

for improvement in the amblyopic eye following loss of vision in the healthy eye. However, Rahi and colleagues[45] incorporated both aspects and presented three models that estimated the age-specific incidence of permanent visual impairment or blindness in individuals with amblyopia. These data were combined with UK life table data (2002–4) describing age-specific mortality rates in the general population in order to describe the proportion of living amblyopes in the unilateral and bilateral vision loss states at each age.

In the reference case, it was assumed that individuals with amblyopia have the same lifetime survival profile as the general population. In a sensitivity analysis, an increased relative risk of mortality was applied to individuals in the bilateral vision loss state.

A previous analysis of orthoptic screening[165] referenced utility effects of unilateral visual impairment to a study by Brown and colleagues.[170] This study used the time trade-off method on adult patients with ocular disease who sought treatment for ocular examination with a best-corrected VA of 20/20–20/25 in either one eye or both eyes. Multiple regression analysis showed that there was a significant difference in utility values between those with two good eyes and those with one good eye ($p \leqslant 0.001$), after controlling for the number of co-morbid diseases ($p \leqslant 0.262$), age ($p \leqslant 0.493$), gender ($p \leqslant 0.190$), and number of ocular abnormalities ($p \leqslant 0.548$). The coefficient for one good eye (referent to two good eyes) was 0.0902 (95% CI –0.144 to –0.038).

Brown and colleagues[170] state that based on patient feedback, the utility gain from bilateral as opposed to unilateral vision includes the tasks that bilateral vision allows a person to accomplish, but may also incorporate the psychological stress induced by knowing that many eye diseases eventually affect both eyes. This latter aspect is of less relevance to amblyopia, as the causal relationship between amblyopia and loss of vision in the fellow eye is less well established than for other eye diseases. Moreover, the question asked respondents to value the existence of a technology that guarantees vision remains normal in both eyes over the remainder of their lifetime. This question does not provide the basis for valuing the health state of unilateral visual impairment relative to no visual impairment. A more intuitive assessment of what is being valued is the product of the impact of (binocular) vision loss and the probability of experiencing binocular vision loss. The latter is obviously higher in individuals with unilateral vision loss (as implied by Brown and colleagues[170]).

Our interpretation is supported by a study examining the relationship between monocular and binocular VAs as predictors of visual disability.[171] A total of 2520 community-dwelling residents aged between 65 and 84 years had their monocular and binocular VA measured, in addition to reading speed, face discrimination, and self-reported difficulty with visual tasks. The results showed less than a one letter difference between monocular and binocular acuities for participants with unequal acuities in the two eyes, in addition to demonstrating that the influence of VA on the performance of everyday tasks can be accounted for by monocular acuity in the better seeing eye.

Kandel and colleagues[50] compared the characteristics of dominant eyes (the fellow eyes of unilateral amblyopia) and normal eyes (normal binocular fixation), primarily in young adults. They found that normal eyes were more sensitive than dominant eyes during the later stages of dark adaptation. In addition to differences in foveal pre-eminence between normal and dominant eyes, there was a measurable acuity difference that favoured normal eyes; dominant eyes also differed in their fixation and in their capacity to respond to moving targets. The authors suggest that these differences may be due to the binocular nature of the disorder or to treatment effects of occlusion. These reported differences are not linked to everyday tasks, as reported by Rubin and colleagues,[171] and so it is difficult to infer any utility impact.

The cost and utility values used in the long-term model are presented in *Table 81*. A constant utility decrement for bilateral vision loss was based on a subjective assessment of the widely varying utility values reported by two separate studies.[172,173] As no reliable direct evidence of a utility effect due to unilateral visual impairment is defined, the reference case analysis assumed no utility decrement associated with unilateral impairment. This assumption is tested in the sensitivity analysis.

Individuals with no vision loss or unilateral vision loss were not assumed to incur vision-specific health and social care costs. Individuals with bilateral vision loss were assumed to incur additional costs, which were estimated primarily from a cost–utility analysis developed as part of the NICE appraisal process for photodynamic

therapy in age-related macular degeneration.[174] In the NICE appraisal, costs to the NHS and local and central government associated with blindness and rapidly deteriorating vision were estimated on the basis of the data presented in *Table 82*. Uprating the presented aggregate costs to 2006 values using the NHS Pay and Prices Index, the estimated initial costs associated with blindness range from £52 to £295 and the annual costs range from £1325 to £16,804. A more recent cost analysis was also identified that presented separate annual costs by age groups (children, working age and the elderly), although the cost estimates could not be disaggregated to exclude non-health and social care costs.[175]

Calibration

Due to the significant areas of uncertainty around many of the model's input parameters, it was necessary to calibrate the model to a series of model outputs that have been observed. The described techniques for calibrating the model have been developed by the research team in a previous model-based analysis of screening for macular degeneration, which have been extended for application in the evaluation of screening for amblyopia.

The general approach to calibration is to identify the combination of input parameters that best predict observed estimates of one or more of the model's output parameters. The adapted calibration approach used is termed a probabilistic calibration approach, which assigns probabilities to a large number of different input parameter sets that represent the probability that each set is the optimal combination of input parameter values.

The following sections describe the observed output parameters that were used as part of the calibration process and the methods of analysis for estimating the probability weights for each sampled set of input parameters. The results of the calibration process are presented in Chapter 9.

Calibration data

Potential output parameters were sourced from the review of the literature and from existing screening programmes in the UK. A number of prevalence estimates were identified, which were

TABLE 81 *Cost and utility values used in the post-screening lifetime model*

Vision state	Cost (range) (£)	Utility decrement (range)
No vision loss	0	0
Unilateral vision loss	0	0 (0–0.02)
Bilateral vision loss	6,719 (1,325–16,804)	0.2 (0.1–0.3)

TABLE 82 *Costs associated with blindness and rapidly deteriorating vision*[174]

	Base case		Low range		High range	
	Annual proportion	Annual cost (£)	Annual proportion	Annual cost (£)	Annual proportion	Annual cost (£)
Blind registration	0.945	97	0.5	40	0.945	170
Low vision aids	0.33	136	0.33	56	0.74	136
Low vision rehabilitation	0.11	205	0.11	125	0.11	309
Housing/council tax benefit	0.45	2,714	0.21	2,413	0.73	3,588
Social security	0.63	1,924	0.17	0	0.63	2,876
Tax allowance	0.05	319	0.05	145	0.18	319
Depression	0.386	392	0.06	392	0.5	392
Hip replacement	0.05	3,669	0.005	1,177	0.247	3,933
Community care	0.06	2,849	0.06	1,138	0.4	4,759
Residential care[a]	0.3	11,133	0.13	5,490	0.56	16,509
Initial cost (£)[b]	160 (170)		52 (56)		295 (315)	
Annual cost (£)[b]	6,295 (6,719)		1,325 (1415)		16,804 (17,937)	

[a] It is assumed that 30% of individuals requiring residential care fund themselves and do not contribute costs from the perspective of the government.
[b] Figures in parentheses are uprated to January 2006.

TABLE 83 *Calibration prevalence data*

	No.	Population	Proportion	95% CI
Strabismus at 36 months	17	333	0.051	0.03 to 0.075
Strabismus at 5 years	24	339	0.071	0.044 to 0.100
Refractive error at 36 months	27	333	0.081	0.054 to 0.111
Amblyopia	216	4500	0.048	0.042 to 0.054

reviewed in Chapter 2. From these data, the prevalence estimates in Table 83 were judged to be most relevant from a UK population perspective and were used in the calibration process.

In addition, data collected from the amblyopia screening programme based at Sandwell and West Birmingham Hospitals were available. These data included screening outcomes recorded over the years 2003–4 and 2004–5 that measured VA in both eyes, clinically significant squint and refractive errors, all of which resulted in a referral for further investigation.

The recorded strabismus variables were No strabismus, Latent (esophoric) strabismus, Latent (exophoric) strabismus, Manifest (esotropic) strabismus (infantile, with accommodative element, consecutive), Manifest (esotropic) strabismus (other) and Manifest (exotropic) strabismus. In observations in which strabismus status was not recorded, but refractive error and/or amblyopia status was recorded, it was assumed that the child had no strabismus.

The recorded refractive error variables were Undefined refractive error, Hypermetropia, Myopia, Hypermetropic astigmatism, Myopic astigmatism, Mixed astigmatism, Hypermetropic anisometropia, Myopic anisometropia and Astigmatic anisometropia. The data do not explicitly record children as having no refractive error. In observations in which refractive error status was not recorded, but strabismus and/or amblyopia status was recorded, it was assumed that the child had no refractive error.

The recorded amblyopia variables were Undefined Amblyopia, Anisometropic amblyopia, Ammetropic amblyopia, Strabismus amblyopia, Stimulus deprivation amblyopia, Meridional amblyopia. The data do not explicitly record children as having no amblyopia. In observations in which amblyopia status was not recorded, but strabismus and/or refractive error status was recorded, it was assumed that the child had no amblyopia.

In cases in which none of the three vision variables were recorded, no assumptions regarding strabismus vision status were made and these observations were discarded.

Unfortunately, significant levels of data recording the outcome of the referral consultation are missing, so it is not possible to identify how many true positives were referred in each referral category. The model does not define the referral cause of children later defined as false positive; any such definition would be subjective and would not inform the calibration process. Therefore, the Birmingham data were analysed to estimate the proportions of referred children at three separate ages at screening (3, 4 and 5 years), representing the combined number of true positives and false positives identified. The results of these analyses are presented in *Table 84*.

The Birmingham data were used to provide a general indication of the model's predictions, with the expectation that the predicted referral rates would be somewhat lower than those observed in Birmingham, although additional evidence supporting such rates is provided by Abrahamsson and colleagues,[37] who found that, in a screening programme for 4-year-old children in Sweden, 23% of the children (71/310) had visited an ophthalmologist before the age of 5 years. This

TABLE 84 *Screening referrals in Birmingham by age at screen*

Age at screen (years)	No.	Population	Proportion	95% CI
3	29	126	0.77	0.698 to 0.841
4	454	2278	0.8	0.784 to 0.817
5	526	2869	0.817	0.802 to 0.831

approach was taken because the Birmingham data were not considered to be representative of the general UK population due to the high proportion of children with a non-European family origin. The impact of family origin is twofold. First, children with a south-east Asian family origin are known to have higher rates of refractive error and strabismus than children with a north European family origin, which will increase the referral rates. Second, anecdotally it is noted that a higher proportion of children with a south-east Asian family origin are referred due to communication problems with children and parents, resulting in referrals due to uncertainty rather than identified abnormalities.

Calibration methods

The calibration methods involved the estimation of probability weights that reflected how accurately alternative input parameter sets predicted the observed output parameters. The first step involved randomly sampling 5000 input parameter sets from the defined probability distributions around each input parameter (as described in the section 'Populating the simplified model', p. 69). These 5000 input parameter sets were then run through the model and the defined calibration output parameters were recorded for each parameter set. The predicted outputs for each input parameter set were then compared to the observed output values using three alternative methods:

- the sum of the absolute differences between the mean value of the observed outputs and the predicted outputs
- the sum of the mean squared differences between the mean value of the observed outputs and the predicted outputs
- the sum of the maximum likelihood estimation (MLE) for each output parameter, where, for example,

  MLE (amblyopia prevalence) = [(observed no. amblyopia cases × ln(predicted proportion amblyopia cases)] + [(observed no. non-amblyopia cases × ln(1 – predicted proportion amblyopia cases)]

For each comparison method, a weight for each input parameter set was defined as the reciprocal of the sum of the differences for the absolute and mean squared differences approaches, and the negative reciprocal of the sum of the MLEs, i.e. the weights increase with increasing accuracy of the predictions. To estimate the probability that each input parameter set is the most accurate or optimal set, the estimated weight for each set was divided by the sum of the weights across all input parameter sets.

In the model, the probability weights were presented as cumulative probabilities so that the final input parameter set has a probability of 1. For each iteration, the model samples a random value between 0 and 1 and identifies the input parameter with the closest cumulative probability, which is then defined as the sampled parameter set for that model iteration.

Model analysis

The amblyopia screening model estimated screening and treatment costs associated with alternative screening programmes (including no screening). The estimated number of remaining cases of amblyopia in the population at age 7 years for each defined screening programme was combined with the estimated lifetime cost and QALY effects of amblyopia that were estimated from the post-screening lifetime model. The lifetime model was run with everyone starting in the unilateral vision loss state, and with everyone starting in the no vision loss state (where individuals can only move to dead), where the estimated difference in QALYs between the two groups is defined as the QALY loss for each additional person with amblyopia in a population.

In the reference case, both costs and QALYs were discounted at 3.5% per annum. Mean estimates of the costs and QALYs informed an incremental analysis of the cost per QALY gained between interventions ordered by increasing effectiveness. PSA provided estimates of the CIs around the ICERs, in addition to informing cost-effectiveness acceptability frontiers.

The EVPI is a monetary representation of the difference in the expected payoff of decisions using perfect information and the payoff using the currently available information.[176] The estimation of the EVPI is based on the net benefit statistic, which is estimated for each screening option as the mean number of QALYs gained multiplied by the monetary value of a QALY, minus the mean costs associated with each screening option.

The outputs from the PSA are used to estimate the EVPI, where each iteration provides a separate observation of the net benefits associated with each screening option (informed by an alternative set of input parameter values). Using the available

information, a single resource allocation decision would be made based on the screening option with the highest mean estimate of net benefits across all iterations. However, if there is uncertainty about which screening option is cost-effective (at the chosen value of a QALY), not all iterations will demonstrate that the same screening option has the highest net benefits. Assuming perfect information, individual allocation decisions could be made for each observation of net benefits within the distribution of net benefits. The EVPI for each patient ($EVPI_{episode}$) is then estimated as the sum of the differences between the net benefits based on the mean net benefit statistic (NB_{μ})and the net benefits base on perfect information (NB_{PI}), divided by the number of iterations:

$$EVPI_{episode} = \frac{\sum_{n=1}^{N} NB_{PI} - NB_{\mu}}{N}$$

where N is the number of iterations in the PSA.

The EVPI for the relevant patient population is estimated by multiplying $EVPI_{episode}$ by the eligible patient population over the period for which the allocation decision is expected to remain, discounted at an appropriate rate. In the case of screening for amblyopia, our estimate of the relevant patient population is based on the estimated number of 6-year-olds in England and Wales in 2006,[177] an assumed duration of the technology of 10 years and an annual discount rate of 3.5%. These data result in an estimated population size of almost 2.6 million children.

Conclusions

This chapter has described the process for developing and populating an amblyopia screening model and a linked lifetime effects model for individuals with amblyopia. The final screening model comprised 120 vision states, although initial plans for an even more complex screening model were necessarily simplified due to the lack of data available to estimate detailed relationships between relevant input parameters. Although guidelines suggest that model structures should not be compromised by data availability,[178] there is a practical limit to the subjective estimation of model parameters in the absence of data. Other authors have adopted a completely random approach to the population of complex screening models, whereby input parameters are allowed to vary between 0 and 1 (for probability parameters).[179] The calibration process then identifies the most accurate parameter sets, which are then manually inspected to exclude sets that contain inappropriate parameter value combinations. This approach is both computationally and manually intensive. It is open to human error, where the values of many variables must be subjectively assessed in combination to identify sensible parameter sets. The conduct of PSAs is also less intuitive than the objective definition of probability weights for the full range of sampled input parameter sets.

The output data against which the amblyopia screening model was calibrated were limited by the available literature, although they provided a reasonable indication of the magnitude of the key output parameters at different ages. Although prevalence data from strabismus were available at different ages, it would have been very useful to estimate also the prevalence of refractive error and amblyopia at multiple ages. The lack of output data provides an additional argument against the use of a more complex model as the output data would not inform more disaggregated representations of the model's variables.

Chapter 9

Cost-effectiveness and model results

Introduction

This chapter presents the results derived from the model described in the previous chapter. Three broad categories of results are presented. First, the results of the calibration process are described, including a comparison of the alternative methods of defining probability weights for each input parameter set. Second, the main cost-effectiveness results are presented with respect to two main outcome measures: cases of amblyopia prevented and QALYs gained. These results include a full range of deterministic and probabilistic sensitivity analyses. Finally, the model outputs are used to estimate the EVPI, which informs future research by estimating the potential value of reducing existing uncertainty around the cost-effectiveness results.[176]

Calibration results

As described in Chapter 8, the cost-effectiveness model contained a range of input parameters that were either unobservable or unobserved. A process of model calibration was required to inform the value of these input parameters, and also the correlations between parameters. The first results from the calibration process compare observed output parameter values with the predicted outputs from the model derived from the 5000 input parameter sets. The input parameter sets were randomly sampled from initially defined probability distributions for each parameter.

Figures 2–5 show the predicted and observed rates of the four main output parameters that were used in the calibration process. The parameters amblyopia incidence at age 7 years, refractive error at age 3 years, strabismus at age 3 years and strabismus at age 5 years were all estimated in the absence of a screening programme. The figures all show that the predicted and observed data are comparable over the estimated CIs for each observed output parameter. The distribution of predicted outputs for the rates of amblyopia at age 7 years is wider than the CI based on the observed data, although this is accepted as the CIs represent only the data reported by one particular study. As reported in Chapter 2,

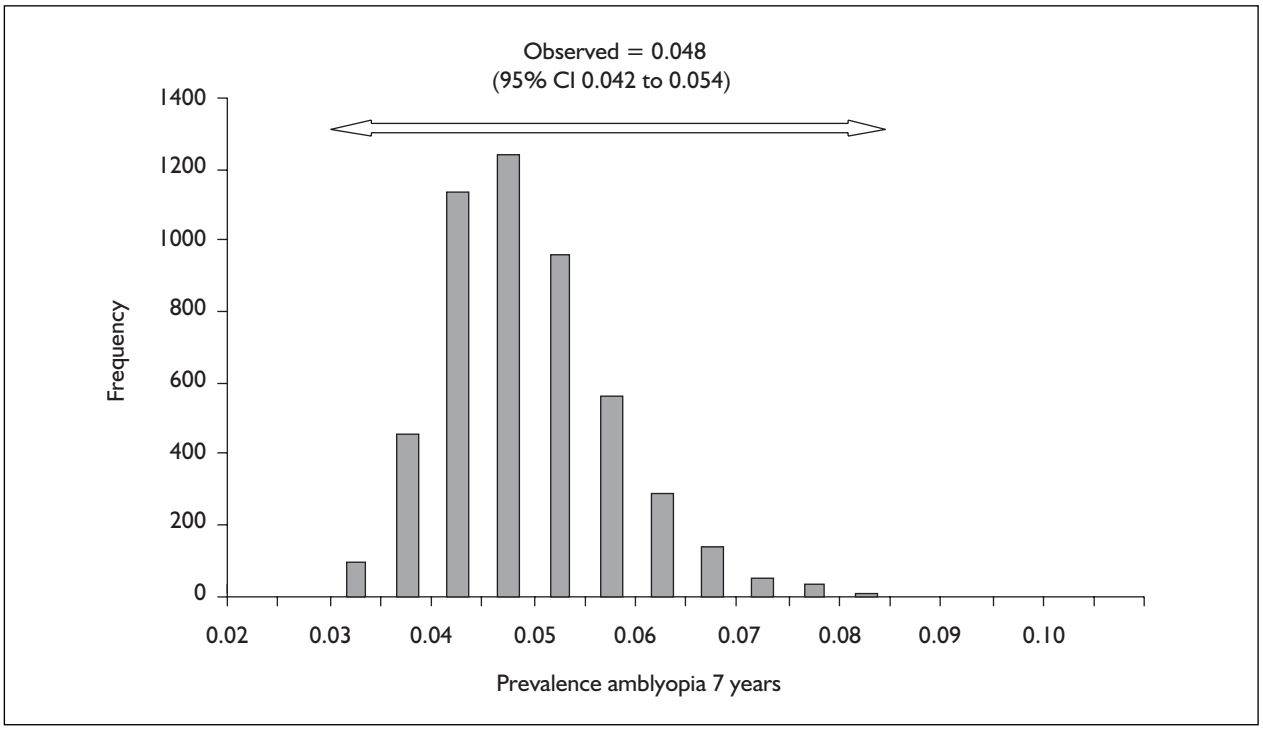

FIGURE 2 *Predicted and observed rates of amblyopia at age 7 years in a non-screened population*

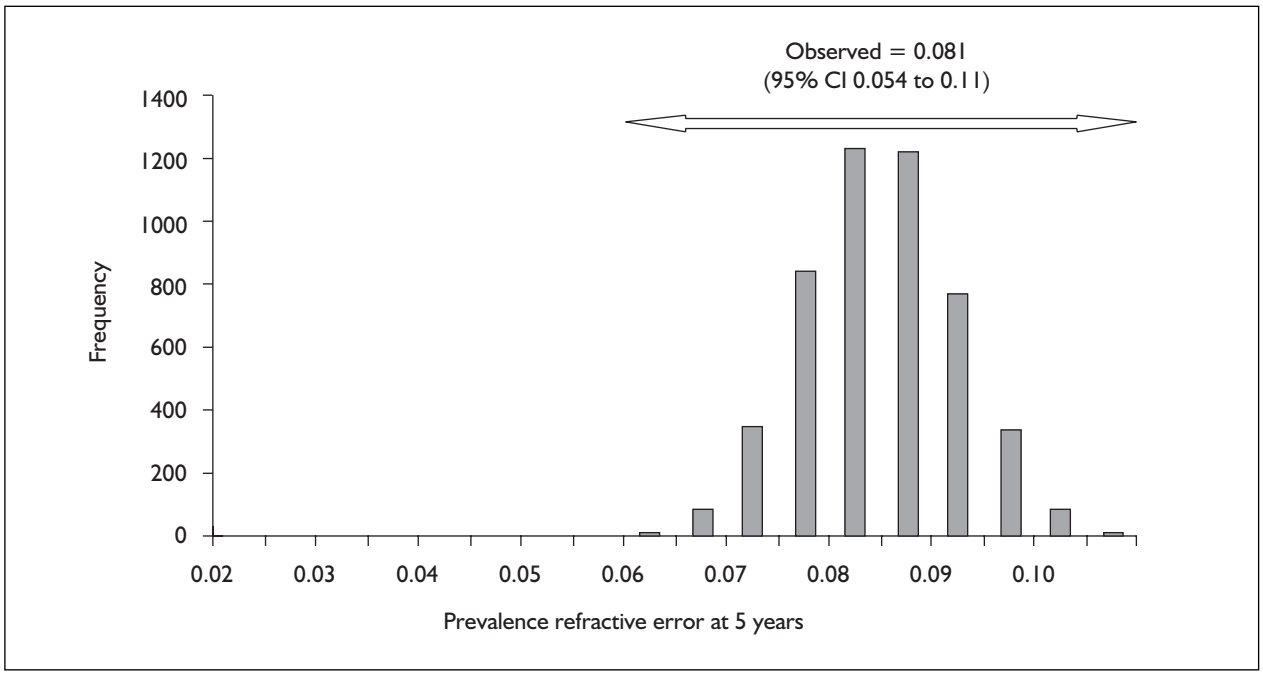

FIGURE 3 *Predicted and observed rates of refractive error at age 3 years in a non-screened population*

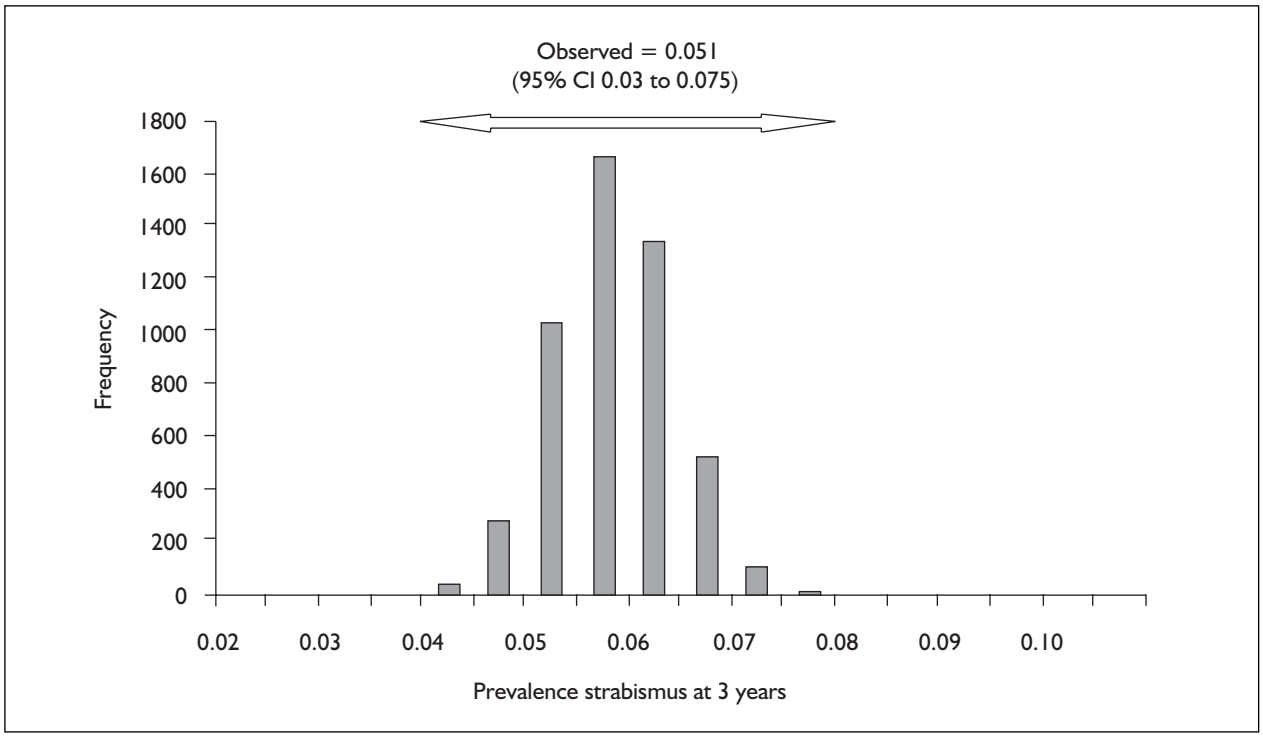

FIGURE 4 *Predicted and observed rates of strabismus at age 3 years in a non-screened population*

numerous other studies reported different rates and this between-study variation is not captured by the presented CIs.

The general closeness of the observed and predicted outputs is to be expected as the model population process involved an iterative process by which parameter values for the most uncertain input parameters were refined on the basis of comparisons between observed and predicted outputs.

In addition to the formal comparison of the above output parameters, an informal comparison of

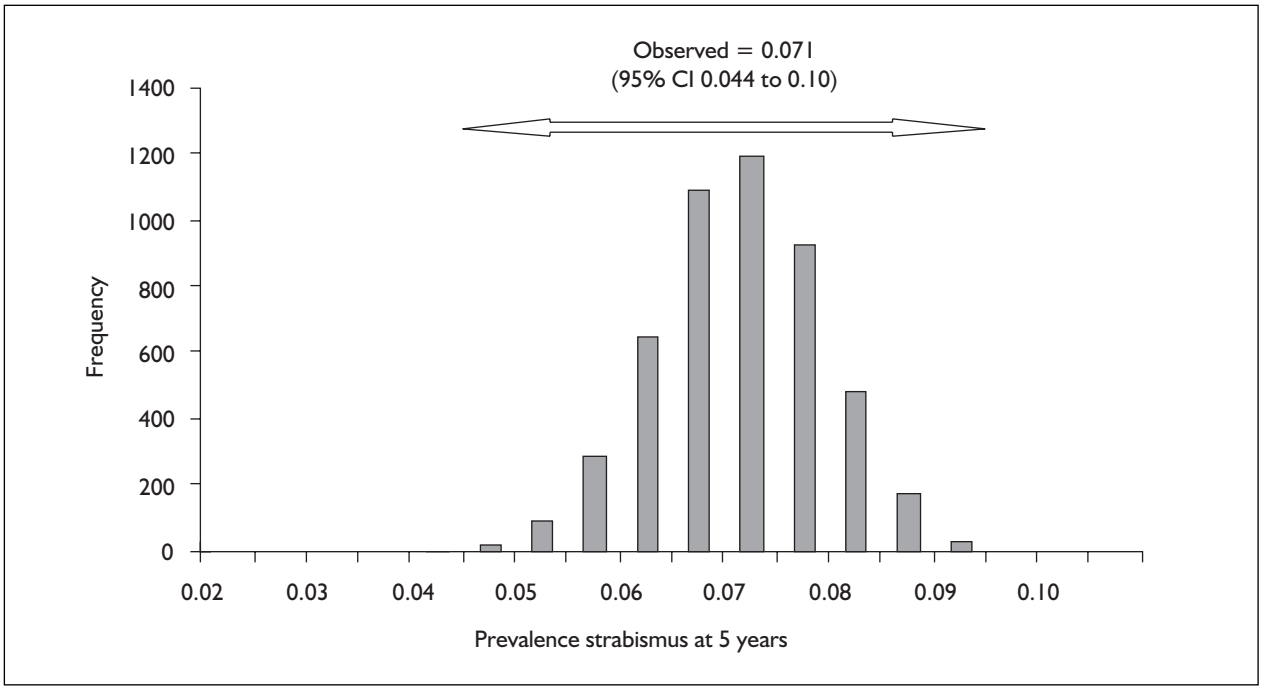

FIGURE 5 *Predicted and observed rates of strabismus at age 5 years in a non-screened population*

predicted and observed rates of referred children at three separate ages at screening (3, 4 and 5 years) was undertaken. *Table 85* compares the predicted outputs at these three ages for a screening programme including only VA testing and a cover–uncover test (i.e. not including autorefraction) with the observed data from Birmingham. As noted in Chapter 8, the Birmingham data are representative of a population with high rates of children with non-north European family origins and so one would expect higher referral rates than in the overall UK population. This result is demonstrated, providing some additional confidence in the calibration process.

The second part of the calibration process involved estimating probability weights for each of the 5000 sampled input parameter sets that represented the relative accuracy of each set in predicting the observed output parameters. The different methods (the absolute difference, mean squared difference and MLE approaches) are compared in the form of the cumulative probability distributions describing the cumulative probability that each input parameter set is the most accurate set. *Figure 6* presents the distributions, which are ordered in increasing order of probability. The alternative calibration methods produced different cumulative distributions, with the MLE approach hardly differentiating between the input parameter sets at all. The other approaches provide a much clearer distinction between the parameter sets, with the mean squared difference approach attaching larger relative weights to the more accurate sets.

TABLE 85 *Predicted and observed referral rates by age at screening*

Age at screening (years)	Proportion children referred for further examination (%)	
	Observed	Predicted
3	77	86.3
4	80.1	85.6
5	81.7	85.3

Cost-effectiveness results

A wide range of model analyses were undertaken to estimate the cost and effects of no screening and screening at 3, 4 and 5 years. With respect to the relevant set of probability weights to use in the analyses, the non-differentiation produced by the MLE approach is considered uninformative and is only used for comparative purposes in the reference case analysis. There is no theoretical basis for choosing between the other two calibration methods, so all other analyses are undertaken using both the absolute difference and mean squared difference calibration approaches.

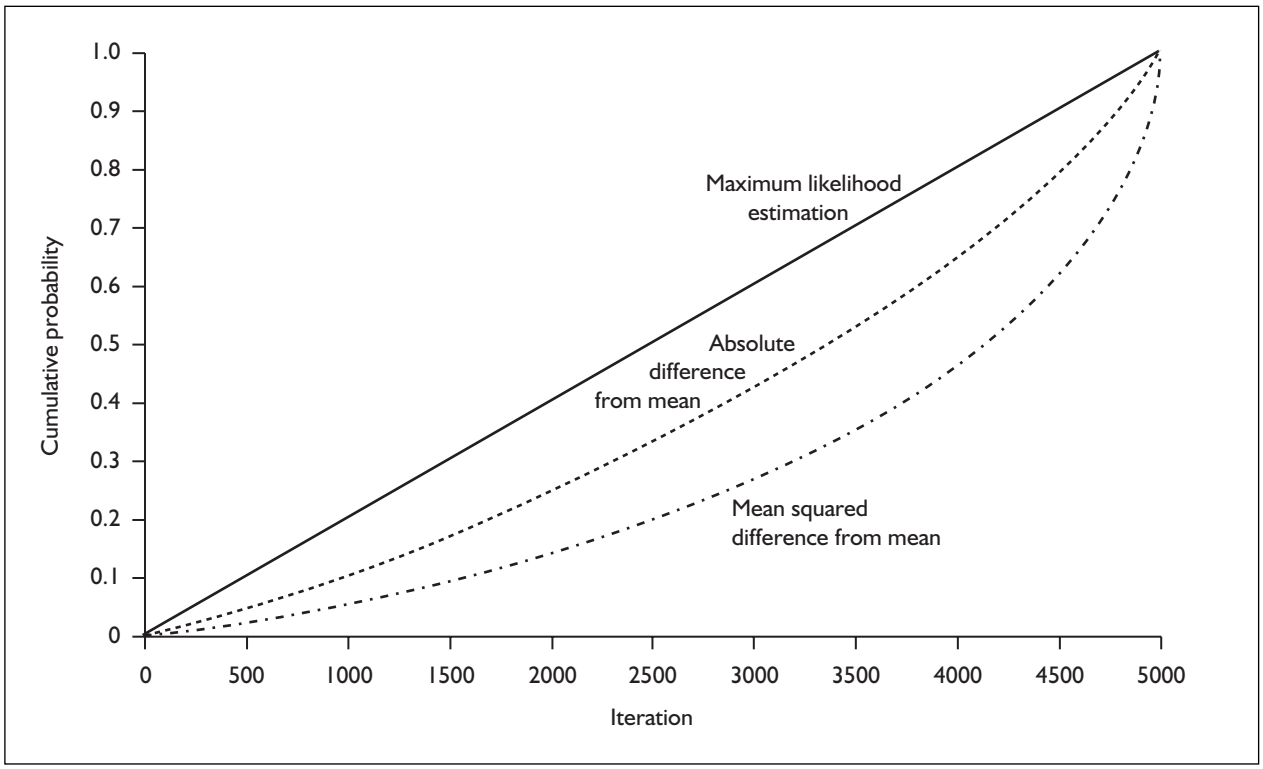

FIGURE 6 *Calibration probability weights comparison by calibration method*

Reference case results

The reference case analyses are based on the mean results of 5000 model iterations in which the calibrated input parameter sets were sampled according to the estimated probability weights. The mean cost parameter values were applied to the mean estimates of the number of children referred, treated (by condition), and remaining cases of amblyopia at age 7 years (lifetime costs) to estimate the incremental cost per case of amblyopia prevented. The mean estimate of the lifetime QALYs lost as a result of amblyopia was then incorporated to estimate the incremental cost per QALY gained from the different screening options.

Tables 86–88 present the reference case results for cases of amblyopia prevented for each of the three calibration methods (absolute difference, mean squared difference and MLE). Each table presents seven screening options (no screening and screening at ages 3, 4 and 5 years, with and without autorefraction). Across all comparisons, there are some screening options that are extendedly dominated (the subsequent screening option has a lower ICER[180]) by at least one other screening option. The ICERs are re-estimated with the dominated options removed.

The results show that screening at later ages is predicted to be slightly more effective; in a

TABLE 86 *Reference case results for the incremental cost per case of amblyopia prevented for a population of 10,000 children (absolute difference calibration method)*

Screening option	Cost (£)	Amblyopia cases	ICER (£)	Adjusted ICER[a] (£)
No screening	572,129	480		
Screen at 3 years without AR	867,120	393	3,368	3,368
Screen at 4 years without AR	941,247	381	6,295	6,295
Screen at 5 years without AR	1,020,281	371	7,956	ED
Screen at 3 years with AR	1,040,358	368	6,958	ED
Screen at 4 years with AR	1,117,707	353	5,164	6,348
Screen at 5 years with AR	1,216,422	351	57,673	57,673

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 87 *Reference case results for the incremental cost per case of amblyopia prevented for a population of 10,000 children (mean squared difference calibration method)*

Screening option	Cost (£)	Amblyopia cases	ICER (£)	Adjusted ICER[a] (£)
No screening	574,673	482		
Screen at 3 years without AR	871,063	398	3,525	3,525
Screen at 4 years without AR	945,154	386	6,054	ED
Screen at 5 years without AR	1,024,449	376	7,962	ED
Screen at 3 years with AR	1,040,960	366	1,633	5,259
Screen at 4 years with AR	1,117,868	351	5,305	5,305
Screen at 5 years with AR	1,216,079	350	73,769	73,769

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 88 *Reference case results for the incremental cost per case of amblyopia prevented for a population of 10,000 children (MLE calibration method)*

Screening option	Cost (£)	Amblyopia cases	ICER (£)	Adjusted ICER[a] (£)
No screening	571,286	480		
Screen at 3 years without AR	866,472	396	3,511	3,511
Screen at 4 years without AR	940,453	384	5,900	ED
Screen at 5 years without AR	1,019,832	374	7,895	ED
Screen at 3 years with AR	1,035,898	366	2,056	ED
Screen at 4 years with AR	1,112,874	351	5,068	5,068
Screen at 5 years with AR	1,211,504	349	60,761	60,761

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

population of 10,000, screening at 5 years instead of at 3 years would be expected to prevent between 12 and 15 additional cases of amblyopia regardless of whether autorefraction is included as a screening test. Screening at 5 years instead of at 4 years would be expected to prevent only an additional 1–2 cases of amblyopia if autorefraction is used, although the gain is around 10 cases in screening programmes that do not use autorefraction. Combining these effectiveness estimates with lifetime costs shows that the incremental cost per case of amblyopia prevented is around £3500 when moving from no screening to screening without autorefraction at 3 years, between £5000 and £7000 for a screening programme at age 4 years and increases significantly to between £57,000 and £73,000 when moving to screening at 5 years.

In the absence of screening, around 78% of the total cost estimate represents costs associated with diagnosis and treatment of amblyopia and/or amblyogenic factors. The remainder of the total costs represents downstream costs associated with the impact of amblyopia on subsequent health and social care-related activities. With screening in place (including autorefraction), the model predicts that between 88 and 94% of total costs are incurred in screening, diagnosis and treatment.

The incremental cost per QALY gained results (*Tables 89–91*) are generated by applying a constant QALY effect (QALYs lost per case of amblyopia), so it is not surprising that they follow a similar pattern to the results presented in *Tables 86–88*. The difference is in the magnitude of the results. Based on a discounted lifetime QALY gain of only 0.0071 QALYs per case of amblyopia prevented, the QALY ICERs are large. Even the ICER for moving from no screening to screening at 3 years is over £500,000, with the ICER for screening at 5 years relative to screening at 4 years between £8.5 and £11 million per QALY gained.

Sensitivity analyses

To test the robustness of the reference case results, a range of one-way and multi-way deterministic sensitivity analyses are reported in which one or more parameter value is altered. A full PSA was also undertaken, where separate cost and QALY

TABLE 89 *Reference case results for the incremental cost per QALY gained for a population of 10,000 children (absolute difference calibration method)*

Screening option	Cost (£)	QALYs lost	ICER (£)	Adjusted ICER[a] (£)
No screening	572,129	3.21		
Screen at 3 years without AR	867,120	2.62	503,842	503,842
Screen at 4 years without AR	941,247	2.55	941,872	941,872
Screen at 5 years without AR	1,020,281	2.48	1,190,317	ED
Screen at 3 years with AR	1,040,358	2.46	1,040,938	ED
Screen at 4 years with AR	1,117,707	2.36	772,630	949,750
Screen at 5 years with AR	1,216,422	2.35	8,628,530	8,628,530

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 90 *Reference case results for the incremental cost per QALY gained for a population of 10,000 children (mean squared difference calibration method)*

Screening option	Cost (£)	QALYs lost	ICER (£)	Adjusted ICER[a] (£)
No screening	574,673	3.22		
Screen at 3 years without AR	871,063	2.66	527,375	527,375
Screen at 4 years without AR	945,154	2.58	905,696	ED
Screen at 5 years without AR	1,024,449	2.51	1,191,275	ED
Screen at 3 years with AR	1,040,960	2.45	244,339	786,769
Screen at 4 years with AR	1,117,868	2.35	793,706	793,706
Screen at 5 years with AR	1,216,079	2.34	11,036,723	11,036,723

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 91 *Reference case results for the incremental cost per QALY gained for a population of 10,000 children (MLE calibration method)*

Screening option	Cost (£)	QALYs lost	ICER (£)	Adjusted ICER[a] (£)
No screening	571,286	3.21		
Screen at 3 years without AR	866,472	2.65	525,309	525,309
Screen at 4 years without AR	940,453	2.56	882,730	ED
Screen at 5 years without AR	1,019,832	2.50	1,181,134	ED
Screen at 3 years with AR	1,035,898	2.44	307,613	ED
Screen at 4 years with AR	1,112,874	2.34	758,272	758,272
Screen at 5 years with AR	1,211,504	2.33	9,090,556	9,090,556

AR, autorefraction.
[a] Adjusted ICERs are the ICERs with the dominated (D) or extendedly dominated (ED) options removed.

parameter values were sampled for each of the 5000 model iterations. In addition, a partially limited PSA was undertaken in which the utility decrement associated with unilateral vision loss was maintained at zero (in the full PSA it varied between 0 and 0.02).

The range of analyses within each set of sensitivity analyses was restricted, based on the reference case results. The reference case results established no significant differences between the alternative calibration methods and so subsequent results are only presented for the mean squared difference calibration approach. This approach was chosen as it most often represented the middle estimate of the outputs reported in *Tables 86–91*. *Table 92* summarises the range of one-way and multi-way sensitivity analyses undertaken and their impact on the estimated lifetime cost (downstream cost of amblyopia) and QALY input parameters.

TABLE 92 *Summary of deterministic sensitivity analyses undertaken*

Analysis	Lifetime cost (£)	QALY loss per case of amblyopia
Reference case: screening cost: £9.26 without autorefractor, £12.90 with autorefractor	225	0.0067
Low screening cost estimates [room rental = £0, 5 minutes screening (7 minutes with autorefractor), £1 cost per invitation, cost per screen]: £5.10 without autorefractor, £6.74 with autorefractor	225	0.0067
Blindness mortality effect (RR = 1.2)	218	0.0074
Increased incidence of bilateral vision loss (Rahi model 1[45])	425	0.0126
Unilateral vision loss utility decrement of 0.02	225	0.5384
Low screening cost estimates; increased incidence of bilateral vision loss (Rahi model 1[45]); including blindness mortality effect (RR = 1.2); and unilateral vision loss utility decrement of 0.02	412	0.5452
Decreased incidence of bilateral vision loss (Rahi model 3[45])	209	0.0062

RR, relative risk.

The results of the deterministic sensitivity analyses are presented in *Tables 94–99*; the relevant reference case results are reproduced in *Table 93*. The use of significantly low cost estimates for screening has some impact on the QALY ICER between no screening and screening at 3 years, reducing it from the reference case £340,750 to £261,238 per QALY gained. As the costs in the screening arms are reduced proportionately, the ICERs between the screening options do not change.

Raising the incidence of bilateral vision loss in amblyopic individuals shows a greater effect, as shown in *Table 95*. The QALY ICER for screening at 3 years almost halves, although it remains at over £260,000 per QALY gained. The ICERs between the screening programmes also decrease substantially, but remain very large.

Table 96 shows the impact of an increased likelihood of mortality for individuals with bilateral vision loss, which has a lesser effect, reducing the screening ICER only to £457,878, and leaving the the ICER from screening at 4 years to screening at 5 years at almost £10 million.

The parameter to which the results are most sensitive is the direct utility effect of unilateral vision loss, which is represented in *Table 97*. This sensitivity analysis shows that if unilateral vision loss is associated with even a small utility decrement, the effects are large. The lifetime model predicts that each person with amblyopia loses 0.5 discounted QALYs over their lifetime. This means that screening at 3 years without autorefraction results in a QALY gain of 45 QALYs in a population of 10,000 children, which translates into an ICER of £6546. Screening at

TABLE 93 *Reference case analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	574,673	482		3.22	
Screen at 3 years without AR	871,063	398	3,525	2.66	527,375
Screen at 4 years without AR	945,154	386	ED	2.58	ED
Screen at 5 years without AR	1,024,449	376	ED	2.51	ED
Screen at 3 years with AR	1,040,960	366	5,259	2.45	786,769
Screen at 4 years with AR	1,117,868	351	5,305	2.35	793,706
Screen at 5 years with AR	1,216,079	350	73,769	2.34	11,036,723

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 94 *Low screening cost estimates sensitivity analysis (population size 10,000)*

	Total costs (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	574,673	482		3.22	
Screen at 3 years without AR	829,494	398	3,031	2.66	453,411
Screen at 4 years without AR	903,585	386	ED	2.58	ED
Screen at 5 years without AR	982,880	376	D	2.51	D
Screen at 3 years with AR	979,390	366	4,640	2.45	694,148
Screen at 4 years with AR	1,056,298	351	5,305	2.35	793,706
Screen at 5 years with AR	1,154,510	350	73,769	2.34	11,036,723

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 95 *Increased incidence of bilateral vision loss sensitivity analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	671,115	482		6.09	
Screen at 3 years without AR	950,690	398	3,325	5.03	263,128
Screen at 4 years without AR	1,022,334	386	ED	4.88	ED
Screen at 5 years without AR	1,099,637	376	ED	4.75	ED
Screen at 3 years with AR	1,114,127	366	5,059	4.62	400,333
Screen at 4 years with AR	1,188,136	351	5,105	4.44	404,003
Screen at 5 years with AR	1,286,081	350	73,569	4.42	5,822,006

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 96 *Blindness mortality effect (relative risk = 1.2) sensitivity analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	576,338	482		3.57	
Screen at 3 years without AR	872,438	398	3,522	2.95	475,878
Screen at 4 years without AR	946,486	386	ED	2.86	ED
Screen at 5 years without AR	1,025,747	376	ED	2.78	ED
Screen at 3 years with AR	1,042,223	366	5,255	2.71	710,174
Screen at 4 years with AR	1,119,081	351	5,302	2.60	716,439
Screen at 5 years with AR	1,217,288	350	73,766	2.59	9,968,324

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

4 years with autorefraction is the most cost-effective option if society is willing to pay at least £10,000 per QALY gained. Screening at 5 years remains non-cost-effective with an ICER of over £100,000.

Combining all of the favourable assumptions demonstrates the dominance of the unilateral vision loss utility parameter, as the results presented in *Table 98* are similar to those presented for the unilateral vision loss sensitivity analysis alone.

Table 99 incorporates a decreased incidence of bilateral vision loss over an amblyope subject's remaining lifetime, which shows that the screening ICER increases slightly to £567,732.

TABLE 97 *Unilateral vision loss utility decrement of 0.02 sensitivity analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	574,891	482		259.66	
Screen at 3 years without AR	871,243	398	3,525	214.39	6,546
Screen at 4 years without AR	945,329	386	ED	207.80	ED
Screen at 5 years without AR	1,024,619	376	ED	202.44	ED
Screen at 3 years with AR	1,041,125	366	5,258	196.99	9,767
Screen at 4 years with AR	1,118,027	351	5,305	189.19	9,853
Screen at 5 years with AR	1,216,238	350	73,769	188.47	137,014

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 98 *Combined low screening cost estimates; increased incidence of bilateral vision loss, blindness mortality effect and unilateral vision loss utility decrement sensitivity analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	665,077	482		262.94	
Screen at 3 years without AR	945,705	398	3,338	217.10	6,122
Screen at 4 years without AR	1,017,502	386	ED	210.42	ED
Screen at 5 years without AR	1,094,930	376	ED	204.99	ED
Screen at 3 years with AR	1,109,546	366	5,071	199.48	9,302
Screen at 4 years with AR	1,183,737	351	5,118	191.58	9,387
Screen at 5 years with AR	1,281,699	350	73,582	190.85	134,963

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

TABLE 99 *Decreased incidence of bilateral vision loss sensitivity analysis (population size 10,000)*

	Total cost (£)	Amblyopia cases	Incremental cost per case prevented[a] (£)	QALYs lost	Incremental cost per QALY[a] (£)
No screening	567,405	482		3.01	
Screen at 3 years without AR	865,062	398	3,540	2.48	567,732
Screen at 4 years without AR	939,338	386	ED	2.41	ED
Screen at 5 years without AR	1,018,782	376	ED	2.34	ED
Screen at 3 years with AR	1,035,446	366	5,274	2.28	845,788
Screen at 4 years with AR	1,112,572	351	5,320	2.19	853,223
Screen at 5 years with AR	1,210,804	350	73,784	2.18	11,833,143

AR, autorefraction.
[a] Incremental cost with the dominated (D) or extendedly dominated (ED) options removed.

Given the impact of the unilateral vision loss utility parameter, two PSAs were undertaken. First, a full PSA is described in which the full set of cost and utility input parameter values were randomly sampled from defined distributions. Second, a restricted PSA is reported in which the cost and utility input parameter values are sampled, other than the unilateral vision loss utility decrement, which is kept constant at zero. The deterministic analyses established that screening programmes that did not include testing with an autorefractor were not cost-effective relative to screening programmes that did include autorefraction as a screening test. Hence the probabilistic sensitivity

analyses are limited to screening programmes with autorefraction.

The PSA generates credible intervals around the mean reference case cost-effectiveness results. The results of the full PSA are presented in *Table 100*, which shows that when the unilateral vision loss utility decrement parameter value is sampled from a uniform distribution between 0 and 0.02 (in combination with variation in all other input parameters), the mean ICER for screening at 3 years compared with no screening is £16,544. The upper credible interval remains high relative to accepted QALY values, at almost £120,000. The mean results show that screening at 4 years gains additional QALYs at a rate £21,957 per QALY, although the upper intervals shows that this option is dominated by screening at 3 years. Screening at 5 years is unlikely to be cost-effective.

The ICERs for cases of amblyopia prevented are not affected by the QALY estimates. These results show that there is relative certainty around the ICER for screening at 3 years compared with no screening, but that there is significant uncertainty around the other comparisons with upper interval showing that the earlier screening options dominate the later screening options.

The partial PSA (*Table 101*), in which no unilateral vision loss utility decrement is assumed, shows similar mean results to the reference case analysis, which is as expected given the relatively small impact of most of the parameters tested in the deterministic sensitivity analysis. The estimated credible intervals show that the QALY ICER for screening is unlikely to go below £0.25 million per QALY gained. The screening programmes at 4 and 5 years remain dominated at the upper intervals.

Cost-effectiveness acceptability frontiers are also presented for each PSA. For a range of monetary values representing society's willingness to pay to gain an additional unit of effect, the frontiers describe the probability that the screening option with the highest expected net benefits is the most cost-effective option. *Figure 7* presents the cost-effectiveness acceptability frontier for QALYs gains derived from the full PSA. This frontier shows that no screening has the highest expected net benefits from a value of a QALY of zero to around £17,000, with an associated high (although declining) probability of being cost-effective. Screening at 3 years has a relatively low probability of being cost-effective while having the highest expected net benefits at values between £18,000 and £22,000. Up to values of a QALY above £300,000, screening at 4 years has the highest expected net benefits, although the probability of cost-effectiveness remains at under 50%.

Figure 8 presents the final frontier, for QALYs gained from the PSA in which the unilateral vision

TABLE 100 *Full PSA (population size 10,000)*

	Total cost (£)	QALYs lost	QALY ICER (95% CI) (£)	Amblyopia cases	Amblyopia ICER (95% CI) (£)
No screening	604,531	116.78		482	
Screen at 3 years	1,069,717	88.61	16,544 (4,465 to 118,870)	366	3,995 (2,105 to 6,959)
Screen at 4 years	1,146,214	85.12	21,957 (3,828 to D)	351	5,277 (1,427 to D)
Screen at 5 years	1,244,953	84.81	316,463 (27,479 to D)	350	74,165 (9,210 to D)

D, dominated.

TABLE 101 *Partial PSA (population size 10,000)*

	Total cost (£)	QALYs lost	QALY ICER (95% CI) (£)	Amblyopia cases	Amblyopia ICER (95% CI) (£)
No screening	604,531	3.27		482	
Screen at 3 years	1,069,717	2.49	588,323 (289,631 to 1,181,154)	366	3,995 (2,105 to 6,959)
Screen at 4 years	1,146,214	2.39	775,378 (204,301 to D)	351	5,277 (1,427 to D)
Screen at 5 years	1,244,953	2.38	10,912,887 (1,313,260 to D)	350	74,165 (9,210 to D)

D, dominated.

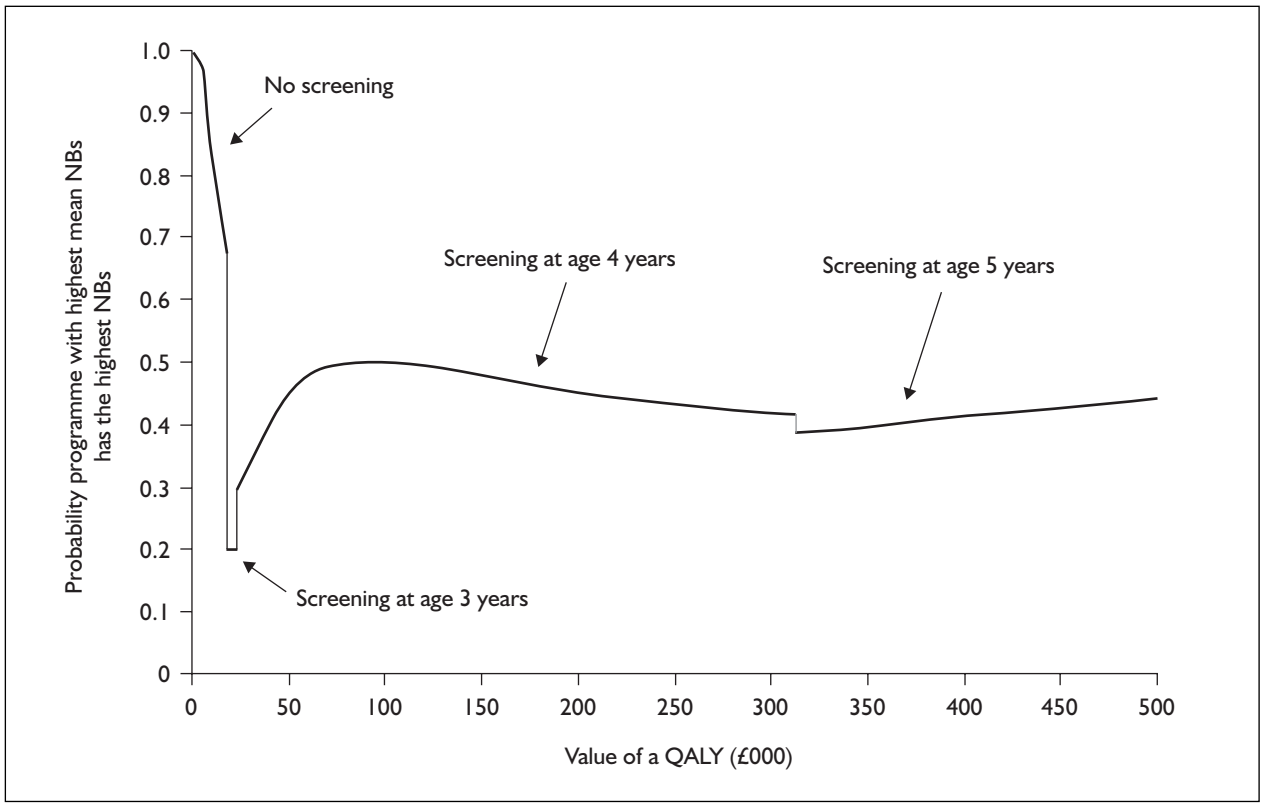

FIGURE 7 *Cost-effectiveness acceptability frontier for QALYs gained: full probabilistic analysis. NB, net benefit.*

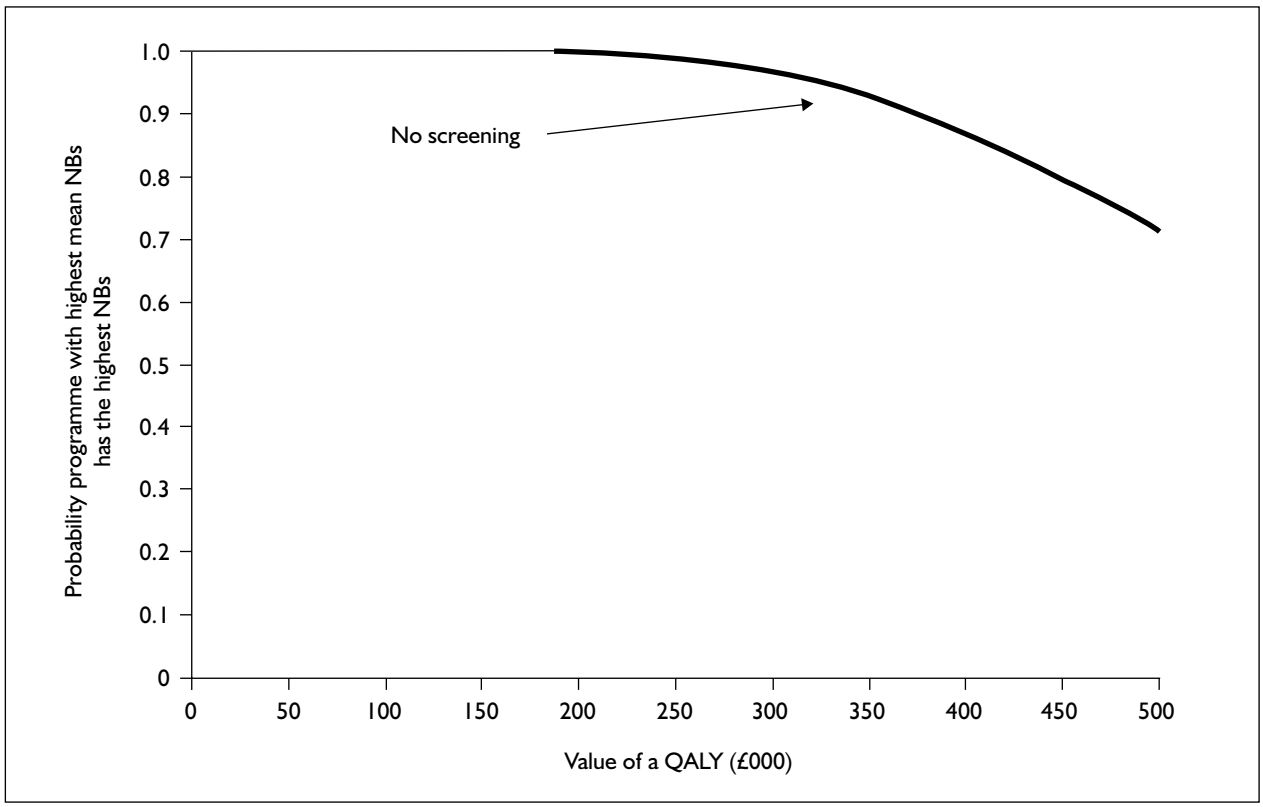

FIGURE 8 *Cost-effectiveness acceptability frontier for QALYs gained: partial probabilistic analysis (unilateral vision loss utility decrement = 0). NB, net benefit.*

loss utility decrement parameter was kept constant at zero. The frontier shows that no screening is expected to produce the most net benefits up to a value of a QALY of £0.5 million. The probability of cost-effectiveness starts at 100%, and remains at 70% at a value of £0.5 million per QALY.

Expected value of perfect information analyses

The EVPI is defined as the difference in the expected payoff of decisions using perfect information and the payoff using the currently available information, which is a function of the value of a QALY. The method of analysis is described in Chapter 8. Two sets of EVPI analyses are reported. *Figure 9* presents the EVPI based on the full PSA in which the unilateral vision loss utility decrement varied between 0 and 0.02. The kinks in the curve occur at the QALY values at which the mean cost-effectiveness decision changes, that is, the screening option with the highest net benefits changes. The curve shows that the value of eliminating uncertainty rises rapidly to a QALY value of £17,000 while no screening remains the option with the highest net benefits. At a value of £17,000 for the estimated population of 2.6 million children, the EVPI reaches almost £45 million. As the QALY value increases and screening options have the highest mean net benefits, the $EVPI_{population}$ decreases until the value of a QALY is around £65,000 and then it starts to rise again.

Figure 10 presents the EVPI for the second PSA, in which the unilateral vision loss utility decrement was held constant at zero (i.e. assuming no utility effect). The curve indicates that the $EVPI_{population}$, even for a population of 2.6 million, is negligible until the QALY value increases to well past £100,000. The costs of uncertainty then increase to around £170,000 at a QALY value of £250,000, while no screening remains the preferred option.

Conclusions

The amblyopia screening model was analysed in detail to estimate the cost and effects of six alternative screening options comprising screening at different ages (3, 4 and 5 years) and using alternative sets of tests (VA testing and cover–uncover tests, with and without autorefraction). The reference cases results showed that screening programmes that included autorefraction dominated or near dominated screening programmes without autorefraction.

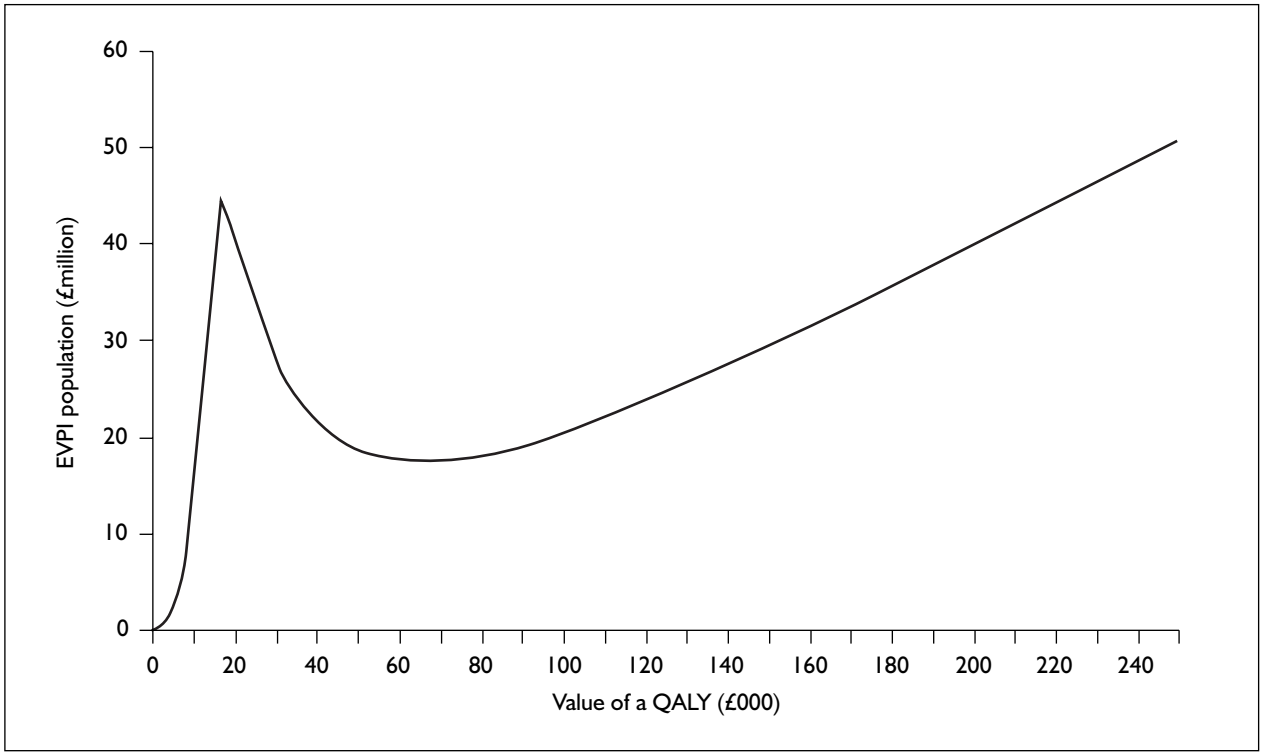

FIGURE 9 *EVPI for the full PSA*

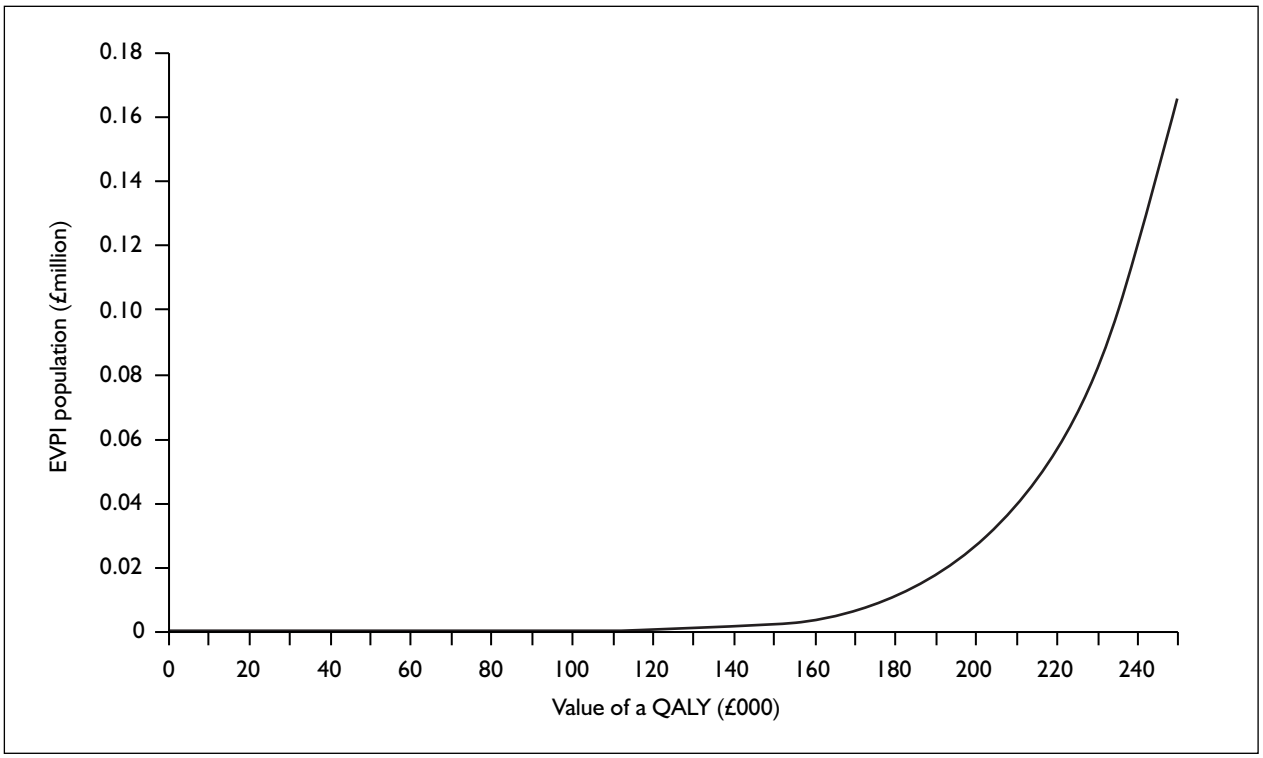

FIGURE 10 *EVPI for the restricted PSA*

Analyses based on the cost per case of amblyopia prevented showed that screening at either 3 or 4 years prevented cases at a low absolute cost (£4000–6000). However, when these results were extrapolated to estimate the cost per QALY gained, the main finding of the reference case analysis is that any form of screening is unlikely to be cost-effective at currently accepted values of a QALY.

The wide-ranging sensitivity analyses found that the results were robust to most parameter changes. The only parameter that radically affected the results was the unilateral vision loss utility decrement parameter, which describes the utility effect of loss of vision in one eye. No direct evidence of a utility effect was identified and the reference case assumed no effect. When a small effect of 0.02 is assumed (i.e. a reduction in utility of 2%), the incremental cost per QALY gained becomes extremely attractive for screening both at 3 years and 4 years.

The latter analyses of the EVPI showed a large EVPI when the unilateral vision loss utility decrement parameter was allowed to vary, but not when it was kept constant at zero.

Chapter 10
Discussion

The preceding chapters have described the range of evidence available to support an evaluation of the cost-effectiveness of alternative screening programmes for the detection and treatment of amblyopia and amblyogenic factors, including strabismus.

Summary of evaluative framework

The systematic review elicited little robust evidence as to the UK prevalence of amblyopia, strabismus and refractive error in children aged up to 7 years. As such, for the purpose of the model, assumptions of prevalence were informed from the relevant UK population studies.

The evidence of statistically significant risk factors associated with amblyopia and strabismus is weak, and the results are not able to inform the development or existence of a suitable screening programme. Screening for amblyopia or strabismus on the basis of ethnicity, low birth weight, maternal smoking during pregnancy or maternal age is neither practical nor appropriate. Children born with very low birth weight or systemic health problems are recognised to be at increased risk of developing amblyopia, strabismus and/or refractive error. However, such children are monitored within the healthcare system under the care of a paediatrician. To this end, it is assumed that any screening programme will be directed at the general population as a whole.

Published data informed by UK studies regarding the type of tests which may be employed as part of a screening programme for amblyopia and strabismus are scarce. The introduction of log-based VA tests within clinical practice invalidates a number of studies, as the use of single optotypes without crowding or standardised progression has been recommended.[106] The use of photoscreening across the UK is varied, with a range of photoscreening equipment available. Published data regarding the sensitivity and specificity of such equipment in a study population similar to that of the UK general population have not been widely identified. The inclusion of stereotests within a screening programme could also be questioned.

Evidence to demonstrate the impact of screening programmes was identified. Papers describing such programmes differ widely in the content of the screening programme itself, the population group examined and the personnel administering the screening. Published data regarding which healthcare professionals should administer visual screening is supportive of orthoptist-led programmes. This is in agreement with published guidelines from professional bodies such as the Royal College of Ophthalmologists.[106]

Successful treatment of amblyopia has been reported using a variety of treatment modalities. Conventional occlusion has been demonstrated to improve VA. The amount of occlusion prescribed appears to affect the rate of VA improvement rather than the final VA outcome. That is, a successful visual outcome may be achieved with few hours of occlusion prescribed over a long treatment period compared with increased hours of occlusion prescribed over a short treatment period. Atropine has also been demonstrated as an appropriate treatment method, with weekend-use atropine shown to be as effective as daily atropine in the treatment of moderate amblyopia. Age at start of amblyopia therapy is a factor in treatment outcome; overall improvement in VA appears to increase significantly with decreasing age. Maintenance and regression of acuity following cessation of treatment have been shown to exist in all types of amblyopia, and following all types of treatment modalities.

The lack of evidence supporting the treatment of strabismus is unsurprising. The outcome measures for strabismus treatment could include restoration of binocularity or improvement in cosmetic appearance. As the presence of strabismus is an amblyogenic factor, treatment could also be considered in terms of reducing amblyopia development. The most appropriate outcome measure may differ depending on a clinician or parent/guardian perspective. Parents/guardians may rank cosmetic appearance as a greater priority to binocular status.

RCTs into the efficacy, effectiveness and efficiency of strabismus treatment are unlikely to be feasible. Ethical considerations in study design prevent

complete abstention of treatment, and decisions regarding treatment are often overridden by clinical need.

Published literature on investigations of the impact of amblyopia therapy upon family life exists. However, none of the studies have adequately addressed the effect of treatment on HRQoL from the child's perspective. Parental reports may provide a substitute for children's HRQoL, but large differences have been shown to exist in proxy agreement at the child–parent level.[155]

The literature suggests that surgical intervention for strabismus leads to improvements in QoL. As with amblyopia, no studies could be found that have appropriately addressed the effect of treatment of strabismus upon HRQoL from the child's perspective. There is a need for paediatric disease-specific HRQoL measures to assess the impact of amblyopia and/or strabismus and their respective treatment.

In addition to the data extracted from the literature reviews, primary data from the ALSPAC and data collected as part of the existing screening programme in Birmingham were also made available. Chapter 8 described the modelling framework that was used to synthesise the data to estimate the costs and effects of screening estimated over the lifetime of a cohort of 10,000 children. The final screening model comprised 120 vision states, although initial plans for an even more complex screening model were necessarily simplified due to the lack of data available to estimate detailed relationships between relevant input parameters. The choice of modelling framework is justified on the basis that there is a practical limit to the subjective estimation of model parameters in the absence of data.

Interpretation of results

The results reported in Chapter 9 showed that screening programmes that included autorefraction dominated screening programmes without autorefraction and so the subsequent analysis concentrated on screening programmes that included autorefraction.

Analyses of the cost per case of amblyopia prevented showed that screening at either 3 or 4 years prevented cases at a low absolute cost (£4000–6000), although it is difficult to interpret these results as the value of preventing amblyopia *per se* is unknown. Therefore, the model extrapolated the screening model end-point (of cases of amblyopia) to a lifetime horizon to estimate the cost per QALY gained. The QALY is a generic outcome measure that represents 1 year spent in perfect (or the best imaginable) health, thus incorporating survival and QoL effects. Utility weights are attached to health states, where a value of zero indicates that state is judged to be equivalent to death and a value of one represents a state equivalent to perfect health. The products of the time spent in different health states and their respective utility weights are summed across the time horizon of an evaluation to estimate the total number of QALYs gained. Although there are methodological difficulties in estimating the utility weights, the great advantage of the QALY as an outcome measure is that it can be used to evaluate all possible healthcare interventions. Comparisons can then be made of the relative effectiveness and cost-effectiveness of interventions across disease areas.

In the UK, decisions made by NICE have been used to imply an approximate value of a QALY of between £20,000 and £30,000.[181] In other words, interventions that gain QALYs at an incremental cost of less than £20,000–30,000 are considered to be a cost-effective use of resources.

The reference case analysis demonstrated that no form of screening for amblyopia is likely to be cost-effective at currently accepted values of a QALY. The wide-ranging sensitivity analyses found that the results were robust to most parameter changes. The only parameter that significantly affected the results described the utility effect of loss of vision in one eye. No direct evidence of a utility effect was identified and the reference case assumed no effect. When a small effect of 0.02 is assumed (i.e. a reduction in utility of 2%), the incremental cost per QALY gained becomes extremely attractive for screening at both 3 and 4 years. Further analyses of the EVPI showed that the potential benefits of further research were large when the unilateral vision loss utility decrement parameter was allowed to vary, but not when it was kept constant at zero.

Following the analysis of the final version of the amblyopia screening model, and linked lifetime effect model (as reported in Chapter 9), we were further persuaded that a more complex screening model would not radically alter the conclusions drawn from the model. This is because the main model results (the incremental cost per QALY estimates) are driven primarily by the utility effects of amblyopia. As an example, doubling the

difference in the number of cases of amblyopia remaining in a population of 10,000 children between no screening and screening at 3 years from 0.8 to 1.6 reduces the incremental cost per QALY from around £600,000 to £300,000. Screening remains extremely inefficient.

The evidence suggests that the physical impact of unilateral vision loss is minimal, in terms of reduced ability to undertake everyday activities. The only utility study to assess the impact of unilateral vision loss hypothesised about a non-physical impact of amblyopia, although Brown and colleagues[172] did not apply appropriate methods to quantify such an impact properly. A well-planned utility study that managed to elicit unbiased and representative estimates of utility in individuals with and without amblyopia (and no bilateral vision loss) would provide a very useful input to update the analyses described in this report. If a utility difference is assumed, even a small effect, screening for amblyopia is likely to be a cost-effective option.

A key reason for identifying and treating amblyopia is often cited as the risk of visual impairment for a person with amblyopia if sight from the good eye is lost through injury or disease. The relevant literature reviewed in Chapter 3 suggests that there is no definitive evidence of a difference in the probabilities of losing vision in the non-amblyopic eye of an amblyope and losing vision in one of two eyes of a non-amblyope. This implies that amblyopes are twice as likely to experience bilateral vision loss, particularly at younger ages where vision loss is mostly related to accidents that occur with independence between the eyes. At old ages, vision loss in one eye due to disease is commonly a risk factor for vision loss in the second eye. However, in the absence of a long-term utility impact of unilateral vision loss, the prevention of the utility loss derived from the increased risk of bilateral vision loss in amblyopes is not sufficient to justify resource use on screening programmes for amblyopia.

From the review of the QoL effects associated with amblyopia, most effects were found to be related to the treatment of amblyopia. A possible argument for screening may be made around the prevention of childhood negative effects of treatment. In the absence of screening, children presenting with amblyopia will generally be treated at a later age, and the evidence suggests that the likelihood of bullying increases with increasing age at treatment. If children are screened and treated preschool, then the incidence of bullying among amblyopes may decrease.

A full review of the magnitude of the short- and long-term effects of bullying was beyond the scope of this study, although two threshold analyses were undertaken to investigate the potential effect of utility decrements associated with bullying. In the first analysis, a QALY decrement was assigned to all children receiving treatment for refractive error, strabismus and/or amblyopia. The QALY decrement was varied to estimate the number of QALYs that would need to be lost per child in order for screening at 3 years to achieve an incremental cost per QALY of under £30,000 compared with no screening. *Table 102* presents the mean cost-effectiveness results from this analysis, which show that if every treated child loses the equivalent of 10% of one QALY as a result of treatment, the incremental cost per QALY gained of moving from no screening to screening at 3 years is £34,401. Screening at later ages is dominated by no screening as well as screening at 3 years due to the increased rate of school-age intervention.

Table 103 presents the results from the second analysis, in which a QALY decrement is only applied to children receiving treatment for amblyopia. These results show that if every child treated for amblyopia after the age of 4 years experiences a loss equivalent to 50% of one QALY, the incremental cost per QALY gained of moving from no screening to screening at 3 years is £37,851.

TABLE 102 *Cost-effectiveness results when assuming a QALY loss of 0.1 for every child receiving treatment for amblyogenic factors and/or amblyopia*

	Total cost (£)	QALYs lost	Incremental cost per QALY (£)
No screening	744,320	51	
Screen at 3 years	1,142,665	39	34,401
Screen at 4 years	1,256,962	84	D
Screen at 5 years	1,388,966	95	D

D, dominated.

TABLE 103 *Cost-effectiveness results when assuming a QALY loss of 0.5 for every child receiving treatment for amblyopia*

	Total cost (£)	QALYs lost	Incremental cost per QALY (£)
No screening	744,320	83	
Screen at 3 years	1,142,665	72	37,851
Screen at 4 years	1,256,962	162	D
Screen at 5 years	1,388,966	179	D

D, dominated.

The evaluation did not incorporate utility effects associated with strabismus. Although the psychosocial implications of strabismus are more accepted and recognised (as reported in Chapter 6), most studies showed that surgical intervention for strabismus leads to improvements in QoL. However, we have assumed that individuals with strabismus that impacts on HRQoL will present clinically. No evidence of treatment effect varying with age was identified, so it is also assumed that the likelihood of effective treatment is independent of age. Therefore, the principal value of identifying strabismus at an earlier age is to attempt to treat the strabismus in order to remove it as an amblyogenic factor.

Conclusions

The cost-effectiveness results from the amblyopia screening and lifetime models show that the cost-effectiveness of screening for amblyopia is dependent on the long-term utility effects of unilateral vision loss. There is limited evidence on any such effect, although our subjective interpretation of the available literature is that the utility effects are likely to be minimal. Any utility study investigating such effects would need to be careful to avoid introducing bias as demonstrated in the study reported by Brown and colleagues.[170]

The reference case model did not represent potential treatment-related utility effects, primarily due to an increased probability of treated children being bullied at school. The evidence indicates that this may be a problem, and additional sensitivity analyses show that small utility effects of bullying would improve the cost-effectiveness of early screening significantly. A prospective study of the utility effects of bullying would usefully inform the analysis, although such a study would need to be carefully planned in order to distinguish whether the overall incidence of bullying decreases with reduced school-age treatment, or whether it is displaced to other children.

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Contribution of authors

Jill Carlton (Research Associate) reviewed the literature and prepared the report. Jon Karnon (Senior Research Fellow) designed the cost-effectiveness proposal, carried out the cost-effectiveness model and prepared the report. Carolyn Czoski-Murray (Research Fellow) designed the effectiveness proposal, reviewed the literature and helped to prepare the report. Kevin J Smith (Honorary Senior Clinical Lecturer in Public Health Medicine, Medical Advisor to the Yorkshire and the Humber Regional Specialised Commissioning Group) contributed to the design of the study, assisted with the selection of the literature and the model assumptions and helped to prepare the report. Jane Marr (Consultant Ophthalmologist) contributed to the design of the study, assisted with the model assumptions and helped to prepare the report.

References

1. Snowdon SK, Stewart-Brown SL. Preschool vision screening. *Health Technol Assess* 1997;**1**(8).
2. Kleinstein RN, Jones LA, Hullett S, Kwon S, Lee RJ, Friedman NE, *et al*. Refractive error and ethnicity in children. *Arch Ophthalmol* 2003;**121**:1141–7.
3. National Screening Committee. *NSC Criteria for appraising the viability, effectiveness and appropriateness of a screening programme*. National Screening Committee; 2003. URL: www.nsc.nhs.uk/pdfs/Criteria.pdf
4. Garber AM, Wieinstein MC, Torrance GW, Kamlet MS. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press; 1996.
5. Gold MR, Siegel JE, Russell LB, Weinstein MC. Theoretical foundations of cost-effectiveness analysis. In Garber AM, Weinstein MC, Torrance GW, Kamlet MS, editors. *Cost-effectiveness in health and medicine*. Oxford: Oxford University Press; 1996. Chapter 2, pp. 25–53.
6. Policy statement: eye examination in infants, children, and young adults by pediatricians. *Pediatrics* 2003;**111**:902–7.
7. Simons K. Preschool vision screening: rationale, methodology and outcome. *Surv Ophthalmol* 1996;**41**:3–30.
8. Simons K. Amblyopia characterization, treatment, and prophylaxis. *Surv Ophthalmol* 2005;**50**:123–66.
9. Kemper A, Harris R, Lieu TA, Homer CJ, Whitener BL. *Screening for visual impairment in children younger than age 5 years: a systematic evidence review for the US Preventive Services Task Force (Provisional record)*. Rockville: US Preventive Services Task Force, 2004. p. 55.
10. Powell C, Wedner S, Richardson S. Screening for correctable visual acuity deficits in school-age children and adolescents. *Cochrane Database Syst Rev* 2004;(4):1–14.
11. Flom MC, Neumaier RW. Prevalence of amblyopia. *Public Health Rep* 1966;**81**:329–41.
12. Hopkisson B, Clarke JR, Oelman BJ. Residual amblyopia in recruits to the British Army. *BMJ* 1982;**285**:940.
13. Stewart-Brown S, Butler N. Visual acuity in a national sample of 10 year old children. *J Epidemiol Commun Health* 1985;**39**:107–12.
14. Newman DK, East MM. Prevalence of amblyopia among defaulters of preschool vision screening. *Ophthalmic Epidemiol* 2000;**7**:67–71.
15. Graham PA. Epidemiology of strabismus. *Br J Ophthalmol* 1974;**58**:224–31.
16. Stidwill D. Epidemiology of strabismus. *Ophthalmic Physiol Opt* 1997;**17**:536–9.
17. Bruce A, Hurst M, Abbott H, Harrison H. The incidence of refractive error and anomalies of binocular vision in infants. *Br Orthoptic J* 1991;**48**: 32–5.
18. McNeil J. Patterns of visual defects in children. *BMJ* 1955;**39**:688–701.
19. Cole RBW. The problem of unilateral amblyopia. *BMJ* 1959;**1**:202–6.
20. da Cunha D, Jenkins EM. Amblyopia in three year olds. *Med Officer* 1961;**106**:146–8.
21. Theodore FH, Johnson RM, Miles NE, Bonser WH. Causes of impaired vision in recently inducted soldiers. *Arch Ophthalmol* 1944;**31**: 399–402.
22. Downing AH. Ocular defects in 60,000 selectees. *Arch Ophthalmol* 1945;**33**:137–45.
23. Glover LP, Brewer WR. Ophthalmologic review of more than 20,000 men at the Altoona induction center. *Am J Ophthalmol* 1944;**27**:346–8.
24. Agaston H. Ocular malingering. *Arch Ophthalmol* 1944;**31**:223–31.
25. Helveston EM. The incidence of amblyopia ex anopsia in young adult males in Minnesota in 1962–63. *Am J Ophthalmol* 1965;**60**:75–7.
26. Cholst MR, Cohen IJ, Losty MA. Evaluation of amblyopia problem in the child. *NY Med J* 1962;**62**:3927–30.
27. de Rotth A. Statistical analysis of 1,000 consecutive new eye patients. *Am J Ophthalmol* 1945;**28**: 1329–34.
28. Russell FL, Kada JM, Hufhines DM. Orange County vision screening project, part 2. Ophthalmological evaluation. *Sight-Saving Rev* 1965;**31**:215–19.
29. Vaughan D, Cook R, Bock R. *Eye test for preschool and school age children*. Stockton, CA: California Medical Eye Council; 1960.
30. Alberman ED, Butler NR, Sheridan MD. Visual acuity of a national sample (1958 cohort) at 7 years. *Dev Med Child Neurol* 1971;**13**:9–14.
31. Commission for Racial Equality. *Ethnic minorities in Great Britain*. 2007. URL: http://www.cre.gov.uk/downloads/factfile02_ethnic_minorities.pdf

32. MacEwen CJ, Chakrabarti HS. Why is squint surgery in children in decline? *Br J Ophthalmol* 2004;**88**:509–11.

33. Arora A, Williams B, Arora AK, McNamara R, Yates J, Fielder A. Decreasing strabismus surgery. *Br J Ophthalmol* 2005;**89**:412.

34. Dobson V, Fulton AB, Sebris SL. Cycloplegic refractions of infants and young children: the axis of astigmatism. *Invest Ophthalmol Vis Sci* 1984;**25**: 83–7.

35. Gwiazda J, Thorn F, Bauer J, Held R. Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. *Clin Vis Sci* 1993;**8**:337–44.

36. Gwiazda J, Scheiman M, Mohindra I, Held R. Astigmatism in children: changes in axis and amount from birth to six years. *Invest Ophthalmol Vis Sci* 1984;**25**:88–92.

37. Abrahamsson M, Fabian G, Andersson AK, Sjostrand J. A longitudinal study of a population based sample of astigmatic children. I. Refraction and amblyopia. *Acta Ophthalmol* 1990;**68**:428–34.

38. Abrahamsson M, Fabian G, Sjostrand J. A longitudinal study of a population based sample of astigmatic children. II. The changeability of anisometropia. *Acta Ophthalmol* 1990;**68**:435–40.

39. Dobson V, Sebris SL. Longitudinal study of acuity and stereopsis in infants with or at-risk for esotropia. *Invest Ophthalmol Vis Sci* 1989;**30**:1146–58.

40. Townshend AM, Holmes JM, Evans LS. Depth of anisometropic amblyopia and difference in refraction. *Am J Ophthalmol* 1993;**116**:431–6.

41. Donahue SP. The relationship between anisometropia, patient age, and the development of amblyopia. *Trans Am Ophthalmol Soc* 2005;**103**:313–36.

42. Ingram RM, Gill LE, Goldacre MJ. Emmetropisation and accommodation in hypermetropic children before they show signs of squint – a preliminary analysis. *Bull Soc Belge Ophtalmol* 1994;**253**:41–56.

43. Abrahamsson M, Sjostrand J. Natural history of infantile anisometropia. *Br J Ophthalmol* 1996;**80**:860–3.

44. Ingram RM, Walker C, Wilson JM, Arnold PE, Dally S. Prediction of amblyopia and squint by means of refraction at age 1 year. *Br J Ophthalmol* 1986;**70**:12–15.

45. Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. *Lancet* 2002;**360**:597–602.

46. Tommila V, Tarkkanen A. Incidence of loss of vision in the healthy eye in amblyopia. *Br J Ophthalmol* 1981;**65**:575–7.

47. Sorsby A. *The incidence and causes of blindness in England and Wales 1963–68. With an appendix on services available for incipient blindness*. Reports on Public Health and Medical Subjects, No. 128. London: Department of Health and Social Security; 1972.

48. Vereecken EP, Brabant P. Prognosis for vision in amblyopia after the loss of the good eye. *Arch Ophthalmol* 1987;**102**:220–4.

49. Rahi JS, Logan S, Borja MC, Timms C, Russell-Eggitt I, Taylor D. Prediction of improved vision in the amblyopic eye after visual loss in the non-amblyopic eye. *Lancet* 2002;**360**:621–2.

50. Kandel GL, Grattan PE, Bedell HE. Are the dominant eyes of amblyopes normal? *Am J Optom Physiol Opt* 1980;**57**:1–6.

51. Laws D, Noonan CP, Ward A, Chandna A. Binocular fixation pattern and visual acuity in children with strabismic amblyopia. *J Pediatr Ophthalmol Strabismus* 2000;**37**:24–8.

52. Chew E, Remaley NA, Tamboli A, Zhao J, Podgon MJ, Klebanoff M. Risk factors for esotropia and exotropia. *Arch Ophthalmol* 1994;**112**:1349–55.

53. Zipf RF. Binocular fixation pattern. *Arch Ophthalmol* 1976;**94**:401–5.

54. Simmers AJ, Gray LS, Spowart K. Screening for amblyopia: a comparison of paediatric letter tests. *Br J Ophthalmol* 1997;**81**:465–9.

55. Newman DK, East MM. Preschool vision screening: negative predictive value for amblyopia. *Br J Ophthalmol* 1999;**83**:676–9.

56. Schmidt P, Maguire M, Dobson V, Quinn G, Ciner E, Cyert L, *et al*. Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision In Preschoolers Study. *Ophthalmology* 2004;**111**:637–50.

57. Ying GS, Kulp MT, Maguire M, Ciner E, Cyert L, Schmidt P, *et al*. Sensitivity of screening tests for detecting vision in preschoolers-targeted vision disorders when specificity is 94%. *Optom Vis Sci* 2005;**82**:432–8.

58. Williams C, Harrad RA, Harvey I, Sparrow JM, ALSPAC Study Team. Screening for amblyopia in preschool children: results of a population-based, randomised controlled trial. *Ophthalmic Epidemiol* 2001;**8**:279–95.

59. Pott JW, Oosterveen DK, Van Hof-van Duin J. Screening for suppression in young children: the polaroid suppression test. *J Pediatr Ophthalmol Strabismus* 1998;**35**:216–22.

60. Pott JW, Kingma C, Verhoeff K, Grootendorst RJ, de Faber JT. The polaroid suppression test in a pediatric population with ophthalmologic disorders. *J AAPOS* 2003;**7**:137–41.

61. Morale SE, Jeffrey BG, Fawcett SL, Stager DR, Salomao SR, Berezovsky A, *et al*. Preschool Worth 4-Shape test: testability, reliability, and validity. *J AAPOS* 2002;**6**:247–51.

62. Ruttum MS, Nelson DB. Stereopsis testing to reduce overreferral in preschool vision screening. *J Pediatr Ophthalmol Strabismus* 1991;**28**:131–3.

63. Schmidt PP, Maguire MG, Moore B, Cyert L, Vision in Preschoolers Study Group. Testability of preschoolers on stereotests used to screen vision disorders. *Optom Vis Sci* 2003;**80**:753–7.

64. Kohl P, Samek M. Refractive error and preferential looking visual acuity in infants 12–24 months of age: year 2 of a longitudinal study. *J Am Optom Assoc* 1988;**59**:686–90.

65. Kennedy R, Sheps SB, Bagaric D. Field trial of the Otago photoscreener. *Can J Ophthalmol* 1995;**30**: 193–7.

66. Ottar WL, Scott WE, Holgado SI. Photoscreening for amblyogenic factors. *J Pediatr Ophthalmol Strabismus* 1995;**32**:289–95.

67. Donahue SP, Johnson TM, Ottar W, Scott WE. Sensitivity of photoscreening to detect high-magnitude amblyogenic factors. *J AAPOS* 2002;**6**: 86–91.

68. Hatch SW, Tibbles CD, Mestito IR, Read R, Traveis L, Richman J. Validity and reliability of the MTI Photoscreener. *Optom Vis Sci* 1997;**74**:859–64.

69. Cordonnier M, Dramaix M. Screening for refractive errors in children: accuracy of the hand held refractor Retinomax to screen for astigmatism. *Br J Ophthalmol* 1999;**83**:157–61.

70. Cordonnier M, Kallay O. Non-cycloplegic screening for refractive errors in children with the hand-held autorefractor Retinomax: final results and comparison with non-cycloplegic photoscreening. *Strabismus* 2001;**9**:59–70.

71. Barry JC, Konig HH. Non-cycloplegic screening for amblyopia via refractive findings with the Nikon Retinomax hand held autorefractor in 3 year old kindergarten children. *Br J Ophthalmol* 2001;**85**:1179–82.

72. Williams C, Lumb R, Harvey I, Sparrow JM. Screening for refractive errors with the Topcon PR2000 Pediatric Refractometer. *Invest Ophthalmol Vis Sci* 2000;**41**:1031–7.

73. Allen SM. The effectivity of screening a comparative study of visual screening. *Br Orthoptic J* 1990;**47**:57–60.

74. Jarvis SN, Tamhne RC, Thompson L, Francis PM, Anderson J, Colver AF. Preschool vision screening. *Arch Dis Child* 1991;**66**:288–94.

75. Allen JW, Bose B. An audit of preschool vision screening. *Arch Dis Child* 1992;**67**:1292–3.

76. De Becker I, MacPherson HJ, LaRoche GR, Braunstein J, Cottle R, McIntyre LL, *et al*. Negative predictive value of a population-based preschool vision screening program. *Ophthalmology* 1992;**99**:998–1003.

77. Williamson TH, Andrews R, Dutton GN, Murray G, Graham N. Assessment of an inner city visual screening programme for preschool children. *Br J Ophthalmol* 1995;**79**:1068–73.

78. McNamara R, Duckworth S. The effect of removing vision testing from child surveillance programmes. *Br Orthoptic J* 1998;**66**:26–31.

79. Robinson B, Bobier WR, Martin E, Bryant L. Measurement of the validity of a preschool vision screening program. *Am J Public Health* 1999;**89**: 193–8.

80. Mulley L. The Airedale Vision Screening Programme: a comparison of referral rates between two preschool age groups. *Br Orthoptic J* 2000;**57**:39–41.

81. Eibschitz-Tsimhoni M, Friedman T, Naor J, Eibschitz N, Friedman Z. Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia. *J AAPOS* 2000;**4**:194–9.

82. Juttmann R, Rotterdam AMblyopia Screening Effectiveness Study (RAMSES) Steering Committee. The Rotterdam AMblyopia Screening Effectiveness Study (RAMSES): compliance and predictive value in the first 2 years. *Br J Ophthalmol* 2001;**85**:1332–5.

83. Barry JC, Konig HH. Test characteristics of orthoptic screening examination in 3 year old kindergarten children. *Br J Ophthalmol* 2003;**87**:909–16.

84. Chui L, Fraser T, Hoar K, LaRoche GR. Negative predictive value of a vision screening program aimed at children aged 3 to 4 years old. *J AAPOS* 2004;**8**:566–70.

85. Rosner J, Rosner J. Parents as screeners for strabismus in their children. *J Vis Impairment Blindness* 1988;**82**:193–4.

86. Paysse EA, Camejo L, Hussein MA, Coats DK. Parent-administered visual acuity testing: is it reliable and can it improve office efficiency? *J AAPOS* 2004;**8**:332–7.

87. The Vision in Preschoolers Study Group. Preschool vision screening tests administered by nurse screeners compared with lay screeners in the vision in preschoolers study. *Invest Ophthalmol Vis Sci* 2005;**46**:2639–48.

88. Edwards RS, Whitelaw AJ, Abbott AG. Orthoptists as pre-school screeners: a 2-year study. *Br Orthoptic J* 1989;**46**:14–19.

89. Bolger PG, Stewart-Brown SL, Newcombe E, Starbuck A. Vision screening in preschool children: comparison of orthoptists and clinical medical officers as primary screeners. *BMJ* 1991;**303**: 1291–4.

90. Bray LC, Clarke MP, Jarvis SN, Francis PM, Colver A. Preschool vision screening: a prospective comparative evaluation. *Eye* 1996; **10**:714–18.

91. Kohler L, Stigmar G. Visual disorders in 7-year-old children with and without previous vision screening. *Acta Paediatr Scand* 1978;**67**:373–7.

92. Edwards RS, Abbott AG, Whitelaw AJ. The outcome of pre-school visual screening. *Br Orthoptic J* 1993;**50**:2–6.

93. Newman DK, Hitchcock A, McCarthy H, Keast-Butler J, Moore AT. Preschool vision screening: outcome of children referred to the hospital eye service. *Br J Ophthalmol* 1996;**80**: 1077–82.

94. Harrad RA, Williams C, Sparrow JM, Northstone K, Harvey I. Visual acuity at 7 years after orthoptic screening at different ages – results of a randomised controlled trial. *Invest Ophthalmol Vis Sci* 2002;**43**:e-Abstract 2941.

95. Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I, ALSPAC Study Team. Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial. *BMJ* 2002;**324**:1549.

96. Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I. Amblyopia treatment outcomes after preschool screening v school entry screening: observational data from a prospective cohort study. *Br J Ophthalmol* 2003;**87**:988–93.

97. Bui CM, Donahue SP. Long-term follow-up of patients with amblyopia initially identified by preschool photoscreening. *Invest Ophthalmol Vis Sci* 2006;**47**:e-Abstract 2936.

98. Hall DMB, Elliman D. *Health for all children*. 4th ed. 2003.

99. National Screening Committee. *Vision screening in children under five years old.* Child Health Sub-Group Report on Vision Screening. London: National Screening Committee; 2005. URL: www.library.nhs.uk/SpecialistLibrarySearch/Download.aspx?resID=88202

100. Hall DMB, Stewart-Brown K. Screening in child health. *Br Med Bull* 1998;**54**:929–43.

101. Department of Health, Social Services and Public Safety. *Health for all children: guidance and principles of practice for professional staff*. Department of Health; 2006 URL: http://www.dhsspsni.gov.uk/guidance_and_principles_of_practice_for_professional_staff_health_for_all_children.pdf

102. Stewart CE. LogMAR-based visual acuity measurements: limits of normality. *Br Ir Orthoptic J* 2006;**3**:9–13.

103. Jones D, Westall C, Averbeck K, Abdolell M. Visual acuity assessment: a comparison of two tests for measuring children's vision. *Ophthalmic Physiol Opt* 2003;**23**:541–6.

104. Stewart C. Comparison of Snellen and log-based acuity scores for school-aged children. *Br Orthoptic J* 2000;**57**:32–8.

105. Shea SJ, Gaccon L. In the absence of strabismus what constitutes a visual deficit in children? *Br J Ophthalmol* 2006;**90**:40–3.

106. Royal College of Ophthalmologists. *Ophthalmic services for children*. Royal Society of Health Journal; 2005. URL: http://rcophth.ac.uk/docs/profstands/ophthalmicservices/OphthalmicServicesforChildrenMay2005.pdf

107. Epelbaum M, Milleret C, Buisseret P, Dufier JL. The sensitive period for strabismic amblyopia in humans. *Ophthalmology* 1993;**100**:323–7.

108. Stewart CE, Fielder AR, Moseley MJ, Stephens DA. Visual function of children with amblyopia during refractive adaptation and occlusion therapy. *Invest Ophthalmol Vis Sci* 2003;**44**:e-Abstract 4245.

109. Stewart CE, Moseley MJ, Stephens DA, Fielder AR, on behalf of the MOTAS Cooperative. Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br J Ophthalmol* 2005;**88**:1552–6.

110. Repka MX, Beck RW, Holmes JM, Birch EE, Chandler DL, Cotter SA, *et al*. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2003;**121**:603–11.

111. Elliott S. A national survey to assess the prevalence of written guidance for occlusion and practice variation in the treatment of amblyopia. *Br Orthoptic J* 2005;**2**:26–31.

112. Pediatric Eye Disease Investigator Group. The course of moderate amblyopia treated with patching in children: experience of the amblyopia treatment study. *Am J Ophthalmol* 2003;**136**: 620–9.

113. Pediatric Eye Disease Investigator Group. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2002;**120**:268–78.

114. Repka MX, Cotter SA, Beck RW, Kraker RT, Birch EE, Everett DF, *et al*. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. *Ophthalmology* 2004;**111**: 2076–85.

115. Holmes JM, Kraker RT, Beck RW, Birch EE, Cotter SA, Everett DF, *et al*. A randomized trial of prescribed patching regimens for treatment of

severe amblyopia in children. *Ophthalmology* 2003;**110**:2075–87.

116. Foley-Nolan A, McCann A, OKeefe M. Atropine penalisation versus occlusion as the primary treatment for amblyopia. *Br J Ophthalmol* 1997;**81**:54–7.

117. Stewart CE, Fielder AR, Moseley MJ, Stephens DA, MOTAS. Dose–response relationship for occlusion therapy for the treatment of amblyopia: initial results from the MOTAS study. *Invest Ophthalmol Vis Sci* 2002;**43**:e-Abstract 2939.

118. Stewart CE, Moseley MJ, Stephens DA, Fielder AR, on behalf of the MOTAS Cooperative. The treatment dose response in amblyopia therapy: results from the monitored occlusion treatment of amblyopia study (MOTAS). *Invest Ophthalmol Vis Sci* 2005;**45**:3048–54.

119. Stewart CE, Moseley MJ, Fielder AR, Stephens DA. Optimization of the dose–response of occlusion therapy for amblyopia: the ROTAS study. *Invest Ophthalmol Vis Sci* 2004;**45**:e-Abstract 2579.

120. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Modelling of treatment dose-response in amblyopia. *Invest Ophthalmol Vis Sci* 2005;**46**: e-Abstract 3595.

121. Clarke MP, Wright CM, Hrisos S, Anderson JD, Henderson J, Richardson SR. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. *BMJ* 2003;**327**:1251.

122. Levartovsky S, Oliver M, Gottesman N, Shimshoni M. Factors affecting long term results of successfully treated amblyopia: initial visual acuity and type of amblyopia. *Br J Ophthalmol* 1995;**79**:225–8.

123. Woodruff G, Hiscox F, Thompson JR, Smith LK. Factors affecting the outcome of children treated for amblyopia. *Eye* 1994;**8**:627–31.

124. Levartovsky S, Oliver M, Gottesman N, Shimshoni M. Long-term effect of hypermetropic anisometropia on the visual acuity of treated amblyopic eyes. *Br J Ophthalmol* 1998;**82**:55–8.

125. Fitzgerald DE, Krumholtz I. Maintenance of improvement gains in refractive amblyopia: a comparison of treatment modalities. *Optometry* 2002;**73**:153–9.

126. Holmes JM, Beck RW, Kraker RT, Astle WF, Birch EE, Cole SR, *et al*. Risk of amblyopia recurrence after cessation of treatment. *J AAPOS* 2004;**8**:420–8.

127. Awan M, Proudlock FA, Gottlob I. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. *Invest Ophthalmol Vis Sci* 2005;**46**: 1435–9.

128. Hussein MAW, Coats DK, Muthialu A, Cohen E, Paysse EA. Risk factors for treatment failure of anisometropic amblyopia. *J AAPOS* 2004;**8**: 429–34.

129. Scott WE, Kutschke PJ, Keech RV, Pfeifer WL, Nichols B, Zhang L. Amblyopia treatment outcomes. *J AAPOS* 2005;**9**:107–11.

130. Levartovsky S, Gottesman N, Shimshoni M, Oliver M. Factors affecting long-term results of successfully treated amblyopia: age at beginning of treatment and age at cessation of monitoring. *J Pediatr Ophthalmol Strabismus* 1992;**29**:219–23.

131. Cobb CJ, Russell K, Cox A, MacEwen CJ. Factors influencing visual outcome in anisometropic amblyopes. *Br J Ophthalmol* 2002;**86**:1278–81.

132. Smith LK, Thompson JR, Woodruff G, Hiscox F. Factors affecting treatment compliance in amblyopia. *J Pediatr Ophthalmol Strabismus* 1995;**32**:98–101.

133. Newsham D. Parental non-concordance with occlusion therapy. *Br J Ophthalmol* 2000;**84**: 957–62.

134. Newsham D. A randomised controlled trial of written information: the effect on parental non-concordance with occlusion therapy. *Br J Ophthalmol* 2002;**86**:787–91.

135. Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. *Arch Dis Child* 2006;**91**:491–4.

136. Spencer RF, Tucker MG, Choi RY, McNeer KW. Botulinum toxin management of childhood intermittent exotropia. *Ophthalmology* 1997;**104**:1762–7.

137. Rutstein RP, Marsh-Tootle W. Clinical course of accommodative esotropia. *Optometry Vis Sci* 1998;**75**:97–102.

138. Ing MR, Okino LM. Outcome study of stereopsis in relation to duration of misalignment in congenital esotropia. *J AAPOS* 2002;**6**:3–8.

139. Paysse EA. Photorefractive keratectomy for anisometropic amblyopia in children. *Trans Am Ophthalmol Soc* 2004;**102**:341–72.

140. Drack AV, Nucci P. Refractive surgery in children. *Ophthalmol Clin North Am* 2001;**14**:457–66.

141. Hutchinson AK. Pediatric refractive surgery. *Curr Opin Ophthalmol* 2003;**14**:267–75.

142. Stewart CE, Fielder AR, Stephens DA, Moseley MJ, on behalf of the MOTAS Cooperative. Treatment of unilateral amblyopia: factors influencing visual outcome. *Invest Ophthalmol Vis Sci* 2005;**46**: 3152–60.

143. Packwood EA, Cruz OA, Rychwalski PJ, Keech RV. The psychosocial effects of amblyopia study. *J AAPOS* 1999;**3**:15–7.

144. van de Graaf ES, van der Sterre GW, Polling JR, van KH, Simonsz B, Simonsz HJ. Amblyopia & Strabismus Questionnaire: design and initial validation. *Strabismus* 2004;**12**:181–93.

145. Parkes LC. An investigation of the impact of occlusion therapy on children with amblyopia, its effect on their families, and compliance with treatment. *Br Orthoptic J* 2001;**58**:30–7.

146. Searle A, Norman P, Harrad R, Vedhara K. Psychosocial and clinical determinants of compliance with occlusion therapy for amblyopic children. *Eye* 2002;**16**:150–5.

147. Choong YF, Lukman H, Martin S, Laws DE. Childhood amblyopia treatment: psychosocial implications for patients and primary carers. *Eye* 2004;**18**:369–75.

148. Horwood J, Waylen A, Herrick D, Williams C, Wolke D. Common visual defects and peer victimization in children. *Invest Ophthalmol Vis Sci* 2005;**46**:1177–81.

149. Williams C, Horwood J, Northstone K, Herrick D, Waylen A, Wolke D, *et al*. The timing of patching treatment and a child's well-being. *Br J Ophthalmol* 2006;**90**:670–1.

150. Rahi JS, Cumberland P, Peckham CS. Does amblyopia affect educational, health and social outcomes? Findings from 1958 British birth cohort. *BMJ* 2006;**332**:820–5.

151. Chua B, Mitchell P. Consequences of amblyopia on education, occupation, and long term vision loss. *Br J Ophthalmol* 2004;**88**:1119–21.

152. Hrisos S, Clarke MP, Kelly T, Henderson J, Wright CM. Unilateral visual impairment and neuro-developmental performance in pre-school children. *Br J Ophthalmol* 2006;**90**:836–8.

153. Satterfield D, Keltner JL, Morrison TL. Psychosocial aspects of strabismus study. *Arch Ophthalmol* 1993;**111**:1100–5.

154. Archer SM, Musch DC, Wren PA, Guire KE, Del Monte MA. Social and emotional impact of strabismus surgery on quality of life in children. *J AAPOS* 2005;**9**:148–51.

155. Theunissen NCM, Vogels GC, Koopman HM, Verrips GHW, Zwinderman HAH, Verloove-Vanhorick SP, *et al*. The proxy problem: child report versus parent report in health related quality of life reserach. *Qual Life Res* 1998;**7**:387–97.

156. Curtis L, Netten A. *Unit costs of health and social care*. London: Personal Social Services Research Unit; 2005. URL: www.pssru.ac.uk/pdf/uc/uc2005/uc2005.pdf

157. Moss SM, Gray A, Legood R, Henstock E. *Evaluation of HPV/LPC cervical cancer screening pilot studies. First report to the Department of Health on evaluation of LBC*. London: National Health Service; 2002. URL: www.cancerscreening.nhs.uk/cervical/lbc-pilot-evaluation.pdf

158. Roderick P, Davies R, Rafferty J, Crabbe D, Pearce R, Bhandari P, *et al*. The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation. *Health Technol Assess* 2003;**7**(6).

159. Konig HH, Barry JC, Leidl R, Zrenner E. Cost-effectiveness of orthoptic screening in kindergarten: a decision-analytic model. *Strabismus* 2000;**8**:79–90.

160. Konig HH, Walter HS, Barry JC. Resource utilisation and cost of amblyopia treatment. *Klin Monatsbl Augenheilkd* 2003;**220**:486–91.

161. Konig HH, Barry JC. Cost effectiveness of treatment for amblyopia: an analysis based on a probabilistic Markov model. *Br J Ophthalmol* 2004;**88**:606–12.

162. Konig HH, Barry JC, Leidl R, Zrenner E. Economic evaluation of orthoptic screening: results of a field study in 121 German kindergartens. *Invest Ophthalmol Vis Sci* 2002;**43**: 3209–15.

163. Konig H, Barry J. Economic evaluation of different methods of screening for amblyopia in kindergarten. *Pediatrics* 2002;**109**:e59.

164. Barry JC, Hartmann A, Pongs UM, Jockel M. Model for cost–benefit relations of amblyopia screening. *Ophthalmologe* 1998;**95**:19–27.

165. Konig HH, Barry JC. Cost–utility analysis of orthoptic screening in kindergarten: a Markov model based on data from Germany. *Pediatrics* 2004;**113**:95–108.

166. Gandjour A, Schlichtherle S, Neugebauer A, Russmann W, Lauterbach KW. A cost-effectiveness model of screening strategies for amblyopia and risk factors and its application in a German setting. *Optometry Vis Sci* 2003;**80**:259–69.

167. Neubauer AS, Neubauer S. Cost-effectiveness of screening for amblyopia. *Klin Monatsbl Augenheilkd* 2005;**222**:110–16.

168. Joish VN. A cost-benefit analysis of vision screening methods for preschoolers and school age children. *J AAPOS*, 2003;**7**:283–90.

169. Arnold RW, Armitage MD, Gionet EG, Balinger A, Kovtoun TA, Machida C, *et al*. The cost and yield of photoscreening: impact of photoscreening on overall pediatric ophthalmic costs. *J Pediatr Ophthalmol Strabismus* 2005;**42**:103–11.

170. Brown MM, Brown GC, Sharma S, Busbee B, Brown H. Quality of life associated with unilateral and bilateral good vision. *Ophthalmology* 2001;**108**:643–8.

171. Rubin GS, Munoz B, Bandeen-Roche K, West SK. Monocular versus binocular visual acuity as measures of vision impairment and predictors of visual disability. *Invest Ophthalmol Vis Sci* 2000;**41**:3327–34.

172. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:47–51.

173. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, *et al*. The impact of age-related macular degeneration on health status utility values. *Invest Ophthalmol Vis Sci* 2005;**46**:4016–23.

174. Meads C, Moore D. The clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2001;**7**(9).

175. Ethical Strategies Ltd. An analysis of the costs of visual impairment and blindness in the United Kingdom. Ethical Strategies; 2003. URL: www.healthyeyes.org.uk/fileadmin/healthy-eyes/downloads/cost-of-blindness.doc

176. Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P. The role of modelling in prioritising and planning clinical trials. *Health Technol Assess* 2003;**7**(23).

177. Population Estimates Unit. *Age structure of England and Wales*. London: Office of National Statistics; 2006. URL: http://statistics.gov.uk/populationestimates/svg_pyramid/default.htm

178. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, *et al*. Principles of good practice for decision analytic modelling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices – Modelling Studies. *Value Health* 2003; **6**:9–17.

179. Goldhaber-Fiebert JD, Stout NK, Ortendahl J, Goldie SJ. *HPV DNA testing, prophylactic HPV vaccination and current US cervical cancer screening guidelines: a cost-effectiveness analysis*. 2006.

180. Karlsson G, Johannesson M. The decision rules of cost-effectiveness analysis. *Pharmacoeconomics* 1996;**9**:113–20.

181. Towse A, Pritchard C, Devlin N. *Cost-effectiveness thresholds: economic and ethical issues*. Office of Health Economics; 2002.

Appendix 1

Literature search strategy

The search strategy was to combine searches of:

- "Amblyopia and strabismus terms" and "screening" terms
- "Amblyopia and strabismus terms" and "diagnosis" terms
- "Amblyopia and strabismus terms" and "treatment" terms
- "Amblyopia and strabismus terms" and "natural history" terms
- "Amblyopia and strabismus terms" and "epidemiology" terms
- "Amblyopia and strabismus terms" and "economics and quality of life" terms.

A search of "Screening terms 2" was performed in isolation

An example of the filter used in MEDLINE (Ovid) is provided below.

Amblyopia and strabismus terms

1 Strabismus
2 Amblyopia
3 Refractive errors
4 (1 or 2 or 3)
5 (amblyopic* or squint* or strabism* or anisometropi* or myopi* or hypermetropi* or astigmati* or ammetropi* or hypermetropic*)
6 (lazy near eye*)
7 (eye* or sight* or vision* or visual*)
8 (problem* or defect* or impair* or deficit or reduce*
9 (7 and 8)
10 (1 or 2 or 3 or 5 or 6 or 9)

Diagnosis terms

1 cover test.tw
2 photoscreener.tw
3 photoscreening.tw
4 photorefractor.tw
5 stereotest.tw
6 stereoacuity.tw
7 diagnos$.ti
8 screen$.ti
9 exp *mass screening/
10 diagnosis/
11 visual acuity test$.tw
12 vision test$.tw
13 or/1-12

Treatment terms

1 occlusion
2 patch*
3 therap* or treatment * or manag*
4 (or 1-3)

Restricted to reviews, meta-analyses and guidelines.

Natural history terms

1 natural history
2 progres*
3 prognos*
4 long term* or long-term*
5 (or 1-4)

Epidemiology terms

1 exp epidemiology/
2 epidemiolog$.ti
3 inciden$.ti
4 prevalen$.ti
5 incidence/
6 prevalence/
7 or/1-6

Economics and quality of life terms

1 exp patient acceptance of health care/
2 exp "costs and cost analysis"/
3 cost$.ti
4 (cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab
5 (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw
6 quality adjusted life year/
7 quality adjusted life.tw
8 (qaly$ or qald$ or qale$ or qtime$).tw
9 disability adjusted life.tw
10 daly$.tw
11 health status indicators/
12 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw
13 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw

14 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw
15 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw
16 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw
17 (euroqol or euro qol or eq5d or eq 5d).tw
18 (hql or hqol or h qol or hrqol or hr qol).tw
19 (hye or hyes).tw
20 health$ year$ equivalent$.tw
21 health utilit$.tw
22 (hui or hui1 or hui2 or hui3).tw
23 disutil$.tw
24 rosser.tw
25 quality of wellbeing.tw
26 qwb.tw
27 willingness to pay.tw
28 standard gamble$.tw
29 time trade off.tw
30 time tradeoff.tw
31 tto.tw
32 exp models, economic/
33 *models, theoretical/
34 *models, organizational/
35 economic model$.tw
36 markov chains/
37 markov$.tw
38 monte carlo method/
39 monte carlo.tw
40 exp decision theory/
41 (decision$ adj2 (tree$ or analy$ or model$)).tw
42 cosmetic appearance
43 psychosocial implications
44 or/1-43

Screening terms 1

1 Schools
2 Child day care centres
3 Child
4 Infant
5 (child* or adolesc* or juvenile* or minor* or school* or kindergarten* or pre-school* (Pre next school*) or preschool* or nurser*:ti)
6 (child* or adolesc* or juvenile* or minor* or school* or kindergarten* or pre-school* (Pre next school*) or preschool* nurser*:ab)
7 vision screening
8 vision disorders di:pc
9 (vision or visual:ti)
10 (vision or visual:ab)
11 (test* or screen*:ti)
12 (test* or screen*:ab)
13 (9 or 10) and (11 or 12)
14 screen*
15 Vision tests
16 Mass screening
17 "sensitivity and specificity"
18 false negative reactions/or false positive reactions
19 sensitivity.tw
20 specificity.tw
21 false negative$.tw
22 false positive$.tw
23 diagnostic accuracy.tw
24 "predictive value of tests"
25 predictive value$.tw
26 likelihood functions/
27 likelihood function$.tw
28 likelihood ratio$.tw
29 orthop*
30 or/1-8 or 13-29

Screening terms 2

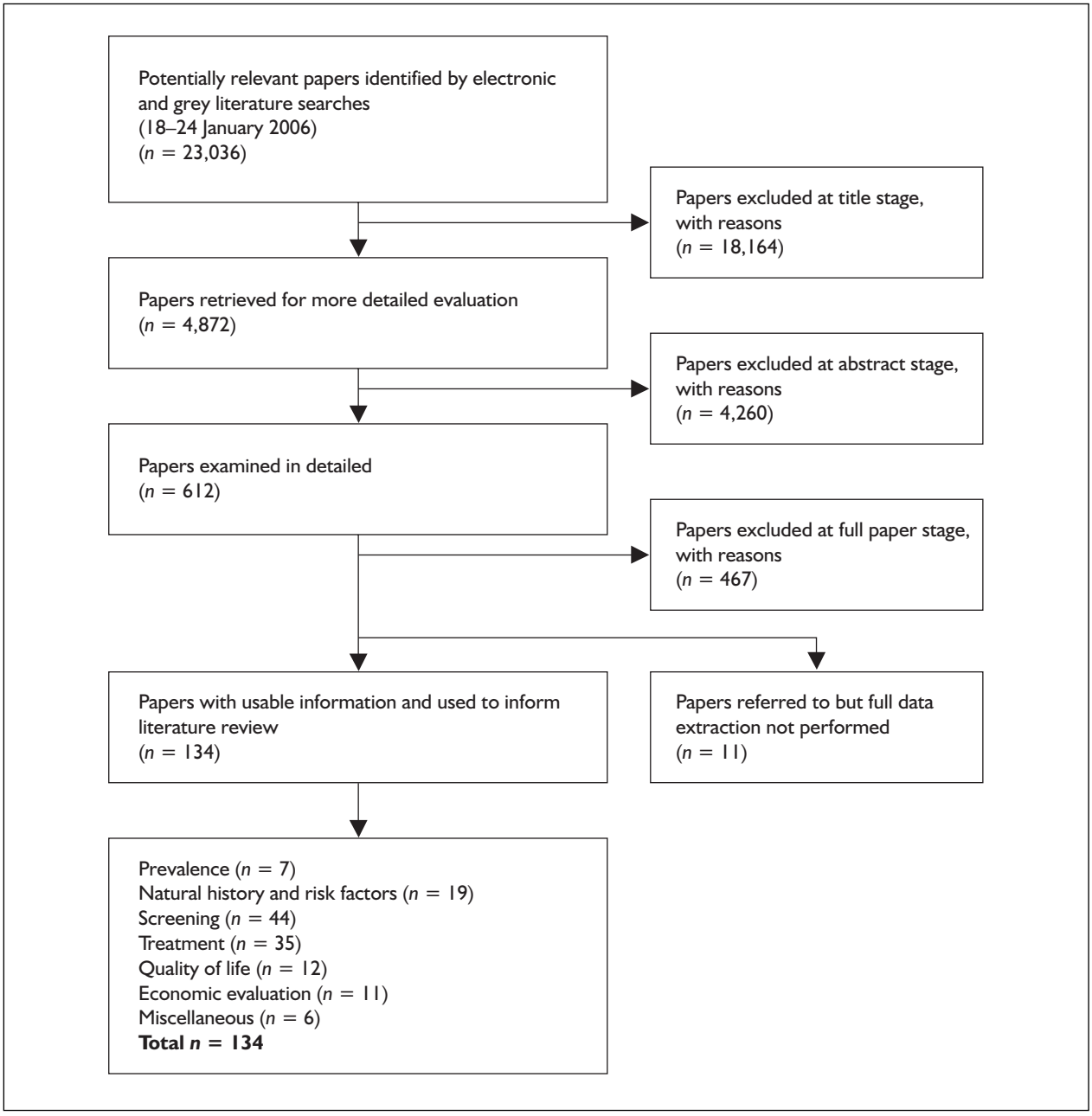
1 Schools
2 Child day care centres
3 Child
4 Infant
5 (child* or adolesc* or juvenile* or minor* or school* or kindergarten* or pre-school* (Pre next school*) or preschool* or nurser*:ti)
6 (child* or adolesc* or juvenile* or minor* or school* or kindergarten* or pre-school* (Pre next school*) or preschool* nurser*:ab)
7 vision screening
8 vision disorders di:pc
9 (vision or visual:ti)
10 (vision or visual:ab)
11 (test* or screen*:ti)
12 (test* or screen*:ab)
13 (9 or 10) and (11 or 12)
14 screen*
15 Vision tests
16 orthop*
17 or (1-6)
18 or (7, 8, 13-16)
19 and (17-18)

Papers identified in the literature review (reference nos)

Prevalence	11–17
Natural history and risk factors	34–52
Screening	54–97
Treatment	107–141
Quality of life	143–152
Economic evaluations	159–169
Other	1, 6–10

Appendix 2

QUOROM flow chart of study identification



Appendix 3

QUOROM statement checklist – prevalence studies

Objective	To identify papers to inform the model regarding the prevalence of amblyopia, strabismus and refractive errors.
Data sources	CDSR, CENTRAL, EMBASE, MEDLINE, MEDLINE in Process, CINAHL, NHS EED, OHE HEED, Science Citation Index, DARE, HTA database, grey literature searching.
Search strategy	"Amblyopia and strabismus terms" and "epidemiology terms" as detailed in Appendix 1.
Selection	Inclusion criteria included primary research, systematic review or high-quality review, representative population-based sample. Exclusion criteria included non-UK-based data.
Data extraction	Performed by JC.
Results	Seven papers identified and included in review.[11–17]

Study	Flom and Neumaier, 1966[11]			
Study setting; type	California, USA; retrospective			
Method of recruitment	2 groups, kindergarten (1959–63) and school, grades 1–6 (1954)			
Study timescale	1 year			
Inclusion/exclusion criteria	Not stated			
Representativeness of sample	Unclear			
Total number of participants	Availability to study	Kindergarten $n = 2055$	School $n = 1221$	Total $n = 3276$
	Available	1561	1201	2762
	Screened by optometrists	1521	1201	2722
	Under professional care, not screened	40	0	40
	Not available	494	20	514
	Not screened, erroneously reported under care	9	0	9
	Not screened, absent school	241	8	249
	Not screened, parental refusal	19	12	31
	Moved from district before analysis	225	0	225
Prevalence of amblyopia	Basis for diagnosis	Kindergarten ($n = 1561$) Amblyopia $n = 15$ (No amblyopia $n = 1546$)	School ($n = 1202$) Amblyopia $n = 14$ (No amblyopia $n = 1187$)	Total sample ($n = 2762$) Amblyopia $n = 29$ (No amblyopia $n = 2733$)
	Passed VA	0 (1546)	0 (1063)	0 (2541)
	Failed VA, follow-up	5 (28)	13 (120)	18 (148)
	Fail VA, no follow-up	2 (8)	1 (4)	3 (12)
	Under professional care	8 (32)	0 (0)	8 (32)
	% of sample	1.0 (99.0)	1.2 (98.8)	1.0 (99.0)

Study	Hopkisson *et al*., 1982[12]
Study setting; type	British Army, UK; retrospective
Method of recruitment	20% random sample of record for 1965 and 1976
Study timescale	Not stated
Inclusion/exclusion criteria	Appreciable ocular disease excluded
Representativeness of sample	Years chosen as furthest apart on records Likely to include more people from social classes IV and V

Prevalence and depth of amblyopia in military recruits in 1965 and 1976 (men)

	1965	1976
Total no. in sample	4000	3746
No. (%) with amblyopia	188 (4.7)	153 (4.1)
No. (%) with 2 lines difference	88 (46.8)	66 (43.1)
No. (%) with >2 lines difference	100 (53.2)	87 (56.9)
No. (%) with left eye weaker	109 (58.0)	77 (50.3)

Prevalence and depth of amblyopia in military recruits in 1965 and 1976 (women)

	1965	1976
Total no. in sample	499	325
No. (%) with amblyopia	28 (5.6)	10 (3.1)
No. (%) with 2 lines difference	10 (35.7)	5 (50.0)
No. (%) with >2 lines difference	18 (64.3)	5 (50.0)
No. (%) with left eye weaker	15 (53.6)	1 (10.0)

Other comments: Mean prevalence, combining both years' results:
Men: 0.044% (95% CI 0.035 to 0.053%)
Women: 0.046 (95% CI 0.031 to 0.061%)
No significant prevalence difference between men and women

Study	Stewart-Brown and Butler, 1985[13]
Study setting; type	UK; birth cohort study
Method of recruitment	Survey of births in 1 week in April 1970, retracted in 1980. Had interviews and medical examinations
Representativeness of sample	Data obtained from a significantly higher proportion of children in non-manual classes: 94.0% of social class I, 90.5% of social class V
Total number of participants	13,782 parental interviews 13,723 medical examinations Total of 13,871 children participated in one or other aspect of survey (estimated 86.7% of survivors from original birth cohort)
Percentage of selected individuals who agreed to participate	12,853 VA data available for analysis
Examination	VA (Sn 80.9%; Stycar 7.6%; SG 5.0%; other 3.0% Median age at vision screening 10.3 years (range 9.9–11.7 years)

Prevalence (%) of vision defects at 10 years

Category of defect	Distant VA only Bilateral (unilateral)	Near VA only Bilateral (unilateral)	Mixed defects Bilateral (unilateral)	Total
Minimal (6/9 or 9)	3.7 (3.6)	1.4 (2.0)	2.9 (0.8)	14.5
Mild (6/12 6/18: 12, 18)	1.3 (0.8)	0.1 (0.1)	1.3 (0.8)	4.5
Moderate (6/24 6/36: 24, 36)	0.7 (0.1)	0.02 (0)	0.7 (0.8)	2.3
Severe (6/60 < 6/60)	0.2 (0.02)	0 (0)	0.2 (0.4)	0.8
Total	5.9 (4.5)	1.5 (2.1)	5.1 (2.8)	22.1

Prevalence of proxy amblyopia by social class (unilateral mixed defects where distant vision is 6/12 or worse)

Social class	*N*	% with defects
I	715	2.1
II	2715	1.7
IIIN	1053	1.7
IIIM	5033	2.1
IV	1303	2.4
V	436	2.5
No father figure and not specified	1598	1.5

p = NS (χ^2 df = 6); unlikely to be clinically significant association between social class and amblyopia

Study	Newman and East, 2000[14]
Study setting; type	Cambridge, UK; retrospective cohort study
Method of recruitment	Unclear
Study timescale	Recruited during 1995 with a date of birth between September and December 1986
Inclusion/exclusion criteria	Not stated
Representativeness of sample	Unclear – population of Cambridge at the time ~271,000
Total number of participants	936 in selected cohort
Percentage of selected individuals who agreed to participate	Records reviewed for 898 (95.9%) Of remaining 38, 30 left, 8 attended special schools Preschool vision status known for 772 (86%) of cohort
Examination	Preschool screening at 3.5 years VA (SSG), CT, OM, 20Δ, TNO School entry testing at 5.5 years, VA Snellen
Referral criteria	VA of 6/9 or worse in either eye Amblyopia defined as 6/9 or worse in worst eye, or 1 line Snellen difference

Preschool vision screening status

	No. of children	%
Attended screening – pass	542	60.4
Attended screening – referred to hospital eye service	55	6.1
Defaulted screening	157	17.5
Already attending hospital eye service at age of screening	18	2.0
Unknown	126	14.0

Attendance rate	At preschool vision screening 597/754 (79.2%)
Prevalence of amblyopia among screening defaulters	1.3% (2/157; 95% CI 0.2 to 4.5%) Both of these children had straight-eyed amblyopia
Prevalence of amblyopia among screening attenders	2.5% (15/597; 95% CI 1.4 to 4.1%) Straight-eyed amblyopia (11), strabismus amblyopia (1), stimulus deprivation amblyopia due to congenital cataract (1) All of these had been detected at preschool screening
Other comments	No significant difference in the prevalence of amblyopia between screening defaulters and screening attenders ($\chi^2 = 0.39$, $p = 0.53$) Any child in cohort already attending hospital eye service at the age of preschool screening identified separately so that they were not included in screening defaulters ($n = 18$)

Study	Graham, 1974[15]					
Study setting; type	Cardiff, UK; prospective					
Method of recruitment	Unclear					
Study timescale	1 year					
Inclusion/exclusion criteria	Unclear					
Representativeness of sample	Born in Cardiff between 1 January and 31 December					
Total number of participants	4832 records obtained					
Percentage of selected individuals who agreed to participate	4787 screened (99%)					
Examination	VA and CT "in school", ?age					
Criteria for inclusion	All manifest deviations; X >9Δ; E> 7Δ; hyperphorias					
Relative prevalence of squints	Type of squint	% of all abnormal CT		Prevalence per 1000		
	Exophoria >9Δ	9.4		6.7		
	Esophoria >7Δ	9.4		6.7		
	Intermittent exotropia	7.0		5.0		
	Manifest exotropia	1.5		1.0		
	Consecutive exotropia	2.4		1.7		
	Fully accommodative	9.4		6.7		
	Conv exc	5.6		4.0		
	Partially accommodative	21.5		15.3		
	Non-accommodative	14.5		10.2		
	Other diagnoses	13.3		9.4		
	Not examined in detail	5.9		4.2		
Prevalence of manifest squint by social class (%)	Social class	I	II	III	IV	V
	Cases of manifest squint	8	13	54	12	13
	Controls	9	15	50	10	15
	i.e. no relationship					

Study	Stidwill, 1997[16]	
Study setting; type	Staffordshire, UK; retrospective	
Method of recruitment	"Random manner" from GP registers	
Study timescale	15 years	
Inclusion/exclusion criteria	Not stated	
Representativeness of sample	Unclear	
Total number of participants	From ~60,000 routine optometry examinations, 3075 of all ages with strabismus, decompensated heterophoria, nystagmus, accommodative and vergence anomalies identified; 2284 (74%) with concomitant strabismus	
Incidence of subtypes of strabismus	Total	3075
	Esotropia	
	Fully accomodative	313 (10%)
	Fully accomodative with conv exc	36 (1%)
	Partly accomodative	802 (26%)
	Partly accomodative with conv exc	38 (1%)
	Non-accomodative basic	363 (11%)
	Non accomodative with V pattern	6
	Non-accomodative with A pattern	4
	Exotropia	
	Exotropia basic	352 (11%)
	Exotropia with V pattern	80 (2%)
	Exotropia with A pattern	32 (1%)
	Microtropia with identity	32 (1%)
Predicted mean period prevalence of binocular anomalies in the general population	Anomaly subtype	Mean prevalence (per 1000)
	All strabismus	50.00
	Concomitant strabismus with A or V patterns	41.66

Study	Bruce *et al.*, 1991[17]			
Study setting; type	Bradford, UK; unclear – ?prospective			
Method of recruitment	"random manner" from GP registers			
Study timescale	1-year period			
Inclusion/exclusion criteria	Not stated			
Representativeness of sample	Unclear			
Total number of participants	699; 366 6–12 months (6 FTA); 333 33–36 months			
% of selected individuals who agreed to participate	(693/699) × 100 = 99.14%			
Examination	Orthoptic – CT, OM, 20Δ, Frisby (33–36 months); visual activity – SSG, Kays, cake dec, objects to occln; photorefrn – Cambridge Paed photorefractor (VPR-1). If refractive error >±1D then had repeat photo after cycloplegia refraction			
Referral criteria	Significant refractive error (>+1.75DS; >–0.50DS; >1.25DC; >0.75D anisometropia) and/or binocular vision abnormality			
Type and incidence of refractive errors	Refractive error type	9–12 months No. (%)	33–36 months No. (%)	Total No. (%)
	No significant refractive error	326 (90.5)	306 (91.9)	632 (91.2)
	Hypermetropia	22 (6.1)	17 (5.1)	39 (5.6)
	Myopia	1 (0.3)	1 (0.3)	2 (0.3)
	Hypermetropic astigmatism	8 (2.2)	7 (2.1)	15 (2.2)
	Myopic astigmatism	1 (0.3)	0 (0)	1 (0.1)
	Mixed astigmatism	2 (0.6)	2 (0.6)	4 (0.6)
Type and incidence of binocular anomaly	Binocular anomaly	9–12 months No. (%)	33–36 months No. (%)	Total No. (%)
	Orthophoria	341 (94.7)	202 (59.5)	543 (77.8)
	Heterophoria	14 (3.9)	120 (35.4)	134 (19.2)
	Int ET	0 (0)	3 (0.9)	3 (0.4)
	Int XT	4 (1.1)	1 (0.3)	5 (0.7)
	Constant ET	1 (0.3)	7 (2.1)	8 (1.1)
	Constant XT	0 (0)	3 (0.9)	3 (0.4)
	Other	0 (0)	3 (0.9)	3 (0.4)
Other comments	Highly signif diff found tw incidence of binoc vision anomalies in two age groups ($\chi^2 = 125.31$, $n = 700$, $p < 0.0001$). When analysing incidence of squint in isolation less signif diff found ($\chi^2 = 7.53$, $n = 699$, $p < 0.01$)			

CT, cover text; ET, esotropia; FTA, failed to attend; OM, ocular movements; Sn, Snellen; SSG, Single Sheridan Gardner; XT, exotropia.

Appendix 4

QUOROM statement checklist – natural history and risk factors studies

Objective	To identify papers to inform the description of the natural history of amblyopia, strabismus and refractive errors and to inform model parameters used to represent the natural history. To identify papers on risk factors associated with amblyopia and/or strabismus
Data sources	CDSR, CENTRAL, EMBASE, MEDLINE, MEDLINE in Process, CINAHL, NHS EED, OHE HEED, Science Citation Index, DARE, HTA database, grey literature searching.
Search strategy	"Amblyopia and strabismus terms" and "natural history terms" as detailed in Appendix 1. "Amblyopia and strabismus terms" and "risk factor terms" as detailed in Appendix 1.
Selection	Inclusion criteria included primary research, systematic review or high-quality review. Exclusion criteria highly selected population; risk factors not applicable to a screening population, e.g. genetic risk markers.
Data extraction	Performed by JC.
Results	19 papers identified and included in review.[34–52]

Study	Study design	Results
Dobson *et al.*[34] 1984 USA	Retrospective review of cycloplegic refractions of children examined between 1968 and 1978	979 patient data records examined – showed higher rates of against-the-rule astigmatism in younger infants Subgroup of 11 children (age <18 months) followed up to 5–11 years after initial examination; 10 of 11 initially had against-the-rule; 6/22 eyes had astigmatism at follow-up; remaining 6 cases continued to have against-the-rule astigmatism
Gwiazda *et al.*[35] 1993 USA	Longitudinal study monitoring emmetropisation and progression of refraction in children from infancy to puberty	72 children examined at regular intervals starting soon after birth and continuing for 9–16 years During first 6 months, mean spherical equivalent is negative (by small amount) Children with negative spherical equivalent in first 6 months with against-the-rule astigmatism became myopic at an earlier age than children with no astigmatism Children with early with-the-rule astigmatism remained emmetropic in childhood whether the spherical equivalent was negative or positive
Gwiazda *et al.*[36] 1984 USA	Longitudinal study monitoring changes in astigmatism from birth to 6 years	48 children included in study Much of early astigmatism was either eliminated or reduced in amount over the follow-up period, with an indication of a shift in axis to with-the-rule Of the 19 children with significant astigmatism in the first year, only one child acquired significant astigmatism (with-the-rule) by 4 years
Abrahamsson *et al.*[37,38] 1990 Sweden	Longitudinal study of population-based sample of children with astigmatism	Reported upon change in refraction and amblyopia and changeability of anisometropia Described progression and impact of astigmatism at age 4 years in 310 children with astigmatism at 1 year (although children were treated at 3 years if astigmatism >1D, ametropia >3D, anisometropia ⩾1D) Increasing or constant astigmatism was identified in 30 of the 310 children at age 4 years 58 children (19%) were found to have anisometropia at some point in the follow-up period; the maximum observed prevalence was 34 at age 2 years, with 28 having anisometropia at 4 years 30% (9/30) with increasing or unchanged astigmatism developed amblyopia compared with 5% (14/280) with decreasing astigmatism
Dobson and Sebris[39] 1989 USA	Longitudinal study describing clinical outcomes in terms of strabismus, hypermetropia, astigmatism and anisometropia at age 36 months	Cohort of 65 children initially examined at 8 months Subjects categorised as infantile esotropes; high hypermetropia (⩾4D); moderate hypermetropia (3–3.75D); family history of strabismus or amblyopia; control group No differences among the groups in absolute acuity scores or interocular differences until the children reached 30–36 months VA was lower in infantile esotropia group

continued

Study	Study design	Results
Townshend *et al.*[40] 1993 USA	Retrospective review of charts to examine the relationship between the depth of anisometropic amblyopia without strabismus and differences in refraction for hypermetropic and myopic patients	A review of 303 charts identified 35 patients aged 7–70 years with untreated anisometropic amblyopia without strabismus (between 1991 and 1992) Strong correlation between depth of amblyopia and differences in refraction for individuals with anisometropic amblyopia, with the correlation being greater for myopic patients
Donahue[41] 2005 USA	Examined the relationship between anisometropia, patient age and the development of amblyopia	VA results of children examined formally following referral from photoscreening programme and found to have anisometropia (>1D) were examined Anisometropic children with superimposed strabismus were classified as strabismic; anisometropic individuals were classed as orthotropic Amblyopia was rare in children aged under 2 years (14%) Prevalence rises, and by age 3 years nearly two-thirds of children with >1D had amblyopia Prevalence of amblyopia increases only slightly after this Results of 506 children referred with strabismus showed that the prevalence of amblyopia was less related to age than it was for anisometropic children There was some trend for strabismic amblyopia to increase in severity in older children; the trend was not as apparent in patients with strabismus as it was for anisometropia
Ingram *et al.*[42] 1994 UK	Longitudinal study examining the emmetropisation process	Identified children aged 6 months with refractive error of +5FD, and described changes in hypermetropia by eye (not child) between 6 months and 3.5 years, stratified by no strabismus, microtropia and strabismus Separate tables presented patient-level data Children who eventually had either a convergent strabismus or microtropia were significantly less likely to have spontaneously reduced their hypermetropia
Abrahamsson and Sjostrand[43] 1996 Sweden	Longitudinal study examining visual acuity and refraction in children with marked anisometropia at 1 year of age	20 children in study with anisometropia between ⩾3 and <5.5D Refractive errors and VA were measured at 6-monthly intervals to age 10 years; then categorised as: ametropia and anisometropia increased at 10 years, all cases developed amblyopia ($n = 6$), 3 cases developed esotropia; decreasing anisometropia and developed either amblyopia ($n = 6$) or convergent strabismus ($n = 1$); or decreasing anisometropia and no amblyopia or convergent strabismus ($n = 7$) 2 of children had no astigmatism, others varied from 0.5 to 3D No obvious relation between amount of astigmatism and amblyopia could be identified

continued

<table>
<tr><th>Study</th><th>Study design</th><th>Results</th></tr>
<tr><td>Ingram et al.[44]
1986
UK</td><td>Retrospective review of data describing the predictive value of refractive error identified at age 1 year on the prevalence of amblyopia and strabismus at age 3.5 years</td><td>Amblyopia was highly likely (48%) if ⩾3.5D on meridional hypermetropia was present at 1 year
45% of children with this refractive error also had strabismus
All those who remained severely defective VA in spite of treatment had either ⩾3.5D of meridional hypermetropia or ⩾4D of meridional myopia at aged 1 year
3.7% of the population at aged 1 year showed high refractive errors
Astigmatism in infancy or later was not significantly associated with strabismus or amblyopia</td></tr>
<tr><td>Rahi et al.[45]
2002
UK</td><td>24-month national surveillance to identify all individuals in the UK with unilateral amblyopic (VA >6/12) who had newly acquired vision loss in the non-amblyopic eye, resulting in acuity of >6/12 or visual-field restriction precluding driving
Information about participants was obtained at presentation and 1 year later
Participants were categorised as having socially significant visual impairment, or visual impairment, severe visual impairment, or blindness, in accordance with WHO taxonomy</td><td>Age and sex distribution of 368 individuals with loss of vision in the non-amblyopic eye
<table>
<tr><th>Sex</th><th>⩽15 years</th><th>16–64 years</th><th>⩾65 years</th></tr>
<tr><td>Male (n = 182)</td><td>7 (47%)</td><td>86 (75%)</td><td>89 (37%)</td></tr>
<tr><td>Female (n = 186)</td><td>8 (53%)</td><td>28 (25%)</td><td>150 (63%)</td></tr>
</table>
Age and sex unknown for one individual; sex unknown for one individual in age ⩾65 years

Category of visual impairment at presentation (n =370) and 1 year later (n = 293[a])
<table>
<tr><th></th><th>Severe visual impairment or blindness</th><th>Visual impairment</th><th>Socially significant visual impairment</th></tr>
<tr><td>At presentation</td><td>86 (23%)</td><td>180 (49%)</td><td>104 (28%)</td></tr>
<tr><td>At 1 year</td><td>87 (30%)</td><td>127 (43%)</td><td>79 (27%)</td></tr>
</table>
[a] Excluding 70 cases with acuity better than 6/12 at 1 year (recovered VA) and 7 missing data

Category of vision loss at presentation by category at 1 year follow-up (n = 363[a])
<table>
<tr><th></th><th>Recovered VA (able to drive)[b]</th><th>Socially significant visual impairment</th><th>Visual impairment</th><th>Severe visual impairment or blindness</th></tr>
<tr><td>Socially significant visual impairment</td><td>38</td><td>47</td><td>14</td><td>4</td></tr>
<tr><td>Visual impairment</td><td>29</td><td>28</td><td>101</td><td>16</td></tr>
<tr><td>Severe visual impairment</td><td>3</td><td>4</td><td>12</td><td>67</td></tr>
</table>
Data are number of people.
[a] Excluding 7 cases missing data (1 unable to drive, 6 visual impairment at presentation)
[b] Cases excluded from estimate of risk of permanent visual impairment</td></tr>
</table>

continued

Study	Study design	Results

Total population lifetime risk and annual rate of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye

	Incidence per 100,000 total UK population (95% CI)
Lifetime risk (cumulative incidence)	
Childhood (by 16 years)	0.35 (0.07 to 0.64)
Working-age adults (by 64 years)	5.67 (4.33 to 7.01)
Older adults (by 95 years)	32.98 (29.06 to 26.89)
Annual rate (age-specific incidence)	
5–15 years	0.04 (0.01 to 0.06)
16–64 years	0.11 (0.09 to 0.13)
65–95 years	0.91 (0.79 to 1.03)

Projected lifetime risk and annual rate of permanent visual impairment or blindness attributable to loss of vision in the non-amblyopic eye in individuals with amblyopia

	Incidence per 100 people with unilateral amblyopia (95% CI)		
	Model 1	Model 2	Model 3
Lifetime risk (cumulative incidence)			
Childhood (by 16 years)	0.04 (0.01 to 0.06)	0.04 (0.01 to 0.06)	0.04 (0.01 to 0.06)
Working age adults (by 64 years)	0.57 (0.45 to 0.69)	0.30 (0.24 to 0.36)	0.30 (0.24 to 0.36)
Older adults (by 95 years)	3.29 (2.91 to 3.69)	1.67 (1.47 to 1.86)	1.21 (1.07 to 1.35)
Annual rate (age-specific incidence)			
5–15 years	0.004 (0.001 to 0.006)	0.004 (0.001 to 0.006)	0.004 (0.001 to 0.006)
16–64 years	0.011 (0.008 to 0.013)	0.005 (0.004 to 0.007)	0.005 (0.004 to 0.007)
65–95 years	0.091 (0.077 to 0.103)	0.046 (0.039 to 0.052)	0.030 (0.026 to 0.034)

Findings suggest that every year, as a result of disease affecting their non-amblyopic eye, at least 185 people in the UK with monocular amblyopia (acuity <6/12) have vision loss to a level that is associated with an important effect on QoL and with increased risk of death, serious morbidity (such as hip fractures after falls) and social isolation

continued

Study	Study design	Results
Tommila and Tarkkanen[46] 1981 Finland	Review of records of patients with amblyopia who lost vision of the healthy eye over 20-year period	Prevalent cases of amblyopia = annual birth rate (60,000) × amblyopia prevalence in 7-year-old children (1.8%) × 20 years = 21,600 (rounded up to 22,000 by authors) The numerator was informed by the number of amblyopic patients who received pleoptic treatment for loss of vision in the healthy eye (23 patients) over a 20-year period at the Helsinki eye hospital. The number was uprated to 35 to account for the suspected catchment area of the hospital The incidence of loss of vision in the healthy eye is estimated to be 1.75 ± 0.3 per 1000 individuals with amblyopia
Sorsby[47] 1972 UK	Analysis of blindness in England and Wales	An analysis of blindness in England and Wales between 1963 and 1968 estimated that in a cohort of 100,000 blind individuals, around 400 would have become blind due to unilateral vision loss in childhood [*sic*] from squint, and subsequent loss of vision in the remaining eye Fifty-two such cases were registered over the 6-year period. The probability of loss of vision in the non-amblyopic eye could be estimated as *p* (loss of healthy eye vision) = cases of amblyopia-led blindness (52)/[adult amblyopia prevalence (5%) × population estimate (48 million) × 6 years] = 0.004 per 1000
Vereecken and Brabant[48] 1984 Belgium	Combination of analysis of data obtained from literature and questionnaire issued to ophthalmologists investigating spontaneous improvement in the amblyopic eye, following loss of vision in the non-amblyopic eye	Included 59 cases identified from the literature and 144 from a questionnaire sent to ophthalmologists in four European countries Of the literature cases, in the pre-pleoptic period (i.e. prior to the introduction of eye exercises), all published cases showed improvement. In the pleoptic period, 22 of 53 cases showed improvement; 21 of the 22 improvements were achieved with treatment The survey data (all in the pleoptic period) showed that 41 of 144 cases showed improvement, 16 reported to be with treatment, 25 without treatment. Tables 12 and 13 describe the results by the degree of improvement and by age of loss of vision in the non-amblyopic eye. The majority of those experiencing improvement gained significant vision, which age at beginning of treatment is interpreted (by the authors) as showing no relationship between age and outcome *Degree of improvement in the amblyopic eye* No. of improved cases Literature (*n* = 59) / Survey (*n* = 144) Excellent: 7 / 10 Good: 14 / 24 Fair: 7 / 7 Total: 28 / 41

continued

Study	Study design	Results
		Improvement rates by age at loss of vision in the non-amblyopic eye
		Age (years) / No. of cases / No. of improved results 9–21 / 21 / 10 21–31 / 22 / 8 31–41 / 18 / 7 41–51 / 17 / 3 51–61 / 22 / 9 >61 / 27 / 4
		Major part of improvement in VA always occurred during the first weeks after loss of the good eye
		5 patients had received treatment for the amblyopic eye prior to losing the good eye (3 of these patients experienced improvement after loss of the good eye), some evidence that prior treatment even if unsuccessful at the time improves the likelihood of improvement after loss of the good eye
Rahi *et al.*[49] 2002 UK	Data obtained from survey of ophthalmologists of patients with diagnosis of amblyopia who had lost vision in their good eye to determine the likelihood, and factors predictive of, improved vision in the amblyopic eye after loss of vision in the non-amblyopic eye	Table presents the outcomes at 1 year for 254 individuals aged ⩽11 years with loss of vision in the non-amblyopic eye, which shows a significant minority do gain vision in the amblyopic eye
		Vision in amblyopic eye at 1 year Outcome / No. (%) Some increase in VA / 48 (17) ⩾2 lines increase in VA / 25 (9) No change / 185 (66) VA worse / 21 (8)
		Table presents the results of a multivariate analysis on factors that may affect the probability of an improvement in VA in the amblyopic eye
		All of the factors appear to have a significant effect
		It was not possible to differentiate between alternative treatments, so it may be that more effective treatments have a greater effect

continued

Study	Study design	Results
		Multivariate analysis for any improvement in VA
		Predictive factor — Proportional OR (95% CI) — *p*-Value
		Age (per increasing year) — 0.98 (0.96 to 0.99) — 0.027
		New optical treatment for amblyopic eye:
		Untreated (174) — Baseline
		Treated (80) — 70.1 (11.97 to 410.7) — <0.0001
		Acuity of non-amblyopic eye at presentation:
		6/24 or better (98) — Baseline
		6/36 or worse (156) — 3.79 (0.96 to 15.01) — 0.057
		Acuity of amblyopic eye at presentation:
		6/36 or worse (169) — Baseline
		6/24 or better (85) — 5.38 (1.53 to 18.97) — 0.009
Laws *et al.*[51] 2000 UK	Prospective study comparing the binocular fixation pattern and presence of amblyopia in strabismic children	53 children with manifest strabismus were examined with binocular fixation pattern and logMAR VA measured. The authors used a modification of the Zipf classification of re-fixation pattern When the authors interpreted the results of binocular fixation pattern, they found a significant trend towards amblyopia from grade 1 (alternation) to grade 4 (no uniocular fixation) ($\chi^2 = 24.78$, $p < 0.001$). That is, patients who had a freely alternating strabismus did not have amblyopia, and those with maintained or preferred fixation with a given eye did exhibit amblyopia in the non-preferred eye
Chew *et al.*[52] 1994 USA	Cohort study, pregnant mothers enrolled 1959–66	Examinations of offspring performed at time of delivery, 4 months, 7 years Also examined by paediatric neurologist or paediatrician at ages 1 and 7 years Esotropia (ET) or exotropia (XT) diagnosed by paediatrician or neurologist at 1- and 7-year examinations using corneal reflections For this study, children were identified as cases if the exam at 7 years revealed strabismus or there was history of treatment for strabismus; to confirm diagnosis, ophthalmologist randomly reviewed 550 (40%) recorded with the diagnosis of ET and 559 (100%) of XT 53,043 children (45% white, 47% black, 7% Puerto Rican, 1% other) enrolled in whole study By 7-year follow-up 1784 had died; total number of survivors who returned for 7-year examination was 40,897 (80% of 7-year-old children had their 7-year examination) Analysis was limited to white and black children, exclusion of 1670 children Total sample size for this study was 39,227

continued

Study	Study design	Results

Characteristics of children with and without strabismus: no. (%)

Variable	Children with ET	Children with XT	Children without strabismus
Maternal race			
White	740 (62.3)	228 (46.5)	17931 (47.8)
Black	447 (37.7)	262 (53.5)	19619 (52.2)
Maternal age (years)			
<20	205 (17.3)	95 (19.4)	8876 (23.6)
20–24	421 (35.5)	182 (37.1)	13206 (35.2)
25–29	269 (22.7)	103 (21.0)	7913 (21.1)
30–34	184 (15.5)	64 (13.1)	4515 (12.0)
⩾35	108 (9.1)	46 (9.4)	3040 (8.1)
Birth weight (g)			
<2500	200 (16.8)	103 (21.0)	3793 (10.1)
2500–2999	277 (23.3)	124 (25.3)	9307 (24.8)
3000–3499	406 (34.2)	153 (31.2)	14804 (39.4)
⩾3500	302 (25.4)	109 (22.2)	9591 (25.5)
Unknown	2 (0.2)	1 (0.2)	55 (0.1)

Univariate analysis of all risk factors evaluated for ET and XT[a]

Risk factor	Association with ET, *p*	Association with ET, association with increasing risk	Association with XT, *p*	Association with XT, association with increasing risk
Maternal				
Race (white versus black)	<0.0001	White	0.33	–
Age	0.001	↑	0.18	–
Education	0.33	–	0.26	–
Socioeconomic index	0.74	–	0.05	↓
Cigarettes per day	<0.0001	↑	<0.0001	↑
Years smoked, adjusted for age	0.03	↑	0.02	↑
Father's age	0.008	↑	0.18	–

[a] Dash (–) indicates no association ($p > 0.10$); ↑, direct association; ↓, inverse association

Appendix 5

QUOROM statement checklist – screening studies

Objective	To identify papers to inform suitable tests to be considered for a screening programme for amblyopia, strabismus and/or refractive errors To identify papers on risk factors associated with amblyopia and/or strabismus To identify papers that report on the impact of screening programmes upon treatment outcomes
Data sources	CDSR, CENTRAL, EMBASE, MEDLINE, MEDLINE in Process, CINAHL, NHS EED, OHE HEED, Science Citation Index, DARE, HTA database, grey literature searching
Search strategy	"Amblyopia and strabismus terms" and "screening" as detailed in Appendix 1
Selection	Inclusion criteria included identification of potential screening test/programme Exclusion criteria highly selected population
Data extraction	Performed by JC
Results	44 papers identified and included in review[54–97]

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td>Simmers et al.[54]
1997
UK</td><td>Prospective study comparing VA using Glasgow acuity cards (GAC, 3 m test) and Single Sheridan Gardner (SSG)

School-child tested, represent cross-section of geographical and socio-economic class

VA tested randomly using RE and LE for SSG and GAC

SSG vision of 6/6 or better deemed normal</td><td>With SSG, 633 children (90.2%) had VA of 6/6 or better; 69 (9.8%) had VA of 6/9 or less

565 with normal VA achieved VA of 6/6 or better in either eye (EE); Of these, 160 (25.3%) had 6/5 in best eye (BE), 348 (55%) 6/4 BE, 13 (2%) 6/3 BE and 44 (7%) had combination of these VAs in EE

Significant difference in the mean VA (SD) measured with GAC [0.9 (0.08) modified logMAR] and SSG in the visually normal children [1.13 (0.09) modified logMAR, df = 632, $t = -59.08$, $p = 0.0001$]

Normal limits in the measurement of VA were defined as 1.96 from the mean

Results can be used as criteria for detecting amblyopia for each of the acuity tests; considered reduced if it was below lower limits of normality

Limits of normality VA scores
<table>
<tr><th></th><th>Mean (modified logMAR)</th><th>SD (log units)</th><th>Upper limit (+1.96SD)</th><th>Lower limit (–1.96SD)</th></tr>
<tr><td>GAC</td><td>0.9</td><td>0.08</td><td>1.06</td><td>0.74</td></tr>
<tr><td>SSG</td><td>1.13</td><td>0.09</td><td>1.31</td><td>0.95</td></tr>
</table>
Using these criteria, GAC was most sensitive in detecting children with amblyopia (100%) while SSG produced a reduced detection frequency of 74%

Interocular differences in visually normal children
GAC show wide distribution of discrepancies, SSG narrow range of discrepancies, indicating high degree of concordance; mean scale increment calculated for the acuity range over which the majority of population scores lay (6/6–6/3) and was found to be 0.1 log units

95% CI limits for interocular differences in the visually normal population (log units)
<table>
<tr><th></th><th>Scale increment</th><th>95% CI limit</th><th>Clinically significant difference</th></tr>
<tr><td>GAC</td><td>0.025</td><td>0.08</td><td>0.10</td></tr>
<tr><td>SSG</td><td>0.1</td><td>0.11</td><td>0.20</td></tr>
</table>
If these values for a significant interocular difference in acuity are used as criteria for detection for amblyopia, GAC is most sensitive (100%), while SSG identified 55% of children with unilateral amblyopia</td></tr>
</table>

continued

Code/Country	Study design	Numbers
Newman and East[55] 1999 UK	Retrospective cohort study of children resident in Cambridge Health District between September and December 1986; identified from Community Child Health Service database, coverage of ~98% Screening offered to all children at 3.5 years, performed by orthoptist in community setting	Population of Cambridge Health district was 271,000 Referral to hospital eye services (HES) if VA 6/9 or worse in EE, manifest strabismus, decompensating heterophoria, abnormal extraocular movements, abnormal 20Δ, negative TNO screening plate, any other ocular abnormalities In presence of equivocal findings, children recalled for another preschool vision screening by orthoptist 936 in cohort. Community child health records reviewed for 95.9% (898/936) Of remaining 38, 30 had left area, 8 attended special schools for special learning difficulties Screening status available for 86.0% (772/898); 77.3% (597/772) attendance rate, referral rate 9.2% (55/597) Screening status — No. (%) Attended screening, passed — 542 (60.4) Attended screening, referred HES — 55 (6.1) Defaulted screening — 157 (17.5) Already attending HES at age of screening — 18 (2.0) Unknown — 126 (14.0) 0 of 542 who had previously passed screening found to be amblyopic; NPV of screening 100% (95% CI 99.4 to 100%); 15 with amblyopia detected at screening Screening with single optotype VA in isolation NPV for amblyopia of 99.6% (95% CI 98.7 to 99.9%) 18 children already attending the HES at age of screening Screening by VA only would have NPV for amblyopia of 99% (95% CI 98.7 to 99.9%) Other screening tests contribute relatively little to overall detection of amblyopia, are necessary to minimise the risk of amblyopic children being missed by PSVS

continued

Code/Country	Study design	Numbers
Vision in Preschoolers Study Group (VIP)[56] USA 2004	Multi-centre, multi-disciplinary clinical study to evaluate preschool screening tests	Subjects are children enrolled in Head Start; children aged ⩾3 and <5 years All children who failed Head Start vision screening programme asked to participate in study Tests done by licensed eye care professionals, trained as screeners (details in paper) and gold standard examination (GSE) examiners In years 1 and 2, 2211 who had failed the Head Start screening and 1772 who had not failed the screening were selected for enrolment Consent was obtained and eligibility criteria fulfilled for 3121 of the 3983 (89.1%) of children enrolled. GSE performed on 2666 (95.6%) of screened children, of whom 2588 (97.1%) completed VA, CT and cyclo refraction All children were aged 3, 4 or 5 years when screened, but very few 3- or 5-year-olds were tested Significant refractive errors present in 284 (91.3%) of the 311 with group 1 condition, 204 (89.1%) of the 229 with group 2 condition in the absence of a group 1 condition Among the 2588, 755 (29.2%) had ⩾1 targeted disorders: 163 (6.30%) had amblyopia, 110 (4.25%) had strabismus, 539 (20.8%) had significant refractive error, 246 (9.5%) had reduced VA. Significant refractive error was present in 58 (52.7%) of the 110 with strabismus and in 30 (79%) of the 38 with strabismic amblyopia *Sensitivity by VIP hierarchy of conditions with specificity set to 0.90 for tests without established failure criteria*

Screening test	Any condition $n = 346$	Group 1 $n = 139$	Group 2 $n = 108$	Group 3 $n = 99$	Specificity $n = 796$
Lea symbols VA	0.61	0.77	0.57	0.41	0.90
HOTV VA	0.54	0.72	0.41	0.44	0.89
Random Dot E	0.42	0.59	0.33	0.27	0.90
Cover–uncover	0.16	0.24	0.13	0.06	0.98
Non-cyclo retinoscopy	0.64	0.90	0.63	0.29	0.90
Retinomax Autorefractor	0.63	0.87	0.63	0.30	0.90
Year 2	$N = 409$	$N = 172$	$N = 121$	$N = 116$	$N = 1037$
Stereo Smile II	0.44	0.72	0.30	0.20	0.91
Power Refractor II	0.54	0.72	0.43	0.39	0.90
iScreen photoscreener	0.37	0.57	0.24	0.20	0.94
MTI photoscreener	0.37	0.55	0.27	0.19	0.94
SureSight Vision Screener[a]	0.85	0.96	0.90	0.63	0.62
SureSight Vision Screener	0.63	0.81	0.68	0.29	0.90
Retinomax Autorefractor	0.64	0.88	0.55	0.37	0.90

[a] Screening failure defined as recommended by the manufacturer

continued

Code/Country	Study design	Numbers
Vision in Preschoolers Study Group (VIP)[57] USA 2005	Multi-centre, multi-disciplinary clinical study to evaluate preschool screening tests	*Sensitivities in detecting the 4 VIP-targeted disorders with specificity set at 0.94* 0.94 specificity cannot be achieved for HOTV VA, Random Dot E and cover–uncover test. The current sensitivity comparisons were based on 93% specificity for HOTV VA, 92% specificity for Random Dot E and 98% specificity for cover–uncover test. Their sensitivities for cover–uncover tests, iScreen and MTI photoscreeners have been reported previously

	Sensitivity (95% CI)			
Test	Amblyopia	Strabismus	Refractive error	Reduced VA
Non-cyclo refraction	0.88 (0.81 to 0.95)	0.50 (0.36 to 0.64)	0.74 (0.68 to 0.80)	0.38 (0.30 to 0.46)
SureSight	0.80 (0.72 to 0.88)	0.54 (0.42 to 0.66)	63 (0.58 to 0.68)	0.35 (0.26 to 0.44)
Retinomax year 2	0.78 (0.69 to 0.87)	0.53 (0.41 to 0.65)	0.66 (0.60 to 0.72)	0.39 (0.31 to 0.47)
Retinomax year 1	0.77 (0.67 to 0.87)	0.54 (0.40 to 0.68)	0.63 (0.58 to 0.68)	0.36 (0.27 to 0.45)
Lea VA	0.65 (0.54 to 0.76)	0.48 (0.34 to 0.62)	0.58 (0.52 to 0.64)	0.48 (0.39 to 0.57)
MTI	0.63 (0.53 to 0.73)	0.65 (0.53 to 0.77)	0.42 (0.36 to 0.42)	0.24 (0.16 to 0.32)
iScreen	0.62 (0.52 to 0.72)	0.50 (0.38 to 0.62)	0.43 (0.37 to 0.49)	0.27 (0.19 to 0.35)
Stereo Smile II	0.61 (0.51 to 0.71)	0.58 (0.46 to 0.70)	0.37 (0.32 to 0.42)	0.20 (0.13 to 0.27)
Power Refractor	0.57 (0.47 to 0.67)	0.34 (0.22 to 0.46)	0.42 (0.36 to 0.48)	0.27 (0.19 to 0.35)
HOTV VA	0.52 (0.41 to 0.63)	0.44 (0.30 to 0.58)	0.40 (0.34 to 0.46)	0.36 (0.28 to 0.44)
Random Dot E	0.28 (0.18 to 0.38)	0.29 (0.16 to 0.42)	0.23 (0.18 to 0.23)	0.24 (0.17 to 0.31)
Cover–uncover	0.27 (0.17 to 0.37)	0.60 (0.46 to 0.74)	0.16 (0.11 to 0.21)	0.06 (0.02 to 0.10)

A 0.25 difference in sensitivity in detecting amblyopia, 0.30 difference in detecting strabismus, 0.15 difference in detecting significant refractive error and 0.20 difference in detecting reduced VA can be considered to be statistically significant

Williams *et al*.[58] 2001 UK	Population birth cohort study, RCT (ALSPAC)	*Control group* Surveillance by health visitor; examinations at 8 and 18 months Asking family history, observing visual behaviour, CT with *ad hoc* referrals if problem suspected at any time Referral criteria was any suspicion of strabismus or reduced VA *Intervention group* In addition, programme of testing by orthoptist at 8, 12, 25 and 31 months Tested uniocular VA with Cardiff cards (CC) (8, 12, 25 and 31 months), Kays (25 and 31 months), Frisby (12, 18, 25 and 31 months), 20Δ (all ages) Non-cyclo photorefraction used at all examinations Referral criteria were on basis of results of CT were any manifest deviation, latent esophoria, poorly controlled or large exophoria (>10 pd); referral criteria for VA; objection to occlusion of one eye more than other, CC <0.9 logMAR at 12 months, 0.6 at 18 months, 0.4 at 25 months, 0.3 at 31 months; Kays <6/12 at 25 months and 6/9 at 31 months

continued

Code/Country	Study design	Numbers

2029 ALSPAC children allocated to intervention group, 1461 to control group

Of intervention, 1408 (69%) attended at least 1 research clinic

1089 of intervention group (54%) and 939 (64%) of control group attended final assessment research clinic

282 referred to hospital eye services (HES) before 37 months, 147 from intervention group, 135 from control group

Case notes reviewed for 266 (94%); 16 diagnoses obtained from GP

Further 109 referred for HES from final assessment research clinic; 105 (96%) notes reviewed

4138 eligible in ALSPAC cohort

2029 allocated into intervention group; 621 never attended a clinic; 1408 attended at least one clinic

1461 in control group; 522 never attended a clinic

648 eligible not allocated into either group – not in study

Final assessment at 37 months; 1083 from intervention group, 939 control group. 109 referred with suspected strabismus or amblyopia; 105 case notes retrieved, 59 confirmed by HES

Primary outcome (yield of programme); 282 referred before 37 months. 266 notes reviewed, 16 diagnoses established by enquiry to GP

Sensitivities and specificities for cover test for strabismus by the orthoptists for the 876 who attended every clinic (n = *28)*

Age (months)	No. of cases detected (sensitivity)	95% CI for sensitivity	No. of normals identified (specificity)	95% CI for specificity
8	8 (28.6%)	11.9 to 45.3	847 (99.9%)	99.7 to 100
12	7 (25.0%)	9.0 to 41.0	848 (100%)	100
18	7 (25.0%)	9.0 to 41.0	848 (100%)	100
25	15 (53.6%)	35.1 to 72.1	848 (100%)	100
31	18 (64.3%)	46.6 to 82.0	848 (100%)	100
37	21 (75%)	100	848 (100%)	100

continued

Code/Country	Study design	Numbers
Pott *et al.*[59] 1998 The Netherlands	Prospective study	201 5-year-old children
	VA at 40 cm and 6 m using Rotterdam C-chart; acuity values below 2.5 min/arc considered impaired	Post stereo test (PST) performed in 198 (3 not, due to technical reasons!), 1 child failed due to non-cooperation PST data obtained in 197 children (success rate 99.5%); PST showed no suppression in 166 (84.3%) Abnormal results in 31 (15.7%); suppression present in 30 children (of whom 18 had suppression of right eye, 12 of left eye), and one child did not recognise picture
	An interocular difference of 0.2 log steps considered a monocular deficit present	VA assessed in 198 (success rate 98.5%) Binocular VA at 6 m or 40 cm was abnormal in 2 children (1%) and monocular VA was abnormal in 18 (9.1%) All children with low binocular VA also had abnormal monocular VA in one or both eyes Abnormal interocular acuity difference occurred in 20 (10.1%) 25 (12.6%) had abnormal levels when considering both (monocular) VA and interocular acuity difference
	Isotopic photorefraction without cyclo	
	To avoid bias, PST performed before assessment of alignment, VA and photorefraction	*Comparison of PST result and VA*

	No suppression with PST	Suppression or picture not recognised	No PST result
Normal VA	156 (77.6%)	15 (7.5%)	2 (1.0%)
Abnormal VA	10 (5.0%)	15 (7.5%)	
No acuity		1 (0.5%)	2 (1.0%)

Impaired acuity found in 25, of whom 15 had abnormal PST. All 15 had interocular acuity difference of 0.2 log step or more. 9 had refractive errors, 2 had strabismus, 4 showed no obvious ophthalmic problem

10 with abnormal VA showed no suppression with PST; 5 had insignificant interocular differences, but photorefraction showed binocular refractive errors in 3 of them. Other 5 had an interocular difference of 0.2 log step; only 1 of these demonstrated monocular refractive error

1 in whom VA could not be assessed showed suppression with PST, found to have strabismus

Sensitivity of test 60%; specificity 91%

continued

Code/Country	Study design	Numbers
Pott *et al.*[60] 2003 The Netherlands	Prospective study population of children with known ophthalmological disorders Tested over 3-month period Tested with PST before regular examination, then had OD examination, including measurement of alignment, EOM and VA	Age 3–15 years [mean 7.9 (SD 2.7; median 7.6)] (n = 502) PST could not be performed in 34 children (5.6%); in 11 due to developmental delay. When these excluded, success rate in children <4 years 66% (17 of 30); 4–5 years 91% (60 of 66); and >5 years 99% (494 of 497) Suppression of 1 eye present in 375 (65.8%); 38 (6.7%) did not recognise 1 or both pictograms; 30 (5.3%) had alternating suppression 127 (22.2%) had normal PST result *Individuals with strabismus* 3 child alignment not determined (cooperative); strabismus present in 339; 317 (of 339 or 93.5%) had suppression, 22 (6.5%) had normal PST; 0 of children without suppression had amblyopia Amblyopia was present in 84 with abnormal alignment; in 79 of these PST was abnormal, 5 test not done (cooperative); 0 with amblyopia had normal PST results *Subjects with normal eye alignment* Present in 262, refractive error present in 204 of these; refractive error fully corrected 155, under-corrected 49 In 104 (of 262, 39.5%) with normal alignment, no suppression could be elicited with PST Sensitivity of PST 96.2%, specificity 41.1%; PPV in study 62.8%; NPV 91.3%
Morale *et al.*[61] 2002 USA and Brazil	Subjects recruited from research laboratories (76 patients, 36 normal) preschool screening programme in USA (58 normal) and ophthalmic clinics in Brazil (35 patients, 29 normal) and Dallas (20 patients) Subjects included 100 patients with ocular abnormalities, VA of 20/50 or worse or 2 lines difference between eyes were excluded Age range 2–8 years	*Testability* Subjects mean age 4.4 years Testability of Worth-4-Shape in 2–8 year-olds at 35 cm (n = 251) was significantly higher compared with Worth-4-Dot (n = 247; 97.2% versus 84.2%; $p < 0.001$) Worth-4-Shape in 2–8-year-olds at 3 m (n = 252) was significantly higher compared with Worth-4-Dot (n = 247; 85.3% versus 69.2%; $p < 0.001$ In children aged 4–8 years, testability remained significantly higher with the Worth-4-Shape compared with Worth-4-Dot at 35 cm (n = 132; 98.5%, 88.6%; $p < 0.001$) and 3 m (n = 132, 131; 90.9%, 82.4%; $p = 0.04$) *Reliability* Test–retest analysis found comparable concordance for the Worth-4-Shape and Worth-4-Dot for all subjects at 35 cm (n = 111, 84; 91.2% versus 95.2% concordance; $p = 0.28$) and 3 m (n = 91, 77; 94.5% versus 92.2% concordance; $p = 0.55$) 111 subjects were able to complete reliably two tests for the Worth-4-Shape test at 35 cm, and of these 84 were able to complete the two tests for the Worth-4-Dot at 35 cm for this comparison 91 subjects were able to complete the two tests for the Worth-4-Shape at 3 m, and of these 77 were able to complete the two tests for the Worth-4-Dot at 3 m for this comparison

continued

Code/Country	Study design	Numbers
		Concordance was also equivalent when comparing subjects aged <4 years at both 35 cm (n = 32, 16; 96.9% versus 100% concordance; p = 0.48) and 3 m (n = 21, 4; 100% versus 96.8% concordance; p = 0.42) For subjects aged 4–8 years, concordance remained comparable at both 35 cm (n = 79, 68; 97.5% versus 95.6% concordance; p = 0.53) and 3 m (n = 70, 63; 92.9% versus 96.8% concordance; p = 0.32) *Validity* Using clinical gold standard of medical history, bifoveal fixation and stereoacuity, the sensitivity of the Worth-4-Dot was 91.6%, specificity 96.3%, accuracy 93.1% Worth-4-Shape sensitivity 88.7%, specificity 96.6%, accuracy 91.2% Between-test analysis found 97.4% agreement between Worth-4-Shape and Worth-4-Dot tests for all patients tested at 35 cm and 96.9% agreement at 3 m
Ruttum and Nelson[62] 1991 USA	3–4-year-old preschool screened children during 1988–9 eligible Tested with single optotypes at 10 ft, referred for 1 line difference in VA Any child who obtained minimum failing VA result of 1 line difference even after retesting was also tested (Random Dot E stereotest (RDES) at 40 cm and 1.5 m)	Passing result at either distance required 5 consecutive correct responses in this 2-alternative, force choice test All children with 1 line difference were referred for complete ophthalmic examination despite their responses to stereopsis Approximately 3000 children were screened; 76 had 1 line difference result and were referred; 58 of these were examined; 10 were seen by other doctors, results not included in study; 8 not seen at all; total results of study are based on 58 examined compared with the 76 (76% follow-up) 13 of 58 had an abnormal examination: 6 of these had passed the screening Random Dot E Stereo Test (RDES) at 1.5 m and 7 had failed it Sensitivity of RDES was 54% 45 had normal examination: 39 had passed the screening RDES at 1.5 m, 6 had failed it Specificity of RDES was 87% *Of the 6 who had failed examination but passed RDES at 1.5 m:* 1 was given glasses (paper lists VA with and without correction for all 6; could be argued that all would have benefited from treatment); all 6 passed RDES at 40 cm *Agreement between screeners and authors on RDES varied with testing distance* At 1.5 m authors obtained concordant results for 74% of the 58 children and discordant results for 26% False-positive and false-negative results by screeners were evenly divided At 40 cm authors agreed on 93% and disagreed on 7%, with disagreement evenly divided between false-positive and false-negative results Kappa statistic was 0.317 at 1.5 m (poor agreement beyond chance)

continued

Code/Country	Study design	Numbers
Kohl and Samek[64] 1988 USA	Longitudinal study	18 children studied from a randomly selected population of 30 infants Children underwent testing for VA, refractive error and stereoacuity using Stereofly at regular intervals By 24 months, the cumulative percentage positive response to Stereofly was 87% Note that small numbers and repeated testing may invalidate results, possibility of learned response to stereotest in particular
Kennedy *et al*.[65] 1995 Canada	Prospective clinical trial using general population	Total of 1245 kindergarten children in study Standard examination was performed by ophthalmologist and orthoptist in a random sample of 20% of all children with normal screening results ($n = 241$) plus all those with abnormal results ($n = 29$) Assessment of Otago photoscreener: sensitivity 81%; specificity 98%; PPV 77%; NPV 1.6%
Ottar *et al*.[66] 1995 USA	Prospective study to assess MTI photoscreener	949 patients included in study; average age was 28.7 months Underwent assessment with photoscreener and had complete orthoptic and ophthalmological examination including cyclo refraction Sensitivity 81.77%; specificity 90.62%; PPV 68.86%; NPV 95.15%
Donahue *et al*.[67] 2002 USA	Prospective study to assess sensitivity of MTI photoscreener	Used same data set as Ottar *et al*.,[66] but adopted different referral criteria *Sensitivity to detect anisometropia*

Amount[a]	*N*	Passed	Referred	Sensitivity (%)[b]
+1.25 Sph	5	3	2	46
+1.50 Sph	12	10	2	48
+2.00 Sph	6	1	5	89
+2.50 Sph	1	0	1	100
+3.00 Sph	1	0	1	100
+3.50 Sph	1	0	1	100
Total	26	14	12	

[a] Inter-eye difference in refractive error in greatest meridian
[b] Sensitivity to detect amblyogenic factor of this or greater magnitude

continued

Code/Country	Study design	Numbers
		Sensitivity to detect hypermetropia

Amount (D)	*N*	Pass	Refer	Sensitivity (%)
+3.75	2	1	1	53
+4.00	6	3	3	53
+4.25	1	1	0	54
+4.50	7	6	1	55
+5.00	3	1	2	70
+5.25	3	1	2	71
+5.50	8	4	4	71
+5.75	3	0	3	100
+6.00				
>6.00	3	0	3	100
Total	36	17	19	

Sensitivity to detect astigmatism

Amount of astigmatism	*N*	Pass	Refer	Sensitivity (%)
+1.75	11	7	4	57
+2.00	13	7	6	63
+2.25	1	0	1	70
+2.50	14	5	9	69
+2.75	1	1	0	75
+3.00	3	1	2	82
+3.50	4	1	3	88
+4.00	1	0	1	100
+4.50	2	0	2	100
+6.00	1	0	1	100
Total	51	22	29	

Hatch *et al.*[68] 1997 USA	Cross-sectional field study to assess MTI photoscreener	161 children in study aged 2 to 10 years (mean age 6 years 6 months) Underwent examination with photoscreener and VA, objective refraction, CT and ophthalmoscopy Used two referral criteria which altered sensitivity and specificity of test Sensitivity 54% or 53%; specificity 87% or 91%; PPV 52% or 45%

continued

Code/Country	Study design	Numbers
Cordonnier and Dramaix[69] 1999 Belgium	Prospective study to assess the reliability of Retinomax to assess astigmatism	1205 children had non-cyclo screening with Retinomax (aged 9–36 months) 302 had cyclo refraction with Retinomax; 88 had retinoscopy or further examination *Results*

Manifest cylinder	Positive test: *n* (%)	Negative test: *n* (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
⩾2D						
Right eye	20 (23)	68 (77)	52	95	85	76
Left eye	25 (29)	62 (71)	65	90	76	87
⩾1.75D						
Right eye	23 (26)	65 (74)	58	93	83	78
Left eye	35 (40)	52 (60)	83	81	69	90
⩾1.5D						
Right eye	31 (35)	57 (65)	82	93	87	89
Left eye	40 (46)	47 (54)	89	76	65	94

Code/Country	Study design	Numbers
Cordonnier and Kallay[70] 2001 Belgium	Prospective study of Retinomax autorefractor	1218 children; 239 had refractive error (19.6%); 979 had no refractive error (80.4%) on cyclo refraction Of 1218, 302 also had autorefractor assessment *Results of autorefractor test*

Refractive anomaly	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hypermetropia	46	97	55	96
Myopia	87	99	33	100
Astigmatism	37	99	69	96
Anisometropia	66	93	19	99

Code/Country	Study design	Numbers
Barry and Konig[71] 2001 Germany	Prospective study of Retinomax autorefractor in kindergarten children	427 kindergarten children assessed without cyclo using Retinomax GSE by orthoptist performed on all children, also examined by ophthalmologist if abnormal findings present 404 children obtained GSE; 10 (2.5%) had a 'positive' gold standard of unknown and untreated amblyopia *Screening sensitivity*

Screening option	Sensitivity (%)	Specificity (%)
Spherical equivalent ⩾–1 or +3D or >1.5DC, or >1D anisometropia	80	58
Spherical equivalent ⩾–3 to +1.5D or = 2DC, or = 1.5D anisometropia	70	60

continued

Code/Country	Study design	Numbers
Allen[73] 1990 UK	Retrospective study comparing visual screening programme	Examined records of children aged 5 years and under referred to two hospitals in UK and compared number of referrals between two districts (one with and one without an orthoptic screening programme)

Results

Referrals	Screened district, *N* (%)	Non-screened district, *N* (%)
True positive	275 (79)	169 (57)
False positive	73 (21)	129 (43)

Jarvis *et al.*[74]
1991
UK

Compare 3 programmes in terms of: rate of screening coverage of population for which it was intended; rate and timing of target condition identification in the whole population irrespective of the source of referral; sensitivity, specificity and predictive value of the tests

Timing and content of screening in the three areas

Area	Younger cohort	Older cohort	Place and personnel
Northumberland comparison[a]	7–9 months: squint check	30–36 months: squint check[b]	Local arrangement by health visitor, GP, clinical medical officer
Orthoptist[c]	5 months: history and observation, CT, OM, 20Δ, convergence	35 months: as at 5 months and VA (SG or Kays)	By invitation (×2) to community orthoptist in local clinic
Newcastle comparison[d]	9 months: standard check, "doubt about infant or personal/family history of squint"	30 months: standard check, "pick up a thread"	Home visit from HV

[a] Squint check also at 18 months
[b] Always ask parents if they have noticed a squint, then look for obvious squint and look for symmetry of CR, near and dist VA
[c] Superimposed on the Newcastle system (see comparison area)
[d] Other opportunities for universal vision surveillance also occur during the 6 and 18 months

Coverage of screening in the three areas

	Younger cohort			Older cohort		
	Size	Records seen	Coverage[a] (%)	Size	Records seen	Coverage[a] (%)
Northumberland comparison (HV, GP)	1066	903	61	1151	967	84
Newcastle comparison (orthoptist)	1050	1050	71	1026	1026	60
Newcastle comparison (HV)	1410	1321	81	1380	1259	59

[a] As a proportion of records seen

continued

Code/Country	Study design	Numbers

Screening data
8600 records examined from 24 clinics. Represented 93% of target populations in different cohorts

Coverage rates of 60–70% achieved by orthoptist are similar to those in comparison areas

Younger cohort
1050 eligible and called: 305 of these failed to attend (FTA)

742/1050 screened (3 additional referred for screening)

Of screened (745) 701 passed: 41 kept under review; of the 41, 4 not sent for; 1 referred on by GP; 7 FTA; 29 reviewed; of the 29 reviewed, 29 passed

Older cohort
1026 eligible and called: 415 of these FTA

582/1026 screened (29 additional referred for screening)

Of screened (611) 461 passed: 121 kept under review; of the 121, 3 not sent for; 12 referred on by GP; 37 FTA; 81 reviewed; of the 81 reviewed, 58 passed; 11 for re-review; of these 11, 1 not sent for; 7 FTA; 3 re-reviewed; of these 3 re-reviewed, 3 passed

Target population data
138 potential cases of target conditions identified

These children were the 'incident' cases who were first referred after entry into the cohorts at age 5 and 30 months

Preliminary data show little difference between the three programmes for the younger cohorts but a striking difference in favour of orthoptist programme for older cohorts ($\chi^2 = 42.0$ and 24.3, df = 2, $p < 0.001$)

Performance characteristics of PSVS where correct: (a) any target condition and (b) treated target conditions only (numerator/denominator)

	Sensitivity (%)		Specificity (%)		PPV	
	(a)	(b)	(a)	(b)	(a)	(b)
Younger cohorts						
Orthoptist pilot area (5-month screen)	25 (1/4)	50 (1/2)	99.7 (739/741)	99.7 (741/743)	33 (1/3)	33 (1/3)
Newcastle comparison area (9-month HV check)	17 (1/6)	0 (0/3)	99.7 (1132/1136)	99.6 (1134/1139)	20 (1/5)	0 (0/5)
Older cohorts						
Orthoptist area (35-month screen)	100[a] (28/28)	100[a] (21/21)	98.3[a] (570/580)	97.1[a] (570/587)	74 (28/38)	55 (21/38)
Newcastle comparison area (30-month health visitor check)	43 (3/7)	50 (3/6)	100 (807/807)	100 (808/808)	100 (3/3)	100 (3/3)

[a] Fisher exact two-tailed probabilities of difference between orthoptist and comparisons ⩽0.01

continued

Code/Country	Study design	Numbers
Allen and Bose[75] 1992 UK	Audit evaluating preschool vision screening	Screening conducted by medical officers on children aged $3^1/_2$ years consisting of VA using Stycar Results compared with vision tests results recorded following school nurse examinations of VA at age 6 years Random sample of 599 records selected, data available for 531, uptake of screening 53.5% Of 284 children who attended: sensitivity 77%, specificity 96%. PPV of screening programme 50%
De Becker *et al.*[76] 1992 Canada	Prospective study children screened aged between 4.5 and 5.5 years 11,814 eligible for screening by EVSP (enhanced vision screening programme) 11,734 were screened Screening performed by nurses Gold standard performed by orthoptist and ophthalmologist	*Screening examination (failure)* Any anomaly noted on inspection; HOTV chart VA of 6/9–3 or worse in one or both eyes; stereo worse than 200 seconds *Gold standard examination* HOTV; stereo (Randot); Worth-4-Dot; PFR (number and distance); CT (number and distance); prism cover test (number and distance); 4Δ (distance); EOM; convergence; pupils; cyclo refraction and fundus examination *Gold standard examination (failure)* VA of 6/9–3 or less in one or both eyes; difference in VA of 2 lines or more between eyes; stereo <70 seconds Randot; presence of constant/intermittent tropia, monofixation syndrome; myopia ⩾0.75DS; hypermetropia ⩾3.50DS; astigmatism ⩾1.50DC; anisometropia (spherical or cylindrical) ⩾1.00 Subjects divided into 'pass' or 'fail' A geographically stratified random sample of 200 'pass' chosen to have gold standard A geographically stratified random sample of 45 'fail' chosen to have gold standard 43 did not participate; 157 examined In this group, 11 (7%) failed gold standard, 146 passed (93%) Of 45 chosen who had 'fail' EVSP, 36 were examined (80%) Of these, 18 (50%) failed gold standard NPV of 93% (95% CI 89 to 97); PPV of 50% (95% CI 31 to 63) As screening test for amblyopia, strabismus, and/or refractive error, EVSP has NPV of 98.7% (155/157) (95% CI 95.4 to 99.85) As screening test for potentially vision-threatening ocular condition, EVSP has NPV 97.6% (153/157), (95% CI 93.5 to 99.3) Gold standard examination took place within 3 months of screening Examiners were unaware of screening result Of 11 who had failed gold standard, 7 had minor ocular problems, 2 had a potentially vision-threatening condition other than amblyopia, strabismus and/or refractive error Refers to papers to justify why tests performed were chosen

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td>Williamson et al.[77]
1995
UK</td><td>Retrospective study of case records
Screening performed by orthoptists
Screened age 3.5–4.5 years
Screened twice if doubt about referral to ophthalmologist
Those referred had atropine refraction
Prescribed glasses if amblyopia or strabismus present or >+4DS
Excluded from analysis if Sn acuity unavailable (86 excluded)</td><td>History; FH of strabismus, glasses or amblyopia; VA with SSG; CT, number and distance; EOM; 20Δ; stereo with Randot or TNO
Referral criteria: VA of 6/9 or less in EE (including an obvious struggling 6/6 vision), or strabismus, or abnormality of EOM, or FH, or lack of response on 20Δ, or negative stereo
Summary: sent for 90%; screened 51%; attended hospital 39%; completed treatment 33%
Screening tests: using amblyopia definition A (%), baseline VA
<table>
<tr><th>Test</th><th>N</th><th>Worse than 6/9 true-positive</th><th>6/9 or better false-positive</th><th>% or total (all positive)</th></tr>
<tr><td>VA worse than 6/6</td><td>566</td><td>98.8</td><td>87.6</td><td>92.2</td></tr>
<tr><td>VA worse than 6/9</td><td>566</td><td>82.7</td><td>46.9</td><td>62.3</td></tr>
<tr><td>CT</td><td>574</td><td>30.2</td><td>17.3</td><td>22.9</td></tr>
<tr><td>20Δ</td><td>534</td><td>18.8</td><td>7.3</td><td>11.3</td></tr>
<tr><td>Conv</td><td>542</td><td>5.0</td><td>3.9</td><td>4.7</td></tr>
<tr><td>EOM</td><td>574</td><td>11.1</td><td>6.5</td><td>8.1</td></tr>
<tr><td>A or V pattern</td><td>574</td><td>2.0</td><td>6.5</td><td>4.5</td></tr>
<tr><td>Stereo</td><td>510</td><td>31.0</td><td>10.5</td><td>19.2</td></tr>
<tr><td>Family history of amblyopia</td><td>413</td><td>31.2</td><td>17.5</td><td>23.2</td></tr>
<tr><td>Family history of glasses</td><td>516</td><td>75.7</td><td>71.4</td><td>73.3</td></tr>
<tr><td>Family history of strabismus</td><td>512</td><td>37.2</td><td>24.4</td><td>28.3</td></tr>
</table>
</td></tr>
<tr><td>McNamara and Duckworth[78]
1998
UK</td><td>Retrospective survey of referral letters</td><td>157 letters used in study referring ages 1 month to 5 years 1 month; 10 did not state reason for referral
Primary care referrals (%) to orthoptic secondary screening service
<table>
<tr><th>Health professional</th><th>1994–5</th><th>1995–6</th><th>1996–7</th></tr>
<tr><td>Health visitor</td><td>45</td><td>53</td><td>53</td></tr>
<tr><td>Clinical medical officer</td><td>27</td><td>18</td><td>19</td></tr>
<tr><td>GP</td><td>18</td><td>14</td><td>9</td></tr>
<tr><td>School nurse</td><td>10</td><td>15</td><td>19</td></tr>
</table>
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continued

Code/Country	Study design	Numbers

Distribution of diagnoses[a]

Diagnosis	0–5 years, *n* = 635 (%)	<3 years, *n* = 337 (%)	>3 years, *n* = 298 (%)
1. No apparent deviation	179 (28.2)	19.58	37.91
2. Pseudostrabismus	275 (43.3)	66.76	16.77
3. Reduced VA	102 (16.1)	4.45	29.19
4. Straight amblyopia	20 (3.1)	0.29	6.37
5. ET	37 (5.8)	5.34	6.37
6. XT	15 (2.4)	2.37	2.34
7. Paralytic	6 (0.9)	1.18	0.67
8. Convergence insufficiency	1 (0.1)	0.0	0.33

[a] New patient contacts referred by HV to orthoptic secondary screening service 1994–5.

PPV in total sample group, n = *157*[a]

Diagnosis	FH	FC	FT	FH/C	FH/T	FC/T	FH/C/T	Unknown	Total
1. NAD	6	7	21	6	12	3	2	1	58
2. Pseudostrabismus	1	8	8	10	6	8	2	1	44
3. Reduced VA	4	0	8	1	0	2	1	8	24
4. Straight amblyopia	1	0	0	0	1	0	0	0	2
5. ET	0	2	2	0	3	4	4	0	15
6. XT	0	1	1	0	1	1	1	0	5
7. Paralytic	0	0	0	1	0	1	0	0	2
8. CI	0	0	0	0	0	0	0	0	0
Unknown	1	0	2	1	2	1	0	0	7
Total	13	18	42	19	25	20	10	10	157
PPV	41.66	16.66	27.50	11.11	21.73	42.10	60.0		

[a] FC, family concern; FH, family history; FT, failed tests.

PPV for referrals by age and healthcare professional

Age (years)	HV, no. (PPV, %)	CMO, no. (PPV, %)	GP, no. (PPV, %)	SN, no. (PPV, %)	Total no.
0–1	49 (14.3)	0	11 (9.0)	0	60
1–2	176 (10.2)	5 (0)	50 (4.0)	0	231
2–3	112 (18.75)	2 (0)	26 (26.9)	0	140
3–4	76 (31.6)	14 (0)	20 (35.0)	0	110
4–5	177 (52.5)	24 (12.5)	56 (35.7)	0	257
5+	45 (40.0)	337 (6.2)	90 (27.7)	148 (44.6)	620
Total	635	382	253	148	1418

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td>Robinson et al.[79]
1999
Canada</td><td>Examined PSVS conducted by nurses in 3-year period

Conducted by 6–9 public health nurses from 1992 to 1994

Child's records reviewed

Rate of refusal small but increased over the 3 years (from 0.6 to 3.2 to 7.8%)

Nurses trained each year to conduct tests of VA and ocular alignment</td><td>
VA tests: Cambridge Crowding cards at 3 m; classified 6/9 as 'failure'

Ocular alignment: Hirschberg test with small target used with light at 40–50 cm; position of corneal reflections (CR) compared between left and right eyes; If relative positions of CR were asymmetric counted as 'fail'; test was discontinued after second year

Stereoacuity: during second year was introduced; used Titmus; norm of 100 seconds set; if not achieved, this counted as 'fail'

Referral: failures of any component of screening were referred; fail to complete screening also referred (average of 1.8% across 3 years); for each child who failed the screening, nurses referred the next child who passed as a control (a 'next in line' protocol); parents and practitioners were masked to the screening results of all children referred

Data analysis
Goal of screening was to detect strabismus and amblyopia and significant refractive errors

Following defined as being problems if found by practitioner: presence of any strabismus, intermittent or constant, at any fixation distance; anisometropia defined as a difference of 1D or more between the refractive error (spherical equivalent) of the right eye and that of the left eye; hypermetropia of 2D or more in any meridian in each eye (EE); myopia of 1D or more along any meridian in EE; astigmatism of more than 1D in EE

Study population characteristics
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th></tr>
<tr><td>Total</td><td>1174</td><td>1110</td><td>1150</td></tr>
<tr><td>Age, mean (months)</td><td>53.8</td><td>52.9</td><td>51.2</td></tr>
<tr><td>Age, range (months)</td><td>39–67</td><td>37–75</td><td>37–66</td></tr>
<tr><td>Sex, boys (%)</td><td>50.9</td><td>49.5</td><td>52.3</td></tr>
</table>
Results of vision screening
<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th></tr>
<tr><td>Failures, no. (%)</td><td>339 (28.9)</td><td>385 (34.7)</td><td>293 (25.5)</td></tr>
<tr><td>Controls, no.</td><td>312</td><td>297</td><td>240</td></tr>
<tr><td>Forms returned, no. (failures, controls)</td><td>527 (81.7%, 80.4%)</td><td>573 (82.9%, 85.5%)</td><td>405 (77.1%, 74.6%)</td></tr>
<tr><td>PPV (%) (95% CI)</td><td>25.4 (20.2 to 30.5)</td><td>21.6 (17.1 to 26.2)</td><td>32.3 (26.2 to 38.4)</td></tr>
<tr><td>NPV (%) (95% CI)</td><td>93.6 (90.5 to 96.6)</td><td>95.3 (92.7 to 97.9)</td><td>92.6 (88.7 to 96.5)</td></tr>
<tr><td>Yield (%) of true-positives newly diagnosed</td><td>89</td><td>83</td><td>83.6</td></tr>
</table>
Estimated validity
<table>
<tr><th></th><th>Year 1</th><th>Year 2 (with stereo)</th><th>Year 3</th></tr>
<tr><td>Sensitivity (%)</td><td>61.9</td><td>70.9 (83.8)</td><td>60.4</td></tr>
<tr><td>Specificity (%)</td><td>75.6</td><td>69.6 (64.6)</td><td>79.7</td></tr>
<tr><td>Prevalence (%)</td><td>11.8</td><td>10.5</td><td>13.8</td></tr>
</table>
</td></tr>
</table>

continued

Code/Country	Study design	Numbers
		>110 completed vision screening each year and were enrolled into study
		Represented from 92.2 to 99.4% of total population that attended health fairs
		Proportion of children who failed screening ranged from 25.5 to 34.7%
		Number of 'controls' never exactly equal to number of 'failures'
		Proportion of practitioner reports received each year was 81, 84 and 75.2%
		Annual comparisons showed no statistically significant difference between the population received for children who failed the screening and for children referred as controls ($z \leqslant 0.81$, $p > 0.4$)
		PPV varied from 21.6 to 32.3% and NPV from 92.6 to 95.3% over 3 years
		Yield (proportion of children who passed screening and showed no vision problem) is high, where between 83 and 89% of children identified as having a vision problem were so identified for the first time
		Number of true-positives each year was similar (70, 69, 74)
		Overall sensitivity of screening varied from 60.4 to 70.9% for annual measures
		Sensitivity highest (83.8%) during year 2, when the estimate was based on only the 775 tested with both the Hirschberg and stereo tests
		Specificity was generally higher than sensitivity, from 69.9 to 79.7%
		Specificity at lowest in year 2 (64.5%) when both stereo and Hirschberg tests were used
Mulley[80] 2000 UK	Comparison of two groups, screened at 1.5 and 3.5 years	*1.5 years*: CT, OM, convergence, 20Δ, Frisby or Lang, photorefraction
		Failure: constant or intermittent strabismus; anomaly of OM; photorefraction >+0.50DS, >–1.25DS, >±1.25DC. Not referred on failure of stereo or 20Δ
		3.5 years: VA (Sonksen Silver, Kay or SSG if not linear SG), CT, OM, convergence, 20Δ, stereo (Frisby, Lang or TNO), photorefraction
		Failure: VA worse than 6/6 in EE; constant or intermittent strabismus; anomaly of OM; photorefraction >+0.50DS, >–1.25DS, >±1.25DC. 6/9 on Sonksen with no refractive error on photo were passed. Had to have 6/6 with EE if using single optotype: all children who failed were referred to hospital
		1.5 years: 1422 children seen; 191 referrals (13.4%); attendance rate 59%; 140 notes to analyse (51 cases notes could not be found on FTA appointment); of 140, 105 were true-positive, 35 were false-positive (25%). PPV 75%
		3.5 years: 917 children seen; 133 referrals (14%); attendance rate 67%; 110 notes to analyse (9 records unavailable and 14 FTA); of 110, 96 were true-positive, 14 false-positive (12.7%). PPV 87%
		Total: 457 children as attending both assessments; 15 true-positive at 1.5 years; 7 were discharged with no glasses or treatment and found to be error free at the 3.5-year screening; OR 1.9643 (95% CI 1.1139 to 3.4636; $p < 0.05$)

continued

Code/Country	Study design	Numbers
Eibschitz-Tsimhoni *et al.*[81] 2000 Israel	Compared two groups at 8 years for prevalence and severity of amblyopia Amblyopia defined as corrected VA of 20/40, of >1 line difference in corrected VA between both eyes	*Group 1*, n = *808*: screened group; examined by ophthalmologist or orthoptist trained in retinoscopy: examination includes case history, Hirschberg, 'fix-and-follow', cover test *Group 2*, n = *782*: not screened; both groups similar in ethnic/racial mix, social classes, healthcare facilities, education, nutrition, climate 998 invited for screening at 1–2.5 years; of these, 180 did not comply, 808 did Of 808, screened for amblyopia and amblyogenic risk factors (RF) at 1–2.5 years: 779 amblyopia or RF for amblyopia not found. Re-examination at 8 years found 3 with amblyopia (FN) and 776 no amblyopia (TN) Of 808, 29 (3.58%) had amblyopia, or RF for amblyopia suspected. Then had confirmatory examination 18 (of 29) found to be at risk for amblyopia – treated (TP). Of these, 5 had amblyopia and 13 no amblyopia 11 (of 29) found no amblyogenic RF (FP) Control group of 782 examined at 8 years, 20 had amblyopia, 762 no amblyopia Prevalence of amblyopia of 8 years lower in screened than in non-screened population; 8 of 808 (1%) versus 20 of 782 (2.6%), $p = 0.0098$ Prevalence of severe amblyopia (⩽20/60) in the amblyopic eye was 1 of 808 (0.1%) compared with 13 of 782 (1.7%), $p = 0.00026$ Screened for amblyopia sensitivity 85.7% as calculated from prevalence of amblyopia in 8-year study population Specificity was 98.6%; PPV 62.1%, NPV 99.6%
Juttmann (RAMSES)[82] 2001 The Netherlands	All children born between September 1996 and May 1997 (4637) included in RAMSES study Screening programme consists of screening for strabismus at 9, 14 and 24 months at child health centre, VA test by pictures or Sn at 36 and 45 months at child health centre, VA with Sn at 66 months in school	4637 children identified, 565 moved. Study deals with 4072 remaining children; 160 exposed to screening (4%) were referred as a result of abnormal finding 64 (of 101) with positive screening test followed by an effective ref did have some ophthalmic disorder. Of these, 22 did not have symptoms of amblyopia but of other disorders (ptosis, haemorrhage, infections) Other 42 did have clear indications for amblyopia, strabismus in 33, refractive error in 20 PPV for any ophthalmic disorder 0.63 and for amblyopia 0.42

Screening test	Children screened	Coverage (%)
9 months	3619	89
14 months	3678	90
24 months	3244	80
At least once at one of these ages	3958	97

continued

Code/Country	Study design	Numbers
		Number of abnormal findings

Screening test	No. screened	Referred as result of an abnormal finding (for first time)	%
9 months	3619	52	1.9
14 months	3678	54	1.5
24 months	3244	54	1.7
At least once at one of these ages	3958	160	4.0

Results of evaluation at hospital predicted value of positive screening test followed by an effective referral (PPV)

Screening test	No. evaluated by ophthalmologist	Visual disorder not amblyopia	(Probably) amblyopia	PPV all visual disorders	PPV amblyopia
9 months	41	7	15	0.54	0.37
14 months	36	9	12	0.58	0.34
24 months	24	6	15	0.88	0.62
Total	101	22	42	0.63	0.42

Barry and Konig[83] 2003 Germany	Prospective study 121 kindergartens; All 3-year-old children attending eligible for study Nearly all eligible children enrolled <10% of children enrolled could not be examined on scheduled day owing to absence	*Gold standard (GS)* Study population re-examined in kindergarten after 3–6 months by a different orthoptist with a more demanding threshold for monocular VA of >0.63 in each eye (EE) to pass examination (phase 2) Children who reached 0.5 or 0.63 in EE were 'borderline', which entailed referral for gold standard purposes *Criteria for positive gold standard* Newly given glasses therapy if corrected VA ≤0.4 in EE, or difference in VA >2 log lines, except myopia Newly started occlusion in presence of risk factors such as strabismus or high refractive error (≥1.5DS or ≥3DC) *Orthoptic screening*: performed by 5 orthoptists; results positive (any path), negative (within norm limits) or inconclusive (insufficient cooperation, etc.): inspection of anterior segment; CT number distance; OM and AHP; uncorrected monocular VA using Lea single optotypes at 3 m; VA of 0.4, or if line difference >1 line and VA in worse eye equal to 0.5–0.63 Starting VA was 0.4, to pass line 3 of 4 symbols had to be identified; VA testing discontinued when 1.0 reached Sample size 1180: mean age 42.7 months, 50.6% male *Children already treated for amblyopia* 21 (1.8%; 95% CI 1.0 to 2.5%) who had already been treated for amblyopia 11 had strabismic amblyopia 10 refractive/anisometropic amblyopia. Verified by records. For these gold standard rated 'negative' as already treated, excluded from sample for calculation of the specificity of screening in order to avoid a bias towards false-positives

continued

Code/Country	Study design	Numbers

Phase 1: 1047 (88.7%) of 1180 provided conclusive result (ref or no-ref); 133 (11.3%) had inconclusive result

Phase 2: 194 (16.4%) of children examined in phase 1 were not present in days of orthoptist testing, 957 (97.1%) of 986 present were cooperative to test

Gold standard results
1114 (94.4%), including 21 already treated before screening, had gold standard examination; 66 for whom no gold stand result obtained all had 'inconclusive' orthoptic examination results; 42 examined by ophthalmologist. 0 was target disease identified

Positive gold standard results
In 26 children gold standard was positive (2.3%, 95% CI 1.4 to 3.2%). Occlusion started in 7 gold standard positive children, 19 received glasses only

Test characteristics of orthoptic vision screening
Results of phase 1 in 1093 children for whom gold standard obtained and who were not treated for amblyopia or amblyogenic risk factors before screening. Inconclusive results excluded

Screening item	Inconclusive results: no. (%)	Positive results: no. (%)	Negative results: no. (%)	No. of conclusive results	Proof detected gold stand positive cases[a]	Sensitivity (%)	Specificity (%)
Inspection	0 (0)	2 (0.2)	1091 (99.8)	1093	1/26	3.8	99.9
Ocular motility	47 (4.3)	12 (1.1)	1034 (94.6)	1046	3/25	12	99.1
Cover test	51 (4.7)	13 (1.2)	1029 (94.1)	1042	4/25	16	99.1
VA	118 (10.8)	63 (5.8)	912 (83.4)	975	19/22	86.4	95.4
Cumulated	118 (10.8)	79 (7.2)	896 (82)	975	20/22	90.9	93.8

[a] Proportion of detected cases with positive gold standard among all cases with positive gold standard in children with conclusive result for the screening item (equal to sensitivity)

Of 26 gold standard positive, 22 with conclusive results in phase 1 (without 18 already treated)

Sensitivity of screening 90.9% (20/22); specificity 93.8% (894/953); PPV 25.3% (20/79); NPV 99.8% (894/896)

To increase effectiveness, 'inconclusive' results could be rated 'ref' with the 'positive' screening results; would increase sensitivity to 92.3% (23/26); this would decrease specificity considerably

Orthoptic screening: conclusive $n = 993$; sensitivity 90%; inconclusive $n = 121$; sensitivity 0%

Orthoptic examination or ophthalmic examination: conclusive $n = 867$; sensitivity 90%; ophthalmologist $n = 126$; sensitivity 100%; conclusive $n = 87$; sensitivity 90%; ophthalmologist $n = 34$; sensitivity 100%

Combined sensitivity: conclusive 99.0%; ophthalmologist 100%; conclusive 90%; ophthalmologist 100%

Proportion of screened population: conclusive 77.8%; ophthalmologist 11.3%; conclusive 7.8%; ophthalmologist 3.1%

Overall (weighted) modelled sensitivity: 98.4%

continued

Code/Country	Study design	Numbers
Chiu *et al.*[84] 2004 Canada	Prospective study, completed over two summers Performed by nurses (trained by orthoptists) Orthoptists performed GSE (and ophthalmologist) Children aged 36–48 months (3–4 years)	*Screening tests*: VA with linear Lea log symbols; stereo with Frisby; external examination of eye with pen torch, obvious strabismus, gross abnormality of eyes and ocular adenexa *Failing screening*: 6/12–2 or worse in 1 or best eye (BE); stereo worse than 600 seconds; any abnormality noted on inspection *Gold standard*: VA using linear Lea log symbols; stereo (Titmus, Frisby, Worth-4-Dot); ocular alignment (fusional amplitudes, cover test extraocular movements, convergence, 4Δ); pupillary reaction; external examination of eyes; cyclo refraction; slit lamp examination; fundus examination *Failing gold standard*: 6/12–2 or worse in 1 or BE; difference in VA of ⩾2 lines between eyes; stereo <600 seconds Frisby or <400 seconds Titmus; presence of any constant/intermittent tropia, monofixation syndrome; myopia ⩾0.75; hypermetropia ⩾3.50; astigmatism ⩾1.50; anisometropia ⩾1.00; any other anomaly warranting follow-up; inability to complete GSE *Summer 1*: 70 children

	Clinic positive	Sign (failure)	GS negative	Examination (pass)
Age (months)	<41	⩾41	<41	⩾41
Positive screen (failed)	9 (A)	2 (A)	13 (B)	0 (B)
Negative screen (passed)	6 (C)	0 (C)	17 (D)	23 (D)
Sensitivity (%)		A/(A + C)	60	100
Specificity (%)		D/(B + D)	57	100
False-positive rate (%)		1 – specificity	43	0
PPV (%)		A/(A + B)	41	100
NPV (%)		D/(D + C)	74	100

Summer 2: 72 children: 1 child refused drops (excluded)

63 ⩾41 months; 8 <41 months

Data added to existing data

	Clinic positive	Sign (failure)	GS negative	Examination (pass)
Age (months)	<41	⩾41	<41	⩾41
Positive screen (failed)	9 (A)	3 (A)	13 (B)	4 (B)
Negative screen (passed)	3 (C)	3 (C)	28 (D)	78 (D)
Sensitivity (%)		A/(A + C)	75	50
Specificity (%)		D/(B + D)	68	95
False-positive rate (%)		1 – specificity	32	5
PPV (%)		A/(A + B)	41	43
NPV (%)		D/(D + C)	90	96

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td></td><td></td><td>
Summer 1
Kappa values 1.0 ($p < 0.001$) with children aged ⩾41months ($n = 25$)
Since children <41 months ($n = 45$) provided marginally reproducible results ($\kappa = 0.15$, $p > 0.05$), older children sought for second screening session
Overall, little reproducibility between screening and GSE ($\kappa = 0.33$, $p < 0.01$)
Higher reproducibility occurred between screening and GSE in older age group ($\kappa = 0.42$, $p < 0.001$)
Difference between specificity ($p < 0.001$) and sensitivity ($p = 0.004$) values significant
Initially 7 false-negative with GSE ‘fail’ and EVSP ‘pass’
Failed due to amblyopia (1), refractive error found on refraction (5) and orthoptic abnormality (1)
Children with amblyopia re-examined and 1 found to be normal, removed from statistics
</td></tr>
<tr><td>Rosner & Rosner[85]
1988
USA</td><td>Retrospective study of case records</td><td>
Children aged 3–71 months; 536 included in study
Group A: parent believes child has squint, professional agrees
Group B: parent believes child has squint, professional disagrees
Group C: parent believes child has no squint, professional disagrees
Group D: parent believes child has no squint, professional agrees
Group A, 55 (10.3%); group B, 4 (0.7%); group C, 29 (5.4%); group D, 448 (83.6%)
<table>
<tr><th>Age (years)</th><th>A</th><th>B</th><th>C</th><th>D</th><th>Total</th></tr>
<tr><td>0–1</td><td>3</td><td>3</td><td>0</td><td>31</td><td>37</td></tr>
<tr><td>1–2</td><td>5</td><td>1</td><td>2</td><td>43</td><td>51</td></tr>
<tr><td>2–3</td><td>8</td><td>0</td><td>2</td><td>57</td><td>67</td></tr>
<tr><td>3–4</td><td>8</td><td>0</td><td>4</td><td>62</td><td>74</td></tr>
<tr><td>>4</td><td>31</td><td>0</td><td>21</td><td>255</td><td>307</td></tr>
<tr><td>Total</td><td>55</td><td>4</td><td>29</td><td>448</td><td>536</td></tr>
</table>
Sensitivity: 55 of 84 (65%) correctly identified strabismus
Specificity: 448 of 452 (99%) thought no strabismus and correct
PPV 55 of 59 (93%): 59 thought to have strabismus by parents, and 55 did
Once >2 years, parents more accurate in positively identifying strabismus and usually accurate in ruling out strabismus; aged 1–2 years, parents almost always accurate in positively identifying strabismus and reasonably accurate in ruling out strabismus; <1 year, parents not as accurate in positively identifying strabismus, but accurate in ruling out strabismus
</td></tr>
</table>

continued

Code/Country	Study design	Numbers
Paysse *et al.*[86] 2004 USA	Prospective experimental study EVA (electronic visual acuity) tester ATS (Amblyopia Treatment Study) VA testing protocol VA measured by parents and technician (not specified type) Aged 3–9 years 4-month enrolment period	Crowded optotype test Inclusion criteria of VA of 20/125 or better in the tested eye(s) and ability to identify correctly the HTOV optotypes with crowding bar around them; right eye always tested first; VA scores then converted to logMAR Part 1: reliability of parent administered EVA Part 2: efficiency as a result of parent pre-screening *Part 1*: 64 children (127 eyes); tested twice in sequential manner (right eye and left eye, parent; right eye and left eye, technician) Right eye ($n = 59$), $r = 0.91$; left eye ($n = 61$), $r = 0.81$ Mean age 5.6 ± 1.7 years 25 male (37%); 35 (55%) Caucasian, 18 (28%) Hispanic, 9 (14%) African American, 2 (3%) Middle East *Part 2*: 44 children; all eligible eyes tested; randomly assigned to one of two groups Group A: parent prescreen group. VA tested by parent. Technician then tested with Reinforcement Phase and Phase II of ATS protocol Group B: full ATS protocol, measured by technician. Number of optotypes needed to obtain VA was recorded 22 children, 44 eyes in each group A: 4.8 ± 1.5 years, VA 20/29. B: 4.4 ± 1.2 years, VA 20/31 14 patients (64%) in each group were male Group A: 14 (64% Caucasian, 4 (18%) Hispanic, 3 (14%) African American, 1 (0.5%) Middle East Group B: 11 (50%) Caucasian, 5 (23%) Hispanic, 6 (27%) African American 14 patients (64%) in each group were male *Part 1*: 6 had amblyopia; 58 normal VA Reliability of parent-determined VA scores was high compared with technician scores [$r = 0.91$ (right eye) and 0.81 (left eye)] with 93% right eye parent scores and 85% parent scores within 0.11 logMAR of technician score (right eye, $p = 0.15$; left eye, $p = 0.37$; Wilcoxon signed rank test) (right eye, $p = 0.29$; CI = 0.01 ± 0.02 logMAR; left eye, $p = 0.12$, CI = 0.02 ± 0.03 logMAR; paired *t*-test) Of eyes that had different VA on retest, more had a better VA on retest (right eye 35% better versus 23% worse; left eye 34% better versus 20% worse) *Part 2*: mean number of optotypes to obtain to VA score Group A, right eye = 7.5, left eye = 7.1; group B, right eye = 21.7, left eye = 22.4 Right eye, $p = 5.4 \times 10^{-18}$; left eye, $p = 6.5 \times 10^{-18}$ Reliability did not vary by the level of acuity; reliability did not vary by age *Part 1*: Found EVA highly reliable and accurate when used by parents. *Part 2*: Parent prescreening enabled the technician to determine VA with a 300% decrease in number of optotypes shown to child (decrease in testing time)

continued

Code/Country	Study design	Numbers
VIP[87] 2005 USA	Prospective study comparing trained nurses and lay screeners	Results compared with gold standard examination (GSE) by optometrist/ophthalmologist (described in other papers)

Sensitivity by vision in preschoolers (VIP) hierarchy of conditions with specificity set to 0.90 for screening tests

Screening test	Any condition[a] $n = 462$	Group 1 $n = 210$	Group 2 $n = 144$	Group 3 $n = 108$	Specificity $n = 990$
Retinomax autorefractor					
Nurse	0.68	0.88	0.59	0.39	0.90
Lay screener	0.62	0.85	0.49	0.36	0.90
Difference	0.06	0.03	0.10	0.03	
95% CI	0.02 to 0.09	–0.01 to 0.07	0.04 to 0.17	–0.06 to 0.12	
SureSight Vision Screener					
Nurse	0.64	0.83	0.57	0.34	0.90
Lay screener	0.61	0.82	0.51	0.34	0.90
Difference	0.03	0.01	0.06	0.00	
95% CI	–0.01 to 0.06	–0.02 to 0.05	0.00 to 0.12	–0.10 to 0.10	
Linear Lea Symbols (10 ft)					
Nurse	0.49	0.60	0.38	0.42	0.90
Lay screener[b]	0.37	0.50	0.19	0.35	0.90
Difference	0.12	0.10	0.19	0.07	
95% CI	0.05 to 0.19	–0.01 to 0.19	0.08 to 0.29	–0.06 to 0.20	
Single Lea Symbols (5 ft)					
Lay screener	0.61	0.78	0.51	0.40	0.91
StereoSmile II					
Nurse	0.45	0.58	0.37	0.30	0.90
Lay screener	0.40	0.56	0.31	0.23	
Difference	0.05	0.02	0.06	0.07	
95% CI	0.00 to 0.09	–0.05 to 0.09	–0.02 to 0.14	–0.04 to 0.15	
Lay screener[b]	0.47	0.70	0.31	0.26	

[a] Includes all children who had one or more VIP targeted condition regardless of whether the condition was subclassified into group 1, 2 or 3

[b] Lay screeners conducted testing in a VIP in the 2002 academic year. In the 2002 academic year, 391 children had one of more GSE conditions, 172 had group 1 conditions, 121 had group 2 conditions, 98 had group 3 conditions and 1055 had no GSE conditions

continued

Code/Country	Study design	Numbers

Sensitivity by condition type with specificity set to 0.90 for screening[a] tests

Screening test	Amblyopia *n* = 101	Reduced VA *n* = 117	Strabismus *n* = 47	Refractive error *n* = 387	Specificity *n* = 990
Retinomax autorefractor					
Nurse	0.87	0.48	0.62	0.78	0.90
Lay screener	0.81	0.46	0.60	0.71	0.90
Difference	0.06	0.02	0.02	0.06	
95% CI	0.00 to 0.12	–0.06 to 0.09	–0.10 to 0.15	0.03 to 0.10	
SureSight vision screening					
Nurse	0.82	0.52	0.53	0.70	0.90
Lay screener	0.79	0.53	0.49	0.69	0.90
Difference	0.03	–0.01	0.04	0.01	
95% CI	–0.03 to 0.09	–0.08 to 0.08	–0.06 to 0.14	–0.02 to 0.05	
Linear Lea Symbols (10 ft)					
Nurse	0.69	0.53	0.53	0.51	0.90
Lay screener[b]	0.56	0.48	0.39	0.37	0.90
Difference	0.13	0.05	0.14	0.14	
95% CI	0.00 to 0.27	–0.08 to 0.18	–0.05 to 0.31	0.07 to 0.22	
Single Lea Symbols (5 ft)					
Lay screener	0.87	0.61	0.79	0.64	0.91
StereoSmile II					
Nurse	0.64	0.43	0.64	0.47	0.90
Lay screener	0.61	0.37	0.72	0.42	
Difference	0.03	0.06	–0.08	0.05	
95% CI	–0.07 to 0.13	–0.04 to 0.14	–0.21 to 0.04	0.00 to 0.10	
Lay screener[b]	0.74	0.31	0.79	0.49	

[a] Children may have more than one condition

[b] Lay screeners conducted testing in VIP van in the 2002 academic year. In the 2002 academic year, 81 children had amblyopia, 96 had decreased VA, 62 had strabismus, 299 had significant refractive error, 1055 had no GSE conditions

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td>Edwards et al.[88]
1989
UK</td><td>Prospective 2-year study</td><td>Conducted between 1985 and 1987, comparing a community screening programme conducted by orthoptists with a dual system of HV and GP referral
Orthoptist programme: false-positive referral rate 1% (2 of 198 referrals)
Health visitor and GP programme: false-positive referral rate 67% (54 of 81 referrals)</td></tr>
<tr><td>Bolger et al.[89]
1991
UK</td><td>Cohort study using case notes of referrals
Two cohorts selected on basis of residential area and date of birth
Cohort 1: Southmead district born between July 1981 and June 1984
Cohort 2: Bristol and Weston district born between July 1981 and June 1984
Areas are socio-economically similar, both have low proportion of lower social classes and from ethnic minorities</td><td>Cohort 1: 263 referrals from 7105 children
<table>
<tr><th>Amblyopia</th><th>None</th><th>ET</th><th>XT</th><th>Other</th><th>Not known</th><th>Total</th></tr>
<tr><td>Right eye</td><td>21</td><td>13</td><td>3</td><td>0</td><td>0</td><td>37</td></tr>
<tr><td>Left eye</td><td>29</td><td>13</td><td>2</td><td>0</td><td>0</td><td>44</td></tr>
<tr><td>None</td><td>122</td><td>25</td><td>15</td><td>7</td><td>0</td><td>169</td></tr>
<tr><td>Not known</td><td>9</td><td>3</td><td>1</td><td>0</td><td>0</td><td>13</td></tr>
<tr><td>Total</td><td>181</td><td>54</td><td>21</td><td>7</td><td>0</td><td>263</td></tr>
</table>
81 of 263 had amblyopia (figure included 31 who also had strabismus)
Detection rate for amblyopia 11/1000 (95% CI 9 to 14/1000)
Cohort 2: 111 referrals from 2977 children
<table>
<tr><th>Amblyopia</th><th>None</th><th>ET</th><th>XT</th><th>Other</th><th>Not known</th><th>Total</th></tr>
<tr><td>Right eye</td><td>6</td><td>1</td><td>0</td><td>0</td><td>0</td><td>7</td></tr>
<tr><td>Left eye</td><td>2</td><td>5</td><td>0</td><td>0</td><td>0</td><td>7</td></tr>
<tr><td>None</td><td>91</td><td>2</td><td>0</td><td>0</td><td>0</td><td>93</td></tr>
<tr><td>Not known</td><td>2</td><td>0</td><td>0</td><td>1</td><td>1</td><td>4</td></tr>
<tr><td>Total</td><td>101</td><td>8</td><td>0</td><td>1</td><td>1</td><td>111</td></tr>
</table>
14 had amblyopia, 6 also had a squint
Detection rate for amblyopia 5/1000 (95% CI 2 to 7/1000)
Relative detection rate between cohorts was 2.4 (95% CI 1.4 to 4.1)
Referral rate from both areas 37/1000
Severity of amblyopia at initial diagnosis (%)
<table>
<tr><th>Cohort</th><th>6/9</th><th>6/12–6/18</th><th>6/24–6/36</th><th><6/36</th><th>Not known</th><th>Total</th></tr>
<tr><td>1</td><td>18 (22)</td><td>4 (52)</td><td>13 (16)</td><td>7 (9)</td><td>1 (1)</td><td>81 (100)</td></tr>
<tr><td>2</td><td>1 (7)</td><td>10 (71)</td><td>1 (7)</td><td>1 (7)</td><td>1 (7)</td><td>14 (100)</td></tr>
</table>
Proportion of amblyopia with 6/9 was higher in cohort 1; differences were not significant ($\chi^2 = 2.95$; $0.5 > p > 0.1$)</td></tr>
</table>

continued

Code/Country	Study design	Numbers

Change in VA of amblyopic eye from initial assessment to when last seen by second centre (%) (no. of lines of SG improved)

Cohort	0	1	2	3	⩾4	Not known	Total
1	7 (9)	22 (27)	23 (28)	15 (19)	10 (12)	4 (5)	81 (100)
2	2 (14)	4 (29)	4 (29)	2 (14)	1 (7)	1 (7)	14 (100)

No significant differences between groups ($\chi^2 = 0.8$; $p > 0.5$)

With exclusion of 'unknown', 61% (55/90) achieved improvement of 2 lines or more. 12% (11/90) improvement of 4 or more lines

Children in all categories of severity of amblyopia when initially seen achieved improvement

Squint detection rates

Cohort 1, 75 diagnosed with strabismus at second centre (with or without amblyopia); cohort 1, detection rate 11/1000 (95% CI 8 to 13/1000)

Cohort 2, 8 diagnosed with strabismus; cohort 2, detection rate 3/1000 (95% CI 1 to 5/1000)

Relative detection rate: 3.9 (95% CI 1.9 to 15.3)

Changes in squint from init to when seen at second centre (%)

Cohort	Same	Improved	Worse	Not known	Total
1	36 (48)	30 (40)	8 (11)	1 (1)	75 (100)
2	3 (38)	5 (63)	0	0	8 (100)

False-positive referrals

Defined as having neither strabismus or amblyopia at second centre

Cohort 1, 122; cohort 1, 17/1000 (95% CI 14 to 20/1000)

Cohort 2, 91; cohort 2, 31/1000 (95% CI 24 to 37/1000)

1.8× more false-positive referral from cohort 2 than cohort 1 (95% CI 1.4 to 2.0)

Sources of referral (%)

Cohort	Orthoptist	HV	CMO	Not known	Total
1	233 (89)	24 (9)	0	6 (2)	263 (100)
2	0	11 (10)	98 (88)	2 (2)	111 (100)

Uptake rates

Cohort 1: number seen at 3-year screen was 5176 (73%)

Cohort 2: number seen at developmental screen at 3.5 years was 2530 (85%)

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td>Bray et al.[90]
1996
UK</td><td>Observational, prospective study
Children included from three areas (two in Newcastle, one Northumberland)
Aged 30 months between 1 January 1987 and 30 June 1988
Not already known to have visual abnormalities and not already offered screening
Seen at 7 years, those without complete hospital record at this age were examined after 7 years at school by an orthoptist</td><td>Orthoptic Screening Cohort (OSC)
Aged 35 months; by orthoptist in local clinic
Case history; VA (Kays/SSG); CT and ACT; 20Δ; EOM; referred in not 6/6 or manifest or intermittent strabismus
HVSC
Aged 30–36 months; home visit
Case history; ability of child to pick up thread; any manifest strabismus noted
GP (GPSC)
Aged 30 months; GPs, CMOs or HVs in local clinics
Case history; any manifest strabismus noted
Abnormality detected
<table>
<tr><th>Cohort</th><th>Total</th><th>Squint</th><th>Straight-eyed amblyopia</th><th>Refractive errors</th><th>No abnormality</th><th>Missing data</th></tr>
<tr><td>OSC</td><td>109</td><td>19</td><td>43</td><td>14</td><td>30</td><td>3</td></tr>
<tr><td>HVSC</td><td>71</td><td>16</td><td>12</td><td>17</td><td>26</td><td>0</td></tr>
<tr><td>GPSC</td><td>91</td><td>22</td><td>24</td><td>16</td><td>27</td><td>1</td></tr>
</table>
Age of presentation with visual defects (mean/SD/number)
<table>
<tr><th>Cohort</th><th>Squint (excluding micro)</th><th>Straight-eyed amblyopia</th><th>Refractive errors</th></tr>
<tr><td>OSC</td><td>3.8/1.1/19</td><td>3.4/0.8/43</td><td>3.8/1.1/14</td></tr>
<tr><td>HVSC</td><td>3.9/1.3/16</td><td>5.6/0.7/12</td><td>5.4/0.9/16</td></tr>
<tr><td>GPSC</td><td>4.1/1.5/22</td><td>4.5/1.0/25</td><td>5.1/1.3/13</td></tr>
</table>
Visual outcomes of detected abnormalities with strabismus (excluding micro)[a]
<table>
<tr><th>Cohort</th><th>6/6 or better</th><th>6/9–6/12</th><th>6/18</th><th><6/18</th><th>Missing data</th></tr>
<tr><td>OSC initial VA</td><td>4</td><td>7</td><td>3</td><td>4</td><td>1</td></tr>
<tr><td>OSC final VA</td><td>11 (+1)</td><td>3</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>HVSC initial VA</td><td>2</td><td>4</td><td>1</td><td>8</td><td>1</td></tr>
<tr><td>HCSC final VA</td><td>2</td><td>6</td><td>5</td><td>2 (+1)</td><td>0</td></tr>
<tr><td>GPSC initial VA</td><td>4</td><td>5 (+1)</td><td>2 (+1)</td><td>5</td><td>4</td></tr>
<tr><td>GPSC final VA</td><td>8 (+2)</td><td>7 (+2)</td><td>1</td><td>0</td><td>2</td></tr>
</table>
[a] Figures in parentheses refer to patients for whom only either initial or final VA available
OSC 1582; HVSC 2081; GPSC 1701
Attendance rates: OSC 916 (58%); HVSC 80%; GPSC 81%</td></tr>
</table>

continued

Code/Country	Study design	Numbers
		Age of presentation with visual defects: no significant difference between the three cohorts Straight-eyed amblyopia presented at a significantly younger age in OSC than either the HVSC or GPSC ($p < 0.001$, Student's one-tailed *t*-test) Refractive errors were corrected at significantly younger age in OSC than in either comparison group or relative to pooled data from both groups
Kohler and Stigmar[91] 1978 Sweden	3-year study	2178 children born 1963–5; of these, 1530 (70.2%) were previously screened at 4 years, 558 (25.5%) had moved into city at between 4 and 7 years, 60 (2.8%) FTA, 30 (1.4%) were incompletely screened at 4 years *Diagnostic tests*: VA; CT, number and distance; OM; Worth-4-Dot distance, Worth pictures for number; stereo – Wirt; cyclo refraction; Fundus and media; 4Δ in most cases; Visuscope if amblyopic Those referred and examined were classified as: group 0, normal eye examination; group 1, mild visual defects without need for treatment; group 2, refractive disturbances exceeding limits for group 1, but without functional amblyopia; group 3, functional amblyopia, strabismus Groups 2 and 3 were called significant eye disorders Of 2178 screened, 310 (14.2%) were referred for further evaluation 49% of referred children (7% of screened) had significant eye disorders and needed treatment. Glasses given in 133 (6.1%) Over-referral (group 0) was found in 21.9% (3.1% of all screened) Direct correlation between low visual screening acuity and significant eye disorders ($r = 0.51$) – highly significant *Newly detected significant eye disorders in 7-year-olds with and without screening at 4 years*

	Newly detected significant eye disorder, *n* (%)	No newly detected significant eye disorder, *n* (%)	Sum, *n* (%)
Previously screened 4 years	11 (0.7)	1519 (99.3)	1530 (100)
Not previously screened	29 (4.5)	619 (95.5)	648 (100)
Total	40 (1.8)	2138 (98.2)	2178 (100)

continued

Code/Country	Study design	Numbers
Edwards *et al.*[92] 1993 UK	Comparison of results of treatment of screened patients referred and of late referrals	198 referrals made, data available on 128 More surgery performed on screened group compared with late referrals ($p < 0.01$) Of the children initially diagnosed with abnormal VA, more in the late referral group failed to achieve 6/9 or better in the worse eye ($p < 0.05$) Of the 131 who had been screened, 75 (57.2%) had completed treatment (achieving 6/6 or better) compared with only 34 (30.4%) in the late referral group Screened group appeared more likely to achieve an excellent VA in the worse eye ($p < 0.01$)
Newman *et al.*[93] 1996 UK	Retrospective study examining outcome of children referred from screening	Conducted over 2-year period (1984–6) Screening programme conduced at aged $3^1/_2$ years by orthoptist; included VA, CT, OM, convergence, 20Δ prism test, stereopsis using TNO) Referred if VA less than 6/6 in EE; manifest strabismus; decompensating heterophoria; abnormal ocular movements; abnormal response to 20Δ prism test, negative response to TNO; any other abnormality Attendance rate at screening 79.3% (6794 children); 348 (5.1%) of those screened were referred PPV of screening 79.9%; 243 cases of 304 referred found to have problem
Harrad *et al.*[94] 2002 UK	Prospective, longitudinal study (ALSPAC)	Part of ALSPAC data, examining differences of groups of children who had received different levels of screening Compared intensive screening (8, 12, 18, 25, 31 and 37 months) with intermediate level (screened at 37 months) with no orthoptic screening

	Intensive group	Intermediate group	No screening group
Prevalence of amblyopia (%)	0.6	1.8	1.2
Likelihood of persistent amblyopia after treatment [OR (95% CI)], comparison with intensive group	–	4.1 (1.1 to 16.6)	7.0 (1.3 to 38.6)
Mean acuities (logMAR)	0.12	0.19	0.27

continued

Code/Country	Study design	Numbers
Williams *et al.* (ALSPAC)[95] 2002 UK	Follow-up of outcomes of treatment for amblyopia in RCT comparing intensive orthoptic screening at 8, 12, 18, 25, 31 and 37 months (intensive group) with orthoptic screening at 37 months only (control group)	Of 3490 children in trial, 1929 attended final examination; 15 had organic ocular pathology or developmental delay and were excluded 1088/2029 (54%) in intensive group; 826/1490 (55%) in control group as originally randomised *Prevalence of amblyopia at 7.5 years of age* Found less often at 7.5 years in intensive group than in control group Prevalence of amblyopia A was 1.45% (95% CI 0.89 to 2.35%) in intensive group and 2.66% (95% CI 1.76 to 4.0%) in control group ($\chi^2 = 3.4$, df = 1, $p = 0.06$) Prevalence of amblyopia B was 0.63% (95% CI 0.30 to 1.32%) in intensive group and 1.81% (95% CI 1.10 to 2.98%) in control group ($\chi^2 = 5.6$, df = 1, $p = 0.02$) 4 children with amblyopia A in intensive group and 6 in control group had not had previous patching treatment. All but 1 child had defaulted from all previous invitations to the study vision screening clinics. The difference in the proportions of untreated amblyopia in the intensive and control groups was not significant (Fisher's exact test, $p = 0.42$) *Cumulative incidence of amblyopia* No significant differences existed in the proportions of children previously treated with patching in the two groups In intensive group 40/1088 (3.7%; 95% CI 2.71 to 4.97%) were given patches; cf. 40/826 (4.8%; 95% CI 3.56 to 6.52%) in the control group ($\chi^2 = 1.31$, df = 1, $p = 0.25$) When the children with untreated amblyopia were added in, the difference between the groups in the total number of treated or untreated children with amblyopia was still not significant: 4.0% (95% CI 3.02 to 5.39%); cf. 5.6% (95% CI 4.09 to 7.22%) ($\chi^2 = 2.1$, df = 1, $p = 0.14$) Data show that the cumulative incidence of amblyopia in each group was similar *Prevalence of residual amblyopia at 7.5 years after patching treatment* Residual amblyopia was more likely to be present despite previous treatment in the control group (10/40) than in the intensive group (3/40) The difference for amblyopia A was not significant (OR 1.56, 95% CI 0.62 to 3.92) For amblyopia B the difference was more marked (OR 4.11, 95% CI 1.04 to 16.29) *VA in the worst seeing eye after patching treatment* VA in the amblyopic eye was significantly better for treated children in the intensive group than for similar children in the control group: mean acuity 0.15 (95% CI 0.085 to 0.215); cf. 0.26 (95% CI 0.173 to 0.347) The corresponding acuities for children who had not had watching treatment were –0.02 (95% CI –0.024 to –0.016) and –0.01 (95% CI –0.016 to –0.004) in the two groups (two factor univariate analysis of variance, $p < 0.001$ for effect of group and $p < 0.001$ for interaction between group and whether given patch or not)

continued

<table>
<tr><th>Code/Country</th><th>Study design</th><th>Numbers</th></tr>
<tr><td></td><td></td><td>Age at first referral to HES
A higher proportion of children who received patching treatment were first seen in the HES before 3 years in the intensive group (19/40) than in the control group (5/40). $\chi^2 = 10.06$, df = 1, $p = 0.002$

No difference existed between the groups in the proportions of children referred after the study interventions had finished, i.e. between 37 months and school age (13/40 vs 10/40; $\chi^2 = 0.24$, df = 1, $p = 0.62$)</td></tr>
<tr><td>Williams et al. (ALSPAC)[96]
2003
UK</td><td>Cohort study</td><td>8042 children attended, 1917 were involved in the RCT and reported on in other paper

Of remaining 6125, another 44 had known developmental delay, organic eye disease or developmental syndromes and were excluded from this analysis; 6081 reported here

Of these, 1516 (24.9%) had been offered preschool orthoptic screening, and 1019 (16.7%) had actually received it

Prevalence of amblyopia in 7.5-year-old children
Similar proportions of children in each group with amblyopia A had strabismus at final assessment (including micro); 4/11 (36%) in the group had PSVS, 38/100 (38%) in group who received no PSVS: $p = 0.82$, $\chi^2 = 0.05$, df = 1
<table>
<tr><th>Definition of amblyopia</th><th>Prevalence in children who had PSVS ($n = 1019$): no. (%)</th><th>Prevalence in children who did not have PSVS ($n = 5062$): no. (%)</th><th>Unadjusted OR (95% CI), p-value</th><th>Adjusted[a] OR (95% CI), p-value</th></tr>
<tr><td>A: 0.2+ logMAR or more between best acuity of each eye</td><td>11 (1.1)</td><td>100 (2.0)</td><td>0.53 (0.27 to 1.03)
$p = 0.052$</td><td>0.63 (0.32 to 1.23)
$p = 0.237$</td></tr>
<tr><td>B: worse eye sees worse than 0.3 logMAR</td><td>7 (0.7)</td><td>65 (1.3)</td><td>0.53 (0.22 to 1.20)
$p = 0.108$</td><td>0.72 (0.32 to 1.60)
$p = 0.550$</td></tr>
<tr><td>C: worse eye sees 0.18 logMAR or worse</td><td>19 (1.9)</td><td>171 (3.4)</td><td>0.54 (0.32 to 0.88)
$p = 0.011$</td><td>0.65 (0.38 to 1.10)
$p = 0.161$</td></tr>
</table>
[a] Adjusted for sex, highest level of maternal education, birth weight, family history of strabismus/amblyopia, and duration of breastfeeding, as these were the factors that remained significantly associated with VA in the worse seeing eye, in a multivariable analysis</td></tr>
<tr><td>Bui and Donahue[97]
2006
USA</td><td>Retrospective review of existing screening programme</td><td>Reviewed 50 charts from a series of over 400 children

Of 50 patients, 18 (36%) had some form of amblyopia and were treated with glasses and/or occlusion

Of the amblyopic patients, 10 (56%) achieved $\geq$0.3 logMAR equivalent vision; 6 showed at least 2 lines of improvement</td></tr>
</table>

Appendix 6

QUOROM statement checklist – treatment studies

Objective	To identify papers reporting on treatment of amblyopia, strabismus and/or refractive errors
Data sources	CDSR, CENTRAL, EMBASE, MEDLINE, MEDLINE in Process, CINAHL, NHS EED, OHE HEED, Science Citation Index, DARE, HTA database, grey literature searching
Search strategy	"Amblyopia and strabismus terms" and "treatment" as detailed in Appendix 1
Selection	Inclusion criteria included primary research, high-quality reviews or guidelines; data reported.
Data extraction	Performed by JC
Results	35 papers identified and included in review[107–141]

Study	Study design	Results
Epelbaum *et al.*[107] 1993 France	Retrospective study of data of strabismic patients to examine the sensitive period for amblyopia	Data from 1975 to 1990 ($n = 407$) Amblyopia was defined by a difference in acuity between the two eyes of at least 0.3 (when the Snellen acuity is expressed as a decimal) Amblyopia was purely strabismic in 336 patients (83%); the age at beginning of therapy averaged 27 months (range of 21 days to 107 months) Defined occlusion efficacy as the reduction ratio of interocular acuity difference at the start and end of treatment Results showed that the efficacy of occlusion therapy did depend on the age of initial treatment, with progressively deteriorating efficacy with increasing age Treatment efficacy was found to be virtually nil at the age of 12 years
Stewart *et al.*[108] 2003 UK	Prospective study examining the changes in visual function during refractive adaptation and occlusion	Data obtained from 94 subjects (mean age = 5.1 ± 1.4 years) with amblyopia associated with strabismus ($n = 34$), anisometropia ($n = 23$) and both anisometropia and strabismus ($n = 37$) 86 required refractive correction and underwent 18 weeks of glasses wear Those subjects whose amblyopia persisted were prescribed 6 hours occlusion per day Outcome variables (VA, CS) were assessed at 6-weekly intervals during refractive adaptation and at 2-weekly intervals during occlusion until gains in visual function ceased to be statistically verifiable Patch wear was objectively recorded using ODM Mean VA in the amblyopic eyes at the start and end of treatment was 0.69 ± 0.38 and 0.44 ± 0.42 logMAR, respectively Mean letter CS in amblyopic eyes at the start and end of refractive adaptation was 1.46 ± 0.29 and 1.61 ± 0.12 log units, respectively 13 subjects who gained normal VA during this phase were not occluded Mean VA in amblyopic eyes at the start and end of occlusion was 0.5 ± 0.35 and 0.2 ± 0.25 logMAR, respectively Mean letter CS in amblyopic eyes at the start and end of occlusion was 1.60 ± 0.13 and 1.65 ± 0.07 log units, respectively VA in the fellow eyes at the start and end of treatment was 0.15 ± 0.13 and 0.02 ± 0.1 logMAR, respectively Mean letter CS in fellow eyes at the start and end of treatment was 1.63 ± 0.05 and 1.65 ± 0.03 log units, respectively

continued

Study	Study design	Results
Stewart *et al.*[109] 2004 UK	Prospective study examining the changes in visual function during refractive adaptation and occlusion	Data were collected from 65 children with previously untreated amblyopia and significant refractive error (mean age 5.1 ± 1.4 years); amblyopia was associated with anisometropia (n = 18), strabismus (n = 16) and both anisometropia and strabismus (n = 31) The mean (SD) VA in the amblyopic eyes at recruitment was 0.77 (0.41) and ranged from 0.1 to 1.6 logMAR, respectively Following a period of 18 weeks of refractive adaptation, amblyopic eye VA (SD) improved significantly from 0.67 (0.40) to 0.43 (0.37) and was statistically significant ($p < 0.001$). This represents a mean improvement or 0.24 (0.18), range 0.00–0.60 log units, respectively Results showed that the change in mean (SD) logMAR VA (from the start of refractive adaptation to the best VA measurement) did not differ significantly by amblyopia type [anisometropia, 0.29 (0.17); mixed 0.19 (0.15); strabismus 0.30 (0.24) (p = 0.29)] Similarly, the change in mean (SD) logMAR VA (from the start of refractive adaptation to the best VA measurement) did not differ significantly by age [under 4 years (n = 19) 0.23 (0.18); 4–6 years (n = 29) 0.24 (0.20); over 6 years (n = 17) 0.16 (0.23)] (p = 0.38) The mean number of weeks taken to achieve best VA of the amblyopic eye did not differ significantly between amblyopia groups (p = 0.52) or with age (p = 0.63) During the refractive adaptation process, 14 study participants (22%) achieved improvement in VA such that they did not require occlusion therapy
PEDIG[110] 2003 USA	Randomised multi-centre clinical trial	Compared 2 versus 6 hours of daily patching for moderate amblyopia in children aged <7 years Defined moderate amblyopia as vision of 20/40 to 20/80 in the amblyopic eye or an interocular VA difference of 3 or more logMAR lines, respectively 189 subjects were recruited into the trial, where 95 were assigned 2 hours of patching and 94 were assigned 6 hours of patching, with both groups undertaking 1 hour of near visual activities while patching All subjects were monitored at 5 and 17 weeks (4 months) The authors report substantial improvement in VA in both groups at both 5 weeks and 4 months At 4 months, 79% of subjects in the 2-hour patching group and 76% of subjects in the 6-hour patching group had an improvement in VA by 2 or more lines from baseline. VA had improved from baseline by an average of 2.40 logMAR lines in each group, with a mean difference in logMAR acuity between the groups of 0.001 (95% CI –0.040 to 0.042) There was no statistical evidence for an interaction between treatment group and either patient age (p = 0.76), cause of amblyopia (p = 0.85) or baseline VA of the amblyopic eye (p = 0.96). The authors therefore concluded that either treatment method produces improvements in VA of similar magnitude

continued

Study	Study design	Results
PEDIG[112] 2003 USA	Randomised multi-centre clinical trial	Assessed the response of patching treatment in moderate amblyopia (20/40 to 20/100) in children who were allocated into groups receiving occlusion for 6 hours daily, or occlusion up to all waking hours, at the investigator's discretion A total of 209 children participated in the study, aged from 3 to 7 years Assessed the response to treatment at 5 weeks, 16 weeks and 6 months following the commencement of therapy Results at 5 weeks demonstrated an improvement in VA from baseline by a mean of 2.2 lines. Patients with a baseline acuity of 20/80 or 20/100 showed a positive association between the number of hours patched and improvement in acuity ($p = 0.05$). This association was not present when the baseline acuity was 20/40 to 20/60 ($p = 0.57$) Results at 6 months showed an improved VA from baseline by a mean of 3.1 lines. Of the group of patients with baseline acuity of 20/80 to 20/100, 20% had a 6-month acuity of 20/25 or better compared with 56% in patients with a baseline acuity of 20/40 to 20/60. This was found to be statistically significant ($p < 0.001$) At 6 months, the number of lines of improvement in acuity from baseline was greater when the baseline acuity was 20/80 to 20/100 than in the 20/40 to 20/60 group (mean lines of improvement 3.6 versus 2.8; $p < 0.001$) The authors concluded that at 6 months the amount of improvement appears to be similar, irrespective of whether 6 hours of daily patching are initially prescribed compared with a greater number of hours. However, a greater number of hours of occlusion initially may improve acuity faster, particularly when the baseline acuity is 20/80 to 20/100. Similar improvements in VA were seen for both strabismic and anisometropic amblyopia
PEDIG[113] 2002 USA	Randomised multi-centre clinical trial	Compared the effect of conventional occlusion and atropine for children with moderate amblyopia (VA in the range 20/40 to 20/100) Patients were subject to a patching regime of a minimum of 6 hours daily for 6 months unless the criteria for successful treatment were met (amblyopic eye improved to 20/30 or better, or had improved 3 or more lines from baseline) If criteria for successful treatment were met, patching time was reduced to a minimum of 7 hours per week; or if the acuity became equal patching was discontinued Patients assigned to the atropine regime were prescribed daily atropine, until the vision in the amblyopic eye met criteria for successful treatment. At this point, the frequency of atropine could be reduced (at the clinician's discretion) 419 patients participated in the study (215 in the patching group, 204 in the atropine group), and were examined at 5, 16 and 26 weeks and 6 months following commencement of treatment Substantial improvement in VA from baseline to 6 months occurred in both groups; VA in the amblyopic eye showed greater improvement initially with patching than with atropine At 5 weeks, VA had improved from baseline by a mean of 2.22 lines in the patching group and 1.37 lines in the atropine group (mean difference in logMAR acuity between groups, 0.087; 95% CI 0.060 to 0.113) At 6 months the mean difference in logMAR acuity between the two treatment groups was 0.034 (95% CI 0.0005 to 0.0064) There was no statistically significant interaction between the cause of amblyopia, age and baseline amblyopic eye acuity and outcome acuity in the amblyopic eye (p-values 0.68, 0.84 and 0.59, respectively)

continued

Study	Study design	Results
PEDIG[114] 2004 USA	Randomised multi-centre clinical trial	Compared the effect of daily atropine with weekend atropine in children younger than 7 years in the treatment of moderate amblyopia (20/40 to 20/80) 168 children were enrolled in the study; 83 were prescribed daily atropine instillation and 85 weekend atropine Similar amounts of improvement in the amblyopic eye from baseline to 4 months occurred in both groups, with a similar course of acuity improvement The improvement in VA in the amblyopic eye averaged 2.3 lines in each group (mean difference in acuity between groups, 0.00 logMAR; 95% CI –0.04 to 0.04) No evidence for an interaction between treatment group and gender ($p = 0.57$), age ($p = 0.72$), iris colour ($p = 0.11$), baseline amblyopic eye acuity ($p = 0.59$), prior amblyopic treatment ($p = 0.65$) or sound eye refractive error ($p = 0.11$) Patients who started with worse amblyopic eye acuity at baseline improved more on average than patients who started with better acuity (2.0 mean line difference in patients with baseline acuity of 20/40–20/50 compared with 2.5 line difference in patients with baseline acuity of 20/63–20/80; $p < 0.001$)
PEDIG[115] 2003 USA	Randomised multi-centre clinical trial	Compared the effect of full-time patching (all hours or all but 1 hour per day) with 6 hours of patching 175 children were included in the study with a range of amblyopia from 20/100 to 20/400 (85 children in the 6-hour group and 90 in the full-time group) Substantial improvement in VA occurred from baseline to 4 months in both groups and the course of acuity improvement appeared similar in both treatment groups At 4-month follow-up there was no statistical evidence for interaction between treatment group and baseline amblyopic acuity ($p = 0.24$), cause of amblyopia ($p = 0.34$) or age ($p = 0.94$) The change in amblyopic eye acuity from baseline to 4-months showed greater variability in the 6-hour group than the full-time group ($p = 0.04$) Patients with a worse amblyopic eye at baseline improved more than those who started with better VA at baseline (5.9 lines of improvement in patients with VA of 20/200 to 20/400 versus 4.1 lines of improvement in patients with baseline VA of 20/100 to 20/160) ($p < 0.001$) Younger patients were also found to show more improvement than older patients (5.5 lines of improvement in patients aged <5 years versus 3.8 lines of improvement in patients aged 5 years or older), which was also statistically significant ($p < 0.001$)

continued

Study	Study design	Results
Foley-Nolan *et al.*[116] 1997 UK	Prospective study to compare the efficacy of atropine and occlusion for amblyopia treatment	Patients were allocated into treatment regimens on an alternate basis, resulting in equal subject numbers in each group ($n = 36$) The atropine group were prescribed daily instillation and the patching group occlusion, the amount of which was based on the age of the child and the amount of amblyopia present Both groups had initial VA ranging from 6/18 to 6/120, with a geometric mean of 6/50 and 6/60 in the atropine and patching groups, respectively Both groups shown to have improvement in VA in the amblyopic eye following treatment ($p < 0.001$) Acuities in the amblyopic eye in the atropine group after treatment ranged from 6/6 to 6/60, with a geometric mean of 6/11; acuities in the amblyopic eye in the patching group after treatment ranged from 6/6 to 6/120, with a geometric mean of 6/19
Stewart *et al.*[117] 2002 UK	Prospective study examining changes observed in VA during amblyopia therapy	57 children with amblyopia (mean age 5.1 ± 1.4 years) with amblyopia associated with strabismus ($n = 22$), anisometropia ($n = 15$) and both anisometropia and strabismus ($n = 20$) 48 subjects required refractive correction and underwent a period of refractive adaptation prior to the commencement of occlusion therapy of 6 hours of daily patching Approximately 85% of the improvement occurred in the first 6 weeks of the occlusion phase Children aged 5 years and younger were reported to have a greater improvement in VA than those aged over 5 years (a change in VA of 0.39 log units versus 0.12 log units) ($p < 0.01$) The relationship between the gain in VA and the total occlusion dose was described by a monotonic function, which appears to be linear up to 160 hours of the total recorded dose
Stewart *et al.*[118] 2004 UK	Prospective study examining changes observed in VA during amblyopia therapy	Involved three phases: baseline; refractive adaptation and occlusion. Children who required spectacle correction entered the refractive adaptation phase, which lasted 18 weeks Those children who did not require spectacle correction, or following refractive adaptation, still had amblyopia were entered into the occlusion phase Occlusion was prescribed for 6 hours daily and was monitored objectively During the occlusion phase, visual function was recorded at regular intervals The mean age of participants was 5.2 ± 1.4 years, $n = 94$ Amblyopia was associated with anisometropia in 23 participants, strabismus in 34 and mixed anisometropia with strabismus in 37 In total, 64 participants (75%) underwent refractive adaptation before entering the occlusion phase Within the refractive adaptation phase, the mean ± SD (range) VA for amblyopic eyes improved from 0.65 ± 0.41 (1.6 to 0.14) to 0.43 ± 0.37 (1.3 to –0.08) logMAR, a mean ± SD (range) improvement of 0.22 ± 0.18 (0 to –0.6 log units) VA change was not significantly different for each type of amblyopia ($p = 0.29$), nor were there significant differences for age ($p = 0.38$). 72 participants entered the occlusion phase of the study

continued

Study	Study design	Results
		Mean ± SD (range) VA in the amblyopic eye improved from 0.50 ± 0.36 (1.6 to 0.0) to 0.15 ± 0.25 (1.02 to –0.15) logMAR, a change of 0.35 ± 0.19 (0.0 to 0.12) log units
		With the exception of only 3 participants, all improvement took place in the first 4 weeks. The mean ± SD improvement in VA increased significantly with decreasing age ($p = 0.0014$)
		Once the authors had accounted for age, analysis revealed that mean ± SD change in VA was not significantly different for each type of amblyopia ($p = 0.03$)
		The total occlusion dose required in order to achieve the observed gains in logMAR VA was described by a monotonic function
		All categories of amblyopia appeared to be linear with an approximate dose–response rate of 0.1 log unit improvement per 120 hours of occlusion
		The overall response did not differ significantly for each amblyopia type ($p > 0.1$). Although dose rates of 2 hours daily and over could be seen to have a similar impact on outcome, the greater doses were seen to reduce the length of treatment time to achieve the best VA
Stewart *et al.*[119] 2004 UK	Prospective study examining changes observed in VA during amblyopia therapy	Compared changes in visual function occurring in response to two prescribed occlusion dose rates: substantial (6 hours daily) and maximal (12 hours daily)
		42 participants entered the study, with amblyopia associated with strabismus ($n = 11$), anisometropia ($n = 19$) and both anisometropia and strabismus ($n = 11$)
		Of the 42 subjects, 41 undertook a period of refractive adaptation prior to randomisation to receive either 6 hours ($n = 22$) or 12 hours ($n = 20$) of occlusion daily
		Changes in VA for the 6-hour group were not significantly different from those for the 12-hour group ($p = 0.56$)
		The mean total dose worn and dose rate to achieve the best VA were not significantly different either ($p = 0.20$ and 0.08, respectively)
		The authors then analysed the results according to dose rates of occlusion actually worn: 0–3 hours ($n = 13$); >3–6 hours ($n = 17$) and >6–12 hours ($n = 11$); significant differences were found between the 0–3-hour group and the >6–12-hour group ($p = 0.009$)
Stewart *et al.*[120] 2005 UK	Prospective study examining changes observed in VA during amblyopia therapy	Reported dose responses to occlusion in treatment outcomes for amblyopia
		Statistically significant differences in observed changes in VA in the three groups of actual worn rates of occlusion (0–3, >3–6 and >6–12 hours daily; $p = 0.04$)
		Significant differences were also found in residual amblyopia ($p = 0.004$) and proportional improvement in VA ($p < 0.0001$) between the groups
		The results indicate that children complying with more occlusion treatment show significantly more improvement than those wearing lower doses
		The authors recommended that in order to achieve acceptable levels of occlusion wear, clinicians should prescribe approximately 6 hours of occlusion daily (on the evidence that the actual dose worn is lower than this)

continued

Study	Study design	Results
Clarke *et al.*[121] 2003 UK	Multi-centre RCT of full treatment with glasses and patching (if required) compared with glasses only or no treatment	177 children aged 3–5 years were included in this multi-centre, UK-based study. Follow-up data were available for 164 children at 54 weeks The results demonstrated that children who received full treatment or glasses treatment alone demonstrated better VA at follow-up than children who had received no treatment The overall treatment effect was small The data were then analysed comparing the initial level of acuity at the start of treatment. The authors reported that children with moderate levels of amblyopia (6/18 to 6/36 at presentation) demonstrated better improvements in acuity, particularly in the group who received full treatment Full treatment showed a substantial effect in the moderate acuity group and no significant effect in the mild acuity group ($p = 0.006$) At the end of the trial, all children were subjected to treatment Follow-up data at 6 months revealed that there were no significant VA differences between the groups
Stewart *et al.*[142] 2005 UK	Prospective study examining changes observed in VA during amblyopia therapy	The study consisted of three distinct phases: baseline, refractive adaptation and occlusion The study included 85 participants with unilateral amblyopia due to strabismus ($n = 32$), anisometropia ($n = 20$) or both anisometropia and strabismus ($n = 33$) Overall improvement (including both refractive adaptation and occlusion phases) of VA increased significantly with decreasing age [under 4 years ($n = 23$) 0.57 ± 0.32 (95% CI 0.05 to 1.475); 4–6 years ($n = 34$) 0.44 ± 0.34 (95% CI 0 to 1.55); older than 6 years ($n = 28$) 0.24 ± 0.18 (95% CI 0–92); $p < 0.0001$] Once age had been accounted for, the change in VA was not significantly different for amblyopia associated with each amblyopia type ($p = 0.03$) The severity of the amblyopic deficit was also cited as a significant factor affecting visual outcome Participants were subcategorised according to the severity of their initial amblyopic deficit (mild, moderate and severe). The authors reported that residual amblyopia differed significantly ($p < 0.001$) between the mild and severe group and the moderate and severe group Other factors reported to affect outcome were BV status and fixation of the amblyopic eye Non-binocular participants (i.e. subjects with strabismus) had significantly greater residual amblyopia ($p = 0.0001$) than binocular participants. Similarly, participants with eccentric fixation (where the subject fixes an object with a point on the retina other than the fovea) had significantly greater residual amblyopia ($p < 0.0001$) than those with central fixation

continued

Study	Study design	Results
Levartovsky *et al.*[122] 1995 Israel	Retrospective review of data to assess the effect of initial VA and type of amblyopia on long-term results of successfully treated amblyopia	The authors continued to monitor patients after the best VA in the amblyopic eye was achieved, and when necessary reintroduced occlusion if the vision in the amblyopic eye deteriorated In total, 94 children were monitored up to the age of at least 9 years Results were reported in two categories: those with initial VA of 20/60 to 20/100 ($n = 45$) and those with initial VA of 20/200 or worse ($n = 49$); and type of amblyopia, strabismic ($n = 56$), anisometropic ($n = 14$) and both anisometropia and strabismus ($n = 24$) VA score at the long-term follow-up examination was compared with that attained by the participant on termination of occlusion therapy The difference between them was classed as the deterioration score. 44 (47%) of participants maintained VA, whereas in 50 (53%) the VA had deteriorated In both initial VA groups, deterioration of VA was evident at the follow-up examination, and the authors deem this difference to be statistically significant (although no details are given) The amount of deterioration seen was significantly higher in children who had started treatment with a VA of 20/100 or worse in the amblyopic eye Deterioration was also evident when participants were categorised according to type of amblyopia The percentage of patients showing deterioration in VA was significantly higher in the mixed amblyopia group than in the other two groups ($p < 0.01$) The amount of deterioration seen at the long-term follow-up examination was also significantly higher in the mixed amblyopia group compared with the strabismic group ($p < 0.01$)
Woodruff *et al.*[123] 1994 UK	Retrospective review of cohort of 961 children treated for amblyopia	Examined the outcome in terms of different types of amblyopia, final VA and initial VA levels, hours of patching and final VA Significantly better visual outcome for anisometropic patients ($p < 0.0001$) and described a significant relationship between the difference in spherical equivalent between the two eyes and final VA amongst those with amblyopia ($p < 0.0001$ for pure anisometropia and $p < 0.0001$ for mixed amblyopia) with worse final VA associated with higher degrees of anisometropia No association with age at the start of treatment and final outcome for all types of amblyopia ($p = 0.08$) or considering each group separately (anisometropic $p = 0.48$; strabismic $p = 0.10$; mixed $p = 0.64$) The level of VA at referral and level of final VA were correlated, and proved to be statistically significant for all types of amblyopia ($p < 0.0001$) A statistically significant relationship was also found between the hours of patching prescribed in the first 3 months of treatment and the final VA for all types of amblyopia ($p = 0.0001$)

continued

Study	Study design	Results
Levartovsky *et al.*[124] 1998 Israel	Retrospective review of records evaluating the effect of hypermetropic anisometropia on the VA of treated amblyopic eyes	86 patients who had been treated by occlusion for unilateral amblyopia, with a follow-up regime similar to that of the previous study Results were reported in terms of the amount of anisometropia present; anisometropia of $\leqslant$1.50D ($n = 74$) and anisometropia $\geqslant$1.75D ($n = 12$) Deterioration was evident in both groups but the difference between the groups was not significant The amount of deterioration in VA at the long-term examination was significantly higher in the group with the larger amount of anisometropia ($p < 0.05$) The overall improvement was better in the group with the small amount of anisometropia ($p < 0.05$)
Fitzgerald and Krumholtz[125] 2002 USA	Retrospective review to examine the maintenance of improvement gains in refractive amblyopia	Reviewed records of children who had undertaken different treatment modalities ($n = 23$), spectacle correction alone ($n = 6$), spectacle correction and occlusion ($n = 10$) and spectacle correction, occlusion and vision therapy ($n = 7$) in terms of treatment to improve binocular status Maintenance gains of VA were evident in all groups, with statistically more maintenance of VA seen in patients treated with glasses, occlusion and vision therapy ($p < 0.1$) All subjects retained at least their initial pretreatment VA, irrespective of treatment outcomes In those where VA did deteriorate, such deterioration lost treatment-related acuity gains only The retention or regression of post-treatment VA was not influenced by post-treatment acuity gains No statistical difference was found in retention of VA gains based on the initial depth of amblyopia
PEDIG[126] 2004 USA	Randomised multi-centre clinical trial	Examined maintenance of VA following treatment for amblyopia in children who had undertaken occlusion or atropine therapy for unilateral amblyopia 145 children who had been successfully treated for anisometropic or strabismic amblyopia were followed without treatment to assess for any recurrence of amblyopia At the time of enrolment into the study, 112 recruits (77%) had stopped occlusion and 33 (23%) had stopped atropine; mean VA at enrolment was 0.13 in the amblyopic eye A recurrence of amblyopia occurred in 30 (21%) patients (95% CI 14 to 28%) by the 52-week follow-up point. A recurrence of amblyopia occurred in 28 (25%) of the patients who had stopped patching treatment (95% CI 17 to 34%) and in 7 (21%) of the patients who had stopped atropine treatment (95% CI 9 to 39%) Of the subjects who had undergone patching treatment, fewer hours of patching stopped at enrolment were associated with a lower recurrence risk ($p = 0.008$) A suggestion of a similar relationship between fewer hours of maximal patching treatment and a lower recurrence risk ($p = 0.18$) was reported. The results suggested that patients who had stopped daily atropine had a higher recurrence risk than those who had stopped less than daily atropine ($p = 0.16$)

continued

Study	Study design	Results
Awan *et al.*[127] 2005 UK	RCT of unilateral strabismic and mixed amblyopia	In a study of 52 patients with strabismic and mixed amblyopia, children were randomly allocated different treatment for 12 weeks. One group were given no patching ($n = 18$), one group were prescribed 3 hours of daily occlusion ($n = 17$) and the final group 6 hours of daily occlusion ($n = 17$) Reported a wide spread of patching times in both the 3- and 6-hour groups, and reported no significant difference between the groups for compliance with patching ($p = 0.33$) Neither age ($p = 0.22$) nor gender had a significant influence on compliance ($p = 0.30$) The initial level of amblyopia present was a significant factor, in that children with worse VA at the start of treatment were less likely to comply with occlusion ($p = 0.03$)
Hussein *et al.*[128] 2004 USA	Retrospective study to explore risk factors for treatment failure of anisometropic amblyopia	Examined the records of 104 children (aged 3–8 years) who were treated with either atropine or patching Data analysed included the age at which treatment was initiated, gender, initial and final VA, initial cycloplegic refraction, the presence of manifest strabismus, treatment modality and treatment compliance (by parental report) at the first follow-up examination Results were presented as ORs for each characteristic. Failure risk factors were found to be age 6 years at the onset of treatment (adjusted OR = 4.69, 95% CI 1.55 to 14.2); the presence of astigmatism of more than 1.50D in the amblyopic eye (adjusted OR = 5.78, 95% CI 1.27 to 26.5); poor compliance with treatment (adjusted OR = 5.47, 95% CI 1.70 to 17.6); and initial VA in the amblyopic eye of 20/200 (6/60 Snellen equivalent) or worse (adjusted OR = 3.79, 95% CI 1.28 to 11.2) Strabismus was not found to be a significant risk factor, neither was the type or amount of anisometropia present
Scott *et al.*[129] 2005 USA	Retrospective study to determine the effectiveness and side-effects of full-time occlusion	Total of 600 cases reviewed; 439 had strabismic amblyopia, 56 anisometropic amblyopia and 105 subjects a combination of strabismic and anisometropic amblyopia The authors reported the duration of occlusion (time taken to reach end-point) was statistically significantly related to the type of amblyopia, the age at initial treatment and the initial visual acuity ($p < 0.0001$) Patients with strabismic amblyopia required a shorter duration of occlusion to reach their end-point than anisometropic patients or those with combination amblyopia ($p < 0.0001$) Older patients and those with worse initial VA required a longer duration of occlusion ($p < 0.0001$) Initial VA also correlated with VA outcome ($p < 0.0001$) Visual outcome was statistically significantly related to age at the initiation of treatment ($p < 0.0001$) The authors reported the presence of occlusion amblyopia in some patients ($n = 155$, 25.8%), a factor which should be considered when prescribing occlusion therapy

continued

Study	Study design	Results
Levartovsky *et al.*[130] 1992 Israel	Retrospective study to examine the effect of age at beginning of treatment and age at cessation of monitoring for amblyopia	104 patients who were previously treated for amblyopia, and were analysed in three age groups according to the age at which treatment started (2–5.5, 5.5–8 and older than 8 years) Deterioration in VA following cessation of treatment occurred in all groups The long-term results were better in the younger group compared to children aged 5.5 years and over; however, this was not statistically significant The study demonstrated that the age at which treatment for amblyopia was started did not affect the final visual outcome after cessation of treatment, provided that monitoring of the VA was continued until after the age of 9 years
Cobb *et al.*[131] 2002 UK	Retrospective review to identify factors influencing visual outcome in anisometropic amblyopes	112 children reviewed No correlation between the age of presentation and final VA in amblyopic eye found ($p = 0.804$) There was a strong trend correlating refractive error and degree of anisometropia with the final VA ($p > 0.001$ and $p = 0.001$, respectively) Mean final VA was significantly worse in strabismic versus non-strabismic children ($p < 0.001$) The authors surmised that children with poorer VA and higher degrees of anisometropia at presentation should be treated "more aggressively" and that children with anisometropic amblyopia should be treated regardless of age
Smith *et al.*[132] 1995 UK	Retrospective study examining the factors affecting treatment compliance in amblyopia	Definition of compliance was attendance of all their prescribed appointments within the first year of treatment Multi-centre study of 961 patients; the authors reported no statistically significant difference in compliance between types of amblyopia (strabismic, anisometropic and mixed), $p = 0.04$ Compliance was neither significantly related to sex ($p = 0.43$), VA at the start of treatment ($p = 0.14$), difference in refractive error between the two eyes ($p = 0.6$) or ethnic group ($p = 0.11$)
Newsham[134] 2002 UK	Prospective study (RCT) of written information and the effect on parental non-concordance with occlusion therapy	Examined whether the use of educational material (in the form of a leaflet) would improve parental understanding of amblyopia and occlusion therapy, and subsequently increase concordance to treatment Parental knowledge and adherence to treatment were assessed by questionnaires The group which received the leaflet demonstrated better knowledge compared with the control group ($p < 0.001$) Non-concordance was significantly higher in the control group ($p < 0.005$) (0.23, 95% CI 0.13 to 0.35 compared with 0.54, 95% CI 0.41 to 0.67)

continued

Study	Study design	Results
Spencer *et al.*[136] 1997 USA	Non-randomised case-controlled study of patients with intermittent exotropia	Study of 32 patients, aged between 3 and 144 months (mean age 41.2 ± 5.8 months) Examined the effect of bilateral injections of botulinum toxin into the lateral rectus muscles for the treatment of intermittent exotropia (minimum distance deviation of 15 prism dioptres) (DS) Patients were observed for 12–44 months after initial injection and satisfactory outcome was considered to be a stable alignment of the eyes to an orthophoric range of ±10 prism dioptres 12 (37.5%) of patients required two or more bilateral injections to achieve stable orthophoria Overall, male patients ($n = 4$) required fewer injections (1.3 ± 0.1) than female patients (2.2 ± 0.4) at a statistically significant level ($p < 0.05$) Differences in the number of injections also appeared to be related to age of the patient at the time of initial injection Patients aged between 24 and 56 months required only a single bilateral injection to achieve orthophoria Patients younger than 24 months or older than 56 months required more frequent injections
Rutstein and Marsh-Tootle[137] 1998 USA	Retrospective review of patients who had previously undergone treatment for accommodative esotropia earlier in childhood	Examined 39 patients who had previously undergone treatment for accommodative esotropia earlier in childhood A shift in refractive error was seen from initial evaluation (+2.77DS) to recall examination (+1.95DS); a mean refractive shift of –0.08DS per year) 5 of the 39 patients not producing a manifest strabismus when viewing an accommodative target without glasses prescription
Ing and Okino[138] 2002 USA	Review of data of subjects with diagnosis of congenital esotropia	Studied the effect of duration of misalignment in congenital esotropia using stereopsis as an outcome measure 90 patients were included in the study and data were collected on age of onset and age at which alignment was achieved (to within 10 prism dioptres) Patients were divided into subgroups based on the age of alignment or duration of alignment. Stereopsis levels were analysed for each subgroup The authors reported that the percentage of patients with stereopsis (80%) was identical for patients aligned at 0–6 months and 7–12 months Patients achieving alignment by 13–24 months had a lower rate of stereopsis (58%) The difference between the groups was statistically significant ($p < 0.5$) The quality of the stereopsis achieved was similar in patients aligned by 6 or 12 months ($p > 0.05$) If duration of misalignment was greater than 12 months, a decrease in quality of stereopsis was evident ($p < 0.001$)

continued

Study	Study design	Results
Paysse[139] 2004 USA	Part retrospective, part prospective study assessing the efficacy of PRK in children with anisometropic amblyopia	11 children were treated with PRK in this retrospective study, with a mean age of 6.1 years (range 2–11 years) Both myopic (n = 8) and hypermetropic (n = 3) children were included in the study Of the 11 patients treated, 9 were able to perform quantitative VA measurements pre- and postoperatively Improvements in VA were evident in 7 of 9 eyes by a minimum of 2 or more Snellen lines Compliance with amblyopia therapy did not improve postoperatively in any patient

Appendix 7

QUOROM statement checklist – quality of life studies

Objective	To identify papers to inform the impact of amblyopia and/or strabismus on QoL
Data sources	CDSR, CENTRAL, EMBASE, MEDLINE, MEDLINE in Process, CINAHL, NHS EED, OHE HEED, Science Citation Index, DARE, HTA database, grey literature searching
Search strategy	"Amblyopia and strabismus terms" and "economics and quality of life terms" as detailed in Appendix 1
Selection	Inclusion criteria included primary research, utility data or appropriate HRQoL measures used and the data reported
Data extraction	Performed by JC
Results	12 papers identified and included in review[143–154]

<table>
<tr><th>Paper</th><th>Method</th><th>Results</th></tr>
<tr><td>Packwood et al.[143]
1999
USA</td><td>20-question survey
Looked at amblyopia alone, not strabismus
Results compared with those of strabismic, normative and psychopathologic groups using the HSC
Inclusion criteria: ⩾15 years of age; unilateral amblyopia with VA worse than 20/40; no previous strabismus surgery; deviation <8Δ</td><td>Approximately 45 surveys were delivered, 26 responded
One excluded as previously unknown history of strabismus surgery
Age 15–64 years (mean age 30.2 years, 17 (68%) were male
Of the 21 adults (defined as ⩾21 years), 8 (38%) were married and 1 (5%) divorced
13 adults (62%) had at least some college education
15 (60%) had VA of 20/80 or worse; 11 (44%) had a VA of worse than 20/200
Past treatment ranged from nothing to varying combination of glasses, occlusion, atropine and exercises
14 (56%) had an occlusion, 8 (32%) for more than 1 year and 2 (8%) for more than 3 years
Effect of amblyopia on fear of losing vision, subjection to ridicule, self-image, job choice and lifestyle
<table>
<tr><th></th><th>Not a concern</th><th>Rarely</th><th>Think about occasionally</th><th>Worry about</th><th>Major lifestyle concern</th></tr>
<tr><td>Fear of losing vision in good eye? (n = 25)</td><td>7 (28%)</td><td>4 (16%)</td><td>8 (32%)</td><td>4 (16%)</td><td>2 (8%)</td></tr>
<tr><td>If patched, subjection to ridicule? (n = 18)</td><td>3 (17%)</td><td>7 (39%)</td><td>4 (22%)</td><td>2 (11%)</td><td>2 (11%)</td></tr>
<tr><td>Effect of amblyopia on self-image? (n = 18)</td><td>6 (24%)</td><td>8 (32%)</td><td>6 (24%)</td><td>2 (8%)</td><td>3 (12%)</td></tr>
<tr><td>Effect of monocular condition on lifestyle? (n = 24)</td><td>12 (50%)</td><td>7 (29%)</td><td>2 (8%)</td><td>2 (8%)</td><td>1 (4%)</td></tr>
<tr><td>Effect of amblyopia on self-image as a child? (n = 24)</td><td>11 (46%)</td><td>5 (21%)</td><td>3 (13%)</td><td>1 (4%)</td><td>4 (17%)</td></tr>
</table>
</td></tr>
</table>

continued

Paper	Method	Results
van de Graaf *et al.*[144] 2004 The Netherlands	A&SQ Designed and validated A&SQ which consisted of 5 domains (English version in Appendix – not validated) Domain 1: fear of losing the better eye Domain 2: distance estimation Domain 3: visual disorientation Domain 4: diplopia Domain 5: problems with social contact and cosmetic problems Compared A&SQ with VFQ-25 and SF-12 with 3 groups of people	Group 1: 68 adult amblyopia and strabismus patients from ophthalmology clinic (NB: difference in numbers in table). Group 2: 53 healthy controls recruited from families, friends and work. Group 3: cohort of 174 outpatients treated 30 years ago (Waterland). Quality of life was best in healthy controls and worst in current outpatients, not only on SF-12 and VFQ-25 but also A&SQ The decrease in QoL as measured by the A&SQ was most outspoken in the outpatient group of amblyopia and strabismus patients, less in the cohort that had been treated 30 years previously and least in the healthy controls, demonstrating an acceptable discriminatory validity of the A&SQ *Description of the three groups* Group: Controls; *N*: 53; Missing: 1; Age (SD) (years): 32.8 (12.4); Male (%): 48.1; Education (%): Low 0.0, Medium 11.5, High 88.5 Group: Waterland; *N*: 172; Missing: 2; Age (SD) (years): 35.9 (2.8); Male (%): 51.2; Education (%): Low 24.3, Medium 34.3, High 41.4 Group: Patients; *N*: 67; Missing: 1; Age (SD) (years): 44.1 (16.1); Male (%): 47.8; Education (%): Low 21.2, Medium 28.8, High 50.0 *Average scores on the three questionnaires: SF-12, VFQ-25 and A&SQ* Controls: SF-12 Average 47.16, Median 47.72, SD 5.46; VFQ-25 Average 93.66, Median 94.21, SD 4.19; A&SQ Average 95.76, Median 98.81, SD 6.27 Waterland: SF-12 Average 47.13, Median 47.38, SD 4.83; VFQ-25 Average 92.40, Median 93.98, SD 6.12; A&SQ Average 83.31, Median 86.07, SD 13.03 Patients: SF-12 Average 45.77, Median 46.59, SD 5.52; VFQ-25 Average 79.16, Median 81.02, SD 12.78; A&SQ Average 67.52, Median 69.82, SD 15.38 *Average scores per A&SQ domain* Controls: Fear loss 97.41; Distance estimation 95.31; Disorientation 94.34; Diplopia 96.23; Contact and cosmetic 94.34 Waterland: Fear loss 77.95; Distance estimation 86.50; Disorientation 91.36; Diplopia 87.43; Contact and cosmetic 79.44 Patients: Fear loss 80.70; Distance estimation 73.69; Disorientation 73.65; Diplopia 53.31; Contact and cosmetic 63.14 Average scores on the A&SQ were highest for the healthy controls and lowest for the outpatient group

continued

<table>
<tr><th>Paper</th><th>Method</th><th>Results</th></tr>
<tr><td>Parkes[145]
2001
UK</td><td>Parents of all children who started occlusion therapy in 1-year period were asked to take part in study by completing questionnaire – no refusals

Parents asked to complete questionnaire shortly before follow-up appointment 2–4 weeks later

Children included in the study if having occlusion for first time</td><td>79 questionnaires given out; 60 returned (76%); 1 illegible so excluded; therefore 59 analysed

Of these, 21 (35%) were girls and 38 boys (65%)

Age at start of treatment ranged from 21 months to 9 years (mean 4 years 10 months); peaks of treatment ages due to age of screening and age of school nurse examination

Tests graded as follows according to the vision of the amblyopic eye:

Kay pictures: mild = 6/9; moderate = 6/12 to 6/18; dense = 6/24 and below. SG singles: mild = 6/9; moderate = 6/12 to 6/24; dense = 6/36 and below. Linear tests: mild = 6/9 to 6/12; moderate = 6/18 to 6/36; dense = 6/60 and below

Child's reaction when occlusion is first put on and density of amblyopia
<table><tr><th>Density of amblyopia</th><th>Strong/moderate objection to occlusion (n = 32)</th><th>No objection/happy to wear occlusion (n = 27)</th></tr><tr><td>Dense</td><td>8</td><td>4</td></tr><tr><td>Moderate</td><td>19</td><td>11</td></tr><tr><td>Mild</td><td>5</td><td>12</td></tr></table>
Child's reaction when occlusion is first put on and compliance
<table><tr><th>Compliance</th><th>Strong/moderate objection to occlusion (n = 32)</th><th>No objection to occlusion (n = 11)</th><th>Happy to put on occlusion (n = 16)</th></tr><tr><td>Worn as recommended</td><td>14</td><td>8</td><td>14</td></tr><tr><td>Worn less than recommended</td><td>13</td><td>3</td><td>2</td></tr><tr><td>Would not wear occlusion</td><td>5</td><td>0</td><td>0</td></tr></table></td></tr>
<tr><td>Searle et al.[146]
2002
UK</td><td>Purpose of study was to examine the extent that psychosocial and clinical variables influence parental compliance with occlusion

Questionnaire completed by parents based on main components of protection motivation theory (i.e. severity of visual impairment; vulnerability; response efficacy; self-efficacy; protection motivation</td><td>238 amblyopic children identified through records at 5 clinics

Inclusion criteria were children who had unilateral amblyopia due to strabismus, anisometropia or both, were under the age of 8 years and who had been prescribed occlusion for a minimum of 2 months

Children with other visual or developmental disorders were excluded

81.5% had been occluding for at least 2 months

Of 238 eligible parents, 41 (17%) called the clinic to cancel appointment and 356 (15%) FTA; 161 attended appointment, 10 refused; final number giving consent was 151 (63.5%)

Parents of 72 female and 79 male children were recruited

Mean age of children was 4.5 years (range 1–8 years)</td></tr>
</table>

continued

Paper	Method	Results
	Responses to individual items were measured on 5-point scales such that high scores indicated high levels of the variable of interest	*Follow-up* Follow-up at ~2 months Parents asked again how many hours they were recommended to patch their child, and how many they achieved Responses of parents who only completed the Time 1 questionnaire and responded again at Time 2 (n = 105) were compared with those who only completed the Time 1 questionnaire (n = 46) No significant differences were found for any of the measures in the Time 1 questionnaire *Clinical data* Recommended patching regimen per day at Time 1 ranged from 30 minutes to 12 hours (mean = 3.4 hours; SD = 2.6) Self-reported patching hours achieved at Time 1 ranged from 0 to 12 hours (mean = 2.4 hours; SD = 2.1) Recommended patching at Time 2 (follow-up) ranged from 30 minutes to 12 hours (mean = 2.9 hours; SD = 2.4) Actual patching at Time 2 ranged from 0 to 12 hours (mean 2 hours; SD 1.9) At study entry 54% of parents that they were achieving orthoptists' recommendations and 53% were achieving orthoptists' recommendations at Time 2 Mean VA score in the amblyopic eye at Time 0 was equivalent to 6/24, which improved to 6/12 at Time 1 (study entry) but remained at this level at Time 2 (n = 105) Actual compliance with patching was measured as the ratio of actual patching hours to the recommended patching hours: the higher the ratio, the more compliant with patching Mean ratios for patching were for Time 1 0.73 (SD = 0.73) and for Time 2 0.75 (SD = 0.55) *Protection Motivation Theory* To construct multi-item, reliable measures of the PMT components, responses to individual items of the questionnaire were factor analysed using principal components analysis (varimax rotation) This confirmed the internal reliability of the main PMT components. Also permitted perceived costs or barriers to treatment to be divided into three separate scales: beliefs regarding the prohibition of activities, perceived emotional distress and stigma The strong Cronbach's alpha coefficient supports the robustness of the internal consistency of these measures which range from 0.72 (stigma) to 0.91 (protection motivation)

continued

Paper	Method	Results
		Predictors of compliance **Time 1** To explore which variables predicted compliance with occlusion at Time 1, a stepwise regression analysis was conducted Belief in the ability to patch (self-efficacy) increased the likelihood of patching and a belief that patching prohibits the child's activities (prohibit) reduced the likelihood of patching **Time 2** Past patching behaviour was the primary predictor of compliance accounting for 23% of the variance This was followed by "response efficacy", explaining a further 8% of the variance, and "prohibit", which was negatively associated with compliance, explaining a further 3% of the variance Those who were successful in patching their children at study entry were more likely to continue to do so, and this was reinforced by the perceived efficacy of the treatment However, a belief that patching would prohibit the child's activities reduced the likelihood of patching as it did in Time 1
Choong *et al.*[147] 2004 UK	Study to assess carers' perception of stress and well-being of child before and during amblyopia treatment	All primary carers with children who were diagnosed with probable amblyopia or reduced vision and about to undergo treatment for the first time were invited to participate. Ongoing study with 93 participants so far, but 65 completed in study and discussed in paper *Demographics of carers* Majority of carers (n = 52) were mothers; 96.9% of the sample were Caucasian; mean age of carers was 32.4 years (SD = 6.3) 15.9% of the sample had tertiary education of higher, 38.1 college, 42.9 secondary, 3.1% primary level 80% of the sample had more than one child other than the one who was seen at the clinic. Among siblings, the majority (80%) did not have amblyopia Carers' understanding of amblyopia was surveyed; 43.1% admitted that they knew little or nothing about the condition *Demographics of amblyopic child* 36 males, 29 females with a mean age of 57.1 months (SD = 20.9) Of these children, 60% attended primary school, 21.5% were in nursery, 12.3% in play groups, 6.2% cared for at home 26 (40%) were diagnosed with anisometropic amblyopia, 24 (36.9%) strabismic amblyopia, 13 (20%) combined strabismic and anisometropic amblyopia, 2 (3.1%) refractive amblyopia Mean VA of the amblyopic eye at presentation was 0.32 (SD = 0.54) using equivalent decimal Snellen notation

continued

Paper	Method	Results

Materials

Used focus group to develop Parental Perception Questionnaire (PPQ) – intended to measure the psychosocial well-being of the child. Higher overall PPQ score indicates lower psychosocial well-being

Parenting Stress Index (PSI): 10-item index measures the degree to which general situations are perceived as stressful. Higher overall score represents a higher perception of stress experienced

Carer–child relationship: depicted by how upset, irritated, patient and attentive the carer felt towards the child. Total score obtained by the summation of carer's response in these areas. Higher score indicates better relationship

Questionnaire components:

Section 1: background information on the carer and child
Section 2: carers' knowledge of amblyopia and compliance with treatment
Section 3: carers' perception of their stress level (PSI)
Section 4: carers' perception of child's psychological and social well-being (PPQ)
Section 5: carers' relationship with the child and other family members

Study protocol: 65 carers all completed questionnaire 1 (pre-treatment phase); 1 had occlusion only, 4 had occlusion and glasses, 1 observed these all excluded from analysis; 59 had glasses only and completed questionnaire 2 (first follow-up phase); from here 31 occlusion and glasses, 28 glasses only and completed questionnaire 2 (second follow-up phase)

Prospective study, repeated-measures design

Mean time interval between pretreatment phase and first follow-up phase 6.9 weeks (SD = 2.4), and first follow-up phase and second follow-up phase 7.4 weeks (SD = 8.6)

Carers' perceived stress

Mean PSI scores of carers in occluded and non-occluded groups (SD):

Phase	Occluded group	Non-occluded group	Between-groups *p*-value
Pretreatment	13.27 (5.30)	13.52 (6.58)	>0.05
First follow-up	13.42 (5.46)	12.81 (5.46)	>0.05
Second follow-up	12.47 (6.74)	13.25 (6.29)	>0.05
Within-group *p*-value	>0.05	>0.05	

Carers' perception of child's psychosocial well-being

Mean PPQ scores of carers in occluded and non-occluded groups (SD):

Phase	Occluded group	Non-occluded group	Between-groups *p*-value
Pretreatment	23.51 (9.38)	20.12 (7.99)	>0.05
First follow-up	22.53 (10.44)	19.33 (7.12)	>0.05
Second follow-up	23.81 (10.44)	20.36 (9.46)	>0.05
Within-group *p*-value	>0.05	>0.05	

continued

Paper	Method	Results

Relationship between carer and child

Mean score of carer–child relationship (SD):

Phase	Occluded group	Non-occluded group	Between-groups *p*-value
Pretreatment	22.87 (3.38)	22.30 (3.93)	>0.05
First follow-up	20.19 (5.10)	20.93 (5.37)	>0.05
Second follow-up	23.06 (3.21)	22.68 (4.10)	>0.05

Mean score of carer–child relationship, how upset and irritated carers in occluded group were with the child across all phases (SD):

	Pretreatment	First follow-up	Second follow-up	Between pretreatment and first follow-up phases *p*-value	Between first follow-up and second follow-up *p*-value
Carer–child relationship	22.87 (3.38)	20.19 (5.10)	23.06 (3.21)	<0.01	<0.01
Upset	5.67 (1.69)	4.43 (2.24)	5.90 (1.08)	0.039 (NS)[a]	<0.01
Irritated	5.53 (1.53)	4.40 (2.33)	5.97 (1.19)	0.027 (NS)[a]	<0.01
Patient	5.77 (1.36)	5.43 (1.65)	5.55 (1.73)	>0.05 (NS)	>0.05 (NS)
Attentive	5.90 (1.12)	5.77 (1.04)	5.65 (1.71)	>0.05 (NS)	>0.05 (NS)

NS, non-significant

[a] As repeated analysis was conducted, Benferroni's correction was used and alpha is set at 0.025.

Mean score of carer–child relationship, how upset and irritated carers in non-occluded group were with the child across all phases (SD):

	Pretreatment	First follow-up	Second follow-up	Between pretreatment and first follow-up phases *p*-value	Between first follow-up and second follow-up *p*-value
Carer–child relationship	22.30 (3.93)	20.93 (5.37)	22.68 (4.10)	>0.05 (NS)	>0.05 (NS)
Upset	5.61 (1.34)	4.86 (2.07)	5.86 (1.33)	>0.05 (NS)	0.038 (NS)[a]
Irritated	5.43 (1.45)	4.61 (2.20)	5.68 (1.54)	>0.05 (NS)	<0.01
Patient	5.63 (1.33)	5.50 (1.64)	5.59 (1.42)	>0.05 (NS)	>0.05 (NS)
Attentive	5.68 (1.39)	5.96 (1.26)	5.71 (1.41)	>0.05 (NS)	>0.05 (NS)

NS, non-significant

[a] As repeated analysis was conducted, Benferroni's correction was used and alpha is set at 0.025.

Effect of glasses on children

Mean score of how upset and irritated carers with children prescribed glasses only (SD):

	Pretreatment	First follow-up	Between-phases *p*-value
Carer–child relationship score	22.60 (3.63)	20.54 (5.20)	<0.01
Upset with child	5.64 (1.52)	4.66 (2.14)	<0.01
Irritated with child	5.48 (1.48)	4.53 (2.24)	<0.01

continued

Paper	Method	Results
Horwood *et al.* (ALSPAC)[148] 2005 UK	Examined data from ALSPAC cohort Usable vision and overt victimisation data were available for 6036 of the children and usable vision and relational victimisation data for 5913 Questionnaire was sent to parents at the same time as the invitation to attend the ALSPAC 7.5-year assessment clinic Bullying behaviour was assessed by trained psychologists at the 8.5-year testing clinic, by a standard interview *Overt victimisation* Having had belongings stolen; having been threatened or blackmailed; having been hit or beaten up; having been called bad/nasty names; having had nasty tricks played on them	Of the 7599 children who completed the vision-testing session, 491 (6.5%) wore glasses frequently, 185 (2.4%) wore glasses only occasionally; 57 (0.8%) children had a "large" angle of strabismus, 96 (1.3%) had a "small" angle; some children (n = 264; 3.5%) had received occlusion treatment *Overlap between binary versions of these 3 vision outcomes in which frequent/occasional glasses wearers were grouped together as were children with large/small angles of strabismus* Glasses 462 (6.1%) Glasses + Patch 117 (1.5%) Glasses + Patch + Strabismus 75 (1.0%) Patch 58 (0.8%) Patch + Strabismus 14 (0.2%) Strabismus 42 (0.6%) Strabismus + Glasses 22 (0.3%) Of the 6815 children with usable victimisation data, 2348 (34.5%) were overt victims 152 children failed to make sufficient responses in the relational section of the interview to be classified Of the remainder, 1106 (16.6%) were relational victims; 716 children were victims of both overt and relational bullying *Uncorrected prevalences of victimisation within categories of vision defects*[a]

	Overt victimisation % (n)			Relational victimisation % (n)		
	No (N = 3730)	Yes (N = 1891)	Total (N = 5621)	No (N = 4635)	Yes (N = 872)	Total (N = 5507)
Wears glasses:		p = 0.015			p = 0.721	
Frequently	59.8 (213)	40.2 (143)	356	85.6 (297)	144 (50)	347
Occasionally	62.1 (72)	37.9 (44)	116	85.1 (97)	14.9 (17)	114
Never	66.9 (3445)	33.1 (1704)	5149	84.0 (4241)	16.0 (805)	5046
Strabismus:		p = 0.688			p = 0.057	
Large (>20)	60.0 (24)	40.0 (16)	40	78.4 (29)	21.6 (8)	37
Small (<20)	67.2 (41)	32.8 (20)	61	94.7 (54)	5.3 (3)	57
None	66.4 (3665)	33.6 (1855)	5520	84.1 (4552)	15.9 (861)	5413
Ever worn a patch:		p = 0.051			p = 0.817	
Yes	59.6 (106)	40.4 (72)	178	83.5 (142)	16.5 (28)	170
No	66.6 (3624)	33.4 (1819)	5443	84.2 (4493)	15.8 (844)	5337
No. of defects:		p = 0.006			p = 0.453	
2 or more	61.5 (96)	38.5 (60)	156	83.7 (123)	16.3 (24)	147
1	59.8 (232)	40.2 (156)	388	86.4 (331)	13.6 (52)	383
None	67.0 (3402)	33.0 (1675)	5077	84.0 (4181)	16.0 (796)	4977

[a] Probabilities are derived by the Pearson χ^2 statistic

continued

Paper	Method	Results
	Relational victimisation Other children not wanting to play with them; trying to get them to do something they did not want to do; withdrawing friendship; telling tales on them; spreading lies or nasty rumours; deliberately spoiling games; doing other things to upset them	*ORs for victimization within categories of vision defects*[a]

	Overt victimisation		Relational victimisation	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Wears glasses:	$p = 0.016$	$p = 0.017$	$p = 0.715$	$p = 0.662$
Frequently	1.36 (1.09 to 1.69)	1.35 (1.09 to 1.69)	0.89 (0.65 to 1.21)	0.88 (0.64 to 1.19)
Occasionally	1.24 (0.85 to 1.81)	1.26 (0.86 to 1.84)	0.92 (0.55 to 1.55)	0.91 (0.54 to 1.53)
Never	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference
Strabismus:	$p = 0.669$	$p = 0.746$	$p = 0.250$	$p = 0.261$
Yes	1.09 (0.73 to 1.65)	1.07 (0.71 to 1.62)	0.70 (0.37 to 1.32)	0.71 (0.37 to 1.33)
No	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference
Ever worn a patch:	$p = 0.054$	$p = 0.048$	$p = 0.818$	$p = 0.822$
Yes	1.35 (1.00 to 1.84)	1.37 (1.01 to 1.86)	1.05 (0.70 to 1.58)	1.05 (0.69 to 1.58)
No	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference
No. of defects:	$p = 0.007$	$p = 0.006$	$p = 0.439$	$p = 0.386$
2 or more	1.27 (0.91 to 1.76)	1.25 (0.90 to 1.75)	1.02 (0.66 to 1.60)	1.02 (0.66 to 1.60)
1	1.37 (1.11 to 1.69)	1.39 (1.12 to 1.71)	0.83 (0.61 to 1.12)	0.81 (0.60 to 1.10)
None	1.00 Reference	1.00 Reference	1.00 Reference	1.00 Reference

[a] Data are both unadjusted and adjusted for sex and socio-economic status (maternal education and family social class)

Uncorrected prevalence of orthogonal victimisation groups within categories of vision defects[a]

	Victimisation status				Total ($N = 5507$)
	None ($n = 3356$)	Overt only ($n = 1279$)	Relational only ($n = 313$)	Both ($n = 559$)	
Wears glasses:			$p = 0.010$		
Frequently	53.9 (187)	31.7 (110)	5.8 (20)	8.6 (30)	347
Occasionally	57.9 (66)	27.2 (31)	4.4 (5)	10.5 (12)	114
Never	61.5 (3103)	22.6 (1138)	5.7 (288)	10.2 (517)	5046
Strabismus:			$p = 0.010$		
Large ⩾20	51.4 (19)	27.0 (10)	5.8 (20)	10.8 (4)	37
Small <20	61.4 (35)	33.3 (19)	4.4 (5)	1.8 (1)	57
None	61.0 (3302)	23.1 (1250)	5.7 (288)	10.2 (554)	5413
Ever worn a patch:			$p = 0.085$		
Yes	52.9 (90)	30.6 (52)	7.1 (12)	9.4 (16)	170
No	61.2 (3266)	23.0 (1227)	5.6 (301)	10.2 (543)	5337
No. of defects:			$p = 0.003$		
2 or more	53.7 (79)	29.9 (44)	7.5 (11)	8.8 (13)	147
1	55.6 (213)	30.8 (118)	4.4 (17)	9.1 (35)	383
None	61.6 (3064)	22.4 (1117)	5.7 (285)	10.3 (511)	4977

[a] Data are the percentage of total subjects in the group, with the number affected in parentheses. Probabilities are derived by the Pearson χ^2 statistic

continued

Paper	Method	Results
Rahi *et al.*[150] 2006 UK	Cohort study to determine any association of amblyopia with diverse educational, health and social outcomes	8861 people at age 16 years who will be eligible; 53% (4653) were male 95.2% (8432) had normal VA, 4.8% (429) had persistent/residual amblyopia

Associations between mild or moderate/severe amblyopia and educational attainment during childhood

Education tests (at age 11 years)	Normal vision (no.)	Amblyopia	No.	Adjusted differences (95% CI) in scores[a]	*p*-Value
Maths[b]	5894	Mild	194	0.02 (–0.10 to 0.15)	0.705
		Moderate/severe	79	–0.09 (–0.29 to 0.11)	0.366
Reading[b]	5938	Mild	197	0.09 (–0.03 to 0.20)	0.151
		Moderate/severe	80	–0.14 (–0.14 to 0.24)	0.600
Copy a design[b]	5622	Mild	186	0.14 (–0.02 to 0.29)	0.078
		Moderate/severe	76	–0.11 (–0.35 to 0.13)	0.370
Verbal score on a general ability test	5526	Mild	184	–0.34 (–1.70 to 1.01)	0.619
		Moderate/severe	73	–0.86 (–2.99 to 1.27)	0.427
Non-verbal score on a general ability test	5525	Mild	184	–0.27 (–1.38 to 0.83)	0.630
		Moderate/severe	73	–0.03 (–1.77 to 1.71)	0.970

[a] Normal vision minus amblyopia, adjusted for social class, sex, age at testing, family size, ever having had strabismus, treatment for amblyopia and previous test scores where appropriate
[b] Standardised education scores (multiples of SD)

Associations between mild or moderate/severe amblyopia and education, employment, social activities, unintended injuries, general and mental health in adult life

Outcome	Normal vision (no.)	Amblyopia	No. affected	Adjusted OR (95% CI) (amblyopia vs normal vision)	*p*-Value
Education (at age 33 years)[a]					
Higher educational attainment	4965	Mild	184	1.22 (0.91 to 1.64)	0.189
		Moderate/severe	65	0.99 (0.61 to 1.61)	0.962
Employment (at age 33 years)[b]					
In paid employment (men)	2416	Mild	69/90 (77)	0.93 (0.55 to 1.60)	0.805
		Moderate/severe	22/33 (67)	0.51 (0.22 to 1.17)	0.112
In paid employment (women)	2502	Mild	59/91 (56)	0.92 (0.57 to 1.50)	0.747
		Moderate/severe	16/27 (60)	0.71 (0.31 to 1.64)	0.427

continued

Paper	Method	Results

Outcome	Normal vision (no.)	Amblyopia	No. affected	Adjusted OR (95% CI) (amblyopia vs normal vision)	*p*-Value
Sport and social functioning (at age 23 years)[c]					
Not done any sport in the previous month	6592	Mild	117/237 (49)	0.94 (0.71 to 1.26)	0.686
		Moderate/severe	41/82 (50)	1.07 (0.65 to 1.75)	0.800
Not been dancing in the previous month	6592	Mild	101/238 (42)	1.00 (0.76 to 1.34)	0.954
		Moderate/severe	33/82 (40)	0.88 (0.54 to 1.44)	0.610
Not been to the cinema in the previous month	6598	Mild	150/238 (63)	0.87 (0.65 to 1.16)	0.339
		Moderate/severe	49/82 (60)	0.76 (0.46 to 1.25)	0.283
General health (at age 33 years)[d]					
Self-report of poorer health	3579	Mild	121	1.04 (0.73 to 1.49)	0.839
		Moderate/severe	51	1.12 (0.64 to 1.95)	0.700
Mental health (at age 33 years)[e]					
Depression, seen GP or specialist in past 10 years	3578	Mild	21/120 (18)	1.54 (0.93 to 2.56)	0.093
		Moderate/severe	8/50 (16)	1.61 (0.74 to 3.53)	0.233
Psychological distress (malaise inventory score >7)	3471	Mild	9/117 (8)	0.88 (0.41 to 1.90)	0.754
		Moderate/severe	4/49 (8)	1.29 (0.44 to 3.79)	0.649
Unintentional injuries (at age 17–33 years)[c]					
Inpatient care	5355	Mild	33/198 (17)	1.56 (1.03 to 2.38)	0.037
		Moderate/severe	9/72 (13)	1.09 (0.50 to 2.40)	0.826
Outpatient care	5356	Mild	107/198 (53)	0.90 (0.65 to 1.24)	0.517
		Moderate/severe	44/72 (61)	1.04 (0.60 to 1.82)	0.882
Road accident as driver	5390	Mild	39/200 (20)	1.28 (0.87 to 1.89)	0.210
		Moderate/severe	22/72 (31)	2.33 (1.29 to 4.20)	0.005
Injury at work	5390	Mild	39/200 (20)	0.78 (0.52 to 1.17)	0.226
		Moderate/severe	17/72 (24)	0.76 (0.40 to 1.45)	0.408

[a] Ordinal regression – odds of achieving higher level of education, independent of actual level considered, adjusted for sex, social class, marital status, ever having strabismus and treatment for amblyopia

[b] Adjusted for highest educational attainment, social class, ever having strabismus and treatment for amblyopia

[c] Adjusted for sex, social class, ever having strabismus and treatment for amblyopia

[d] Ordinal regression – odds of self-report of poorer health, independent of level, adjusted for highest educational attainment, marital status, home behaviour at 16 years, sex, school adjustment at 16 years, previous mental health and change in social class in previous 10 years

[e] Adjusted for highest educational attainment, marital status, home behaviour at 16 years, sex, school adjustment at 16 years, previous mental health and change in social class in previous 10 years

continued

Paper	Method	Results
		Associations between mild or moderate/severe amblyopia and behaviour, social activities and unintended injuries during childhood

Outcome	Normal vision (no.)	Amblyopia	No. (%) affected	Adjusted OR (95% CI)	*p*-Value
Behaviour (at age 7 years):	6987	Mild	24/234 (10)	1.20 (0.77 to 1.88)	0.419
Bristol Social Adjustment Guide (BSAG) score, in upper decile		Moderate/severe	14/94 (15)	1.73 (0.92 to 3.23)	0.087
Sport (at 11 years): "hardly ever"	6463	Mild	24/210 (11)	1.15 (0.72 to 1.85)	0.550
		Moderate/severe	9/89 (10)	1.02 (0.47 to 2.22)	0.951
Social activities – dancing/disco (at 16 years): "hardly ever"	5778	Mild	74/216 (34)	1.32 (0.96 to 1.82)	0.086
		Moderate/severe	20/75 (27)	0.86 (0.49 to 1.53)	0.611
Unintentional injuries needing hospital care:					
Inpatient care up to age 16 years	6757	Mild	71/255 (28)	1.17 (0.86 to 1.59)	0.319
		Moderate/severe	19/88 (22)	0.76 (0.44 to 1.33)	0.334
Outpatient care at age 12–16 years	6807	Mild	60/257 (23)	0.89 (0.65 to 1.23)	0.482
		Moderate/severe	25/89 (28)	1.05 (0.62 to 1.76)	0.858

Chua and Mitchell[151] 2004 Australia	Retrospective study using Blue Mountains Eye study data	Mean age of people with amblyopia seen at baseline 67.0 years Amblyopia did not affect lifetime occupational class ($p = 0.5$) Fewer people completed university degrees ($p = 0.005$)
Hrisos *et al.*[152] 2006 UK	Prospective study	Investigated the influence of VA and stereoacuity on the performance of preschool children on tasks requiring visuo-motor skills and visuo-spatial ability Children with normal VA (6/6) in both eyes and children with unilateral visual impairment (UVI) ranging from 6/9 to 6/60 with no strabismus and normal vision in the fellow eye were assessed on a neuro-developmental test battery of visually guided tasks 50 children, mean age (SD) 52.4 (5.7) months UVI and stereoacuity correlated moderately (Pearson's $r = 0.537$, $p < 0.001$)

continued

<table>
<tr><th>Paper</th><th>Method</th><th>Results</th></tr>
<tr><td>Satterfield
et al.[153]
1993
USA</td><td>Designed survey of 25 questions focusing on medical background information, previous eye problems, past strabismus problems, treatment of strabismus, psychological effects of strabismus and its treatment

Subjects asked to rate the impact of their strabismus

Items included the effect on friendships; ridicule as a result of strabismus; effects on self-esteem

All items were answered 3 times: with regard to childhood, teenage years and adulthood

A rating scale of 5 points was used (1 good, 5 severe problem)

Each item was collapsed into 2-category scale, with responses indicating a problem (ratings of 3–5) and no problem (ratings 1 and 2)</td><td>General current psychological state of the subjects was measured using the HSC

Charts of 190 patients were reviewed, revealing 98 candidates (76 adults, 22 teenagers)

Unable to locate 21 of the candidates (14 adults, 7 teenagers)

77 surveys actually delivered; of these, 43 (56%) were completed (including responses from 4 teenagers)

Respondents ranged from 15 to 81 years old, mean age 38 years; 56% were women

Majority of patients rated their health as excellent or good. 3 (8%) of 39 adults cited depression as a problem

Respondents had primarily horizontal deviations (21 had ET)

Some degree of amblyopia or other cause of visual loss was present in 14 (32%)

Treatment for strabismus ranged from nothing to varying combinations of glasses, surgery, patching, tinted glasses, eye exercises and BT; 40 of the 43 had some intervention for their strabismus. More than half underwent surgery with an average of 1.8 surgeries per subject. Half of the surgeries were performed during childhood

Interventions for the strabismus
<table><tr><th>Intervention</th><th>No. (%) of subjects</th></tr><tr><td>Glasses</td><td>32 (74)</td></tr><tr><td>Surgery</td><td>27 (63)</td></tr><tr><td>Patching</td><td>16 (37)</td></tr><tr><td>Eye exercises</td><td>16 (37)</td></tr><tr><td>Botulinum toxin</td><td>8 (19)</td></tr><tr><td>Contact lenses</td><td>6 (14)</td></tr><tr><td>No intervention</td><td>3 (7)</td></tr></table>
Strabismus interfering with friendships
<table><tr><th></th><th colspan="3">No. (%) of subjects</th></tr><tr><th></th><th>Childhood (n = 43)</th><th>Teen years (n = 43)</th><th>Adulthood (n = 39)</th></tr><tr><td>Interference with same-sex relationships</td><td>14 (33)</td><td>20 (47)</td><td>17 (44)</td></tr><tr><td>Interference with opposite-sex friendships</td><td>15 (35)</td><td>27 (63)</td><td>22 (56)</td></tr></table></td></tr>
</table>

continued

Paper	Method	Results

Ridicule as a result of strabismus or its treatment

	No. (%) of subjects		
	Childhood	Teen years	Adulthood
Ridicule because of strabismus	23/43 (53)	20/43 (47)	18/39 (46)
Ridicule because of glasses if worn	18/31 (58)	9/23 (39)	2/19 (10)
Ridicule because of patch if worn	9/14 (64)	2/2 (100)	0 (0)

Strabismus and its effect on self-image

	No. (%) of subjects		
	Childhood (n = 43)	Teen years (n = 43)	Adulthood (n = 39)
Cosmetic problem	23 (54)	29 (67)	28 (72)
Feeling different	20 (47)	30 (70)	22 (56)
Poor self-image	22 (51)	31 (72)	30 (77)

Subjects with strabismus versus normative, anxiety and depressed subjects measured by the HSC[a]

	Strabismus group (n = 41)	HSC normative group (n = 735)	t-Value[b]	HSC anxiety group (n = 1435)	t-Value[b]	HSC depressed group (n = 367)	t-Value[b]
Somatisation	1.37 ± 0.32	1.15 ± 0.27	5.04	1.91 ± 0.59	5.86	1.89 ± 0.53	6.17
Obsession–compulsion	1.65 ± 0.57	1.16 ± 0.27	10.45	1.95 ± 0.67	2.85	2.30 ± 0.68	6.18
Interpersonal sensitivity	1.61 ± 0.58	1.12 ± 0.24	11.24	2.00 ± 0.68	3.64	2.33 ± 0.67	6.60
Depression	1.50 ± 0.48	1.14 ± 0.28	7.68	2.04 ± 0.63	5.45	2.62 ± 0.63	11.03
Anxiety	1.35 ± 0.45	1.13 ± 0.26	5.05	2.22 ± 0.67	8.26	2.45 ± 0.68	10.13

[a] Values are given as mean ± SD except where noted
[b] $p < 0.01$

continued

<table>
<tr><th>Paper</th><th>Method</th><th>Results</th></tr>
<tr><td>Archer et al.[154]
2005
USA</td><td>Prospective interventional study

Modified version of the RAND Health Insurance Study QoL instrument administered to parents of children with strabismus, with addition of 5 questions that specifically addressed alignment concerns, 2 that addressed parent–child closeness and 1 regarding clumsiness

Questionnaire administered by telephone interviews before and 2 months after corrective surgery

Patients with previous strabismus surgery in past year were excluded</td><td>116 patients asked to participate, 98 did; mean age of the 98 was 4.5 ± 3.3 years with median of 3.2 years

65 had ET, 27 had XT, 6 had mainly vertical deviation

Concluded that children (like adults) derive psychosocial benefits from strabismus surgery. The contribution of these psychosocial benefits to the strabismic child's QoL should be considered, along with binocular function, as a measure of the value of strabismus surgery

Reliability of QoL instrument
<table><tr><th>Subscale (no. of items in subscale)</th><th colspan="3">Cronbach α</th></tr><tr><th></th><th>All (n = 98)</th><th>Age <3.2 years (n = 49)</th><th>Age >3.2 years (n = 49)</th></tr><tr><td>Functional limitations (4)</td><td>0.91</td><td>0.89</td><td>0.93</td></tr><tr><td>Anxiety (5)</td><td>0.77</td><td>0.74</td><td>0.79</td></tr><tr><td>Depression (3)</td><td>0.66</td><td>0.66</td><td>0.65</td></tr><tr><td>Positive well-being (4)</td><td>0.83</td><td>0.74</td><td>0.85</td></tr><tr><td>Social relations (6)</td><td>0.87</td><td>0.90</td><td>0.86</td></tr><tr><td>Current health perceptions (7):</td><td>0.80</td><td>0.73</td><td>0.84</td></tr><tr><td>Current health (3)</td><td>0.84</td><td>0.72</td><td>0.90</td></tr><tr><td>Resistance/susceptibility (2)</td><td>0.75</td><td>0.72</td><td>0.76</td></tr><tr><td>Prior health (2)</td><td>0.71</td><td>0.64</td><td>0.78</td></tr><tr><td>Satisfaction with development (4)</td><td>0.52</td><td>0.62</td><td>0.42</td></tr><tr><td>Eye alignment concerns (5)</td><td>0.62</td><td>0.62</td><td>0.61</td></tr><tr><td>Parent–child closeness (2)</td><td>0.85</td><td>1.00</td><td>0.53</td></tr></table>
Effect of surgery on QoL dimensions
<table><tr><th>Subscale</th><th>Preop – postop[a]</th><th>p-Value[b]</th></tr><tr><td>Functional limitations</td><td>0.22</td><td>0.01</td></tr><tr><td>Anxiety</td><td>0.14</td><td>0.01</td></tr><tr><td>Depression</td><td>0.19</td><td><0.01</td></tr><tr><td>Positive well-being</td><td>0.01</td><td>0.85</td></tr><tr><td>Social relations</td><td>0.20</td><td><0.01</td></tr><tr><td>General health perceptions:</td><td>0.23</td><td><0.01</td></tr><tr><td>Current health</td><td>0.18</td><td>0.01</td></tr><tr><td>Resistance/susceptibility</td><td>0.35</td><td><0.01</td></tr><tr><td>Prior health</td><td>0.18</td><td>0.11</td></tr><tr><td>Satisfaction with development</td><td>0.22</td><td><0.01</td></tr><tr><td>Eye alignment concerns</td><td>0.70</td><td><0.01</td></tr><tr><td>Parent–child closeness</td><td>0.04</td><td>0.06</td></tr></table>
[a] Preop – postop: difference between pre- and postoperative dimension scores. A positive value represents an improvement
[b] p-Values are derived from two-tailed paired Student's t-test</td></tr>
</table>

Appendix 8

Natural history input parameters

Details are given in *Tables 104–111*.

TABLE 104 *The 20 vision states*

No.	State
1	No refractive error, without strabismus
2	Spherical error in 1 eye, no astigmatism, without strabismus
3	Astigmatism in 1 eye, no spherical error, without strabismus
4	Spherical error and astigmatism in 1 eye (same eye), without strabismus
5	Spherical error and astigmatism in 1 eye (different eyes), without strabismus
6	Spherical error in both eyes, no astigmatism, without strabismus
7	Astigmatism in both eyes, no spherical error, without strabismus
8	Spherical error in both eyes, astigmatism in 1 eye, without strabismus
9	Astigmatism in both eyes, spherical error in 1 eye, without strabismus
10	Spherical error and astigmatism in both eyes, without strabismus
11	No refractive error, with manifest strabismus
12	Spherical error in 1 eye, no astigmatism, with manifest strabismus
13	Astigmatism in 1 eye, no spherical error, with manifest strabismus
14	Spherical error and astigmatism in 1 eye (same eye), with manifest strabismus
15	Spherical error and astigmatism in 1 eye (different eyes), with manifest strabismus
16	Spherical error in both eyes, no astigmatism, with manifest strabismus
17	Astigmatism in both eyes, no spherical error, with manifest strabismus
18	Spherical error in both eyes, astigmatism in 1 eye, with manifest strabismus
19	Astigmatism in both eyes, spherical error in 1 eye, with manifest strabismus
20	Spherical error and astigmatism in both eyes, with manifest strabismus

TABLE 105 *Six-monthly transition matrix for transitions between 20 vision states between months 24 and 30*

From	To																			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	1600	2.00	10.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	2.70	3.15	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.29	0.00	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
3	7.20	0.76	8.40	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.00	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
4	0.90	0.10	0.10	1.05	0.10	0.10	0.10	0.10	0.10	0.10	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
5	0.90	0.10	0.10	0.10	1.05	0.10	0.10	0.10	0.10	0.10	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
6	1.80	0.19	0.19	0.19	0.19	2.10	0.19	0.19	0.19	0.19	0.00	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
7	1.80	0.19	0.19	0.19	0.19	0.19	2.10	0.19	0.19	0.19	0.00	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
8	0.90	0.10	0.10	0.10	0.10	0.10	0.10	1.05	0.10	0.10	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
9	0.90	0.10	0.10	0.10	0.10	0.10	0.10	0.10	1.05	0.10	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
10	0.90	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	1.05	0.00	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.30	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.80	2.10	0.26	0.26	0.26	0.26	0.26	0.26	0.26	0.26
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	1.40	0.18	0.18	0.18	0.18	0.18	0.18	0.18
14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	1.40	0.18	0.18	0.18	0.18	0.18	0.18
15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	1.40	0.18	0.18	0.18	0.18	0.18
16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	0.18	1.40	0.18	0.18	0.18	0.18
17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	0.18	0.18	1.40	0.18	0.18	0.18
18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	0.18	0.18	0.18	1.40	0.18	0.18
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	0.18	0.18	0.18	0.18	1.40	0.18
20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.20	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	1.40

TABLE 106 *Six-monthly transition matrix for transitions between 20 vision states between months 30 and 36*

From	To																			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	1600	2.00	10.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	2.25	3.38	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.27	0.00	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.14
3	6.00	0.72	9.00	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.00	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36
4	0.75	0.09	0.09	1.13	0.09	0.09	0.09	0.09	0.09	0.09	0.00	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
5	0.75	0.09	0.09	0.09	1.13	0.09	0.09	0.09	0.09	0.09	0.00	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
6	1.50	0.18	0.18	0.18	0.18	2.25	0.18	0.18	0.18	0.18	0.00	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
7	1.50	0.18	0.18	0.18	0.18	0.18	2.25	0.18	0.18	0.18	0.00	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09
8	0.75	0.09	0.09	0.09	0.09	0.09	0.09	1.13	0.09	0.09	0.00	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
9	0.75	0.09	0.09	0.09	0.09	0.09	0.09	0.09	1.13	0.09	0.00	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
10	0.75	0.09	0.09	0.09	0.09	0.09	0.09	0.09	0.09	1.13	0.00	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.75	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.92	0.92
12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.50	2.25	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	1.50	0.19	0.19	0.19	0.19	0.19	0.19	0.19
14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	1.50	0.19	0.19	0.19	0.19	0.19	0.19
15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	1.50	0.19	0.19	0.19	0.19	0.19
16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	0.19	1.50	0.19	0.19	0.19	0.19
17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	0.19	0.19	1.50	0.19	0.19	0.19
18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	0.19	0.19	0.19	1.50	0.19	0.19
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	0.19	0.19	0.19	0.19	1.50	0.19
20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	1.50

TABLE 107 *Six-monthly transition matrix for transitions between 20 vision states between months 36 and 42*

From	To																			
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	1600	2.00	10.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.90	4.05	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.00	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24	0.24
3	2.40	0.64	10.80	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.00	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64
4	0.30	0.08	0.08	1.35	0.08	0.08	0.08	0.08	0.08	0.08	0.00	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
5	0.30	0.08	0.08	0.08	1.35	0.08	0.08	0.08	0.08	0.08	0.00	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
6	0.60	0.16	0.16	0.16	0.16	2.70	0.16	0.16	0.16	0.16	0.00	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
7	0.60	0.16	0.16	0.16	0.16	0.16	2.70	0.16	0.16	0.16	0.00	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16
8	0.30	0.08	0.08	0.08	0.08	0.08	0.08	1.35	0.08	0.08	0.00	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
9	0.30	0.08	0.08	0.08	0.08	0.08	0.08	0.08	1.35	0.08	0.00	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
10	0.30	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	1.35	0.00	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.60	2.70	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.34
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	1.80	0.23	0.23	0.23	0.23	0.23	0.23	0.23
14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	1.80	0.23	0.23	0.23	0.23	0.23	0.23
15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	1.80	0.23	0.23	0.23	0.23	0.23
16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	0.23	1.80	0.23	0.23	0.23	0.23
17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	0.23	0.23	1.80	0.23	0.23	0.23
18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	0.23	0.23	0.23	1.80	0.23	0.23
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	0.23	0.23	0.23	0.23	1.80	0.23
20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23	1.80

TABLE 108 *Six-monthly transition matrix for transitions between 20 vision states between from month 42 onwards*

From	To																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	1600	2.00	10.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2	0.00	2.25	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.00	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
3	0.00	0.90	6.00	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.00	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20
4	0.00	0.11	0.11	0.75	0.11	0.11	0.11	0.11	0.11	0.11	0.00	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
5	0.00	0.11	0.11	0.11	0.75	0.11	0.11	0.11	0.11	0.11	0.00	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
6	0.00	0.23	0.23	0.23	0.23	1.50	0.23	0.23	0.23	0.23	0.00	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
7	0.00	0.23	0.23	0.23	0.23	0.23	1.50	0.23	0.23	0.23	0.00	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
8	0.00	0.11	0.11	0.11	0.11	0.11	0.11	0.75	0.11	0.11	0.00	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
9	0.00	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.75	0.11	0.00	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
10	0.00	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.75	0.00	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.22	1.22	1.22	1.22	1.22	1.22	1.22	1.22	1.22
12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.50	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56
13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	1.00	0.38	0.38	0.38	0.38	0.38	0.38	0.38
14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	1.00	0.38	0.38	0.38	0.38	0.38	0.38
15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	1.00	0.38	0.38	0.38	0.38	0.38
16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	0.38	1.00	0.38	0.38	0.38	0.38
17	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	0.38	0.38	1.00	0.38	0.38	0.38
18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	0.38	0.38	0.38	1.00	0.38	0.38
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	0.38	0.38	0.38	0.38	1.00	0.38
20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38	1.00

TABLE 109 *The seven visual acuity states*

No.	VA state
1a	Normal in both eyes (no refractive error, without strabismus)
1b	Normal in both eyes (refractive error and/or strabismus)
2	Normal in one eye, moderately affected in the fellow eye
3	Normal in one eye, severely affected in the fellow eye
4	Moderately affected in both eyes
5	Moderately affected in one eye, severely affected in the fellow eye
6	Severely affected in both eyes

TABLE 110 *Visual acuity states by vision states matrix at age 42 months*

Vision state	VA state					
	1	2	3	4	5	6
1	2168	25	5	8	1	6
2	42	1	4	3	1	0
3	46	5	1	2	1	0
4	36	3	1	1	1	0
5	36	1	1	1	1	0
6	24	2	1	1	1	0
7	23	1	1	1	1	0
8	16	1	1	1	1	0
9	17	1	1	2	1	0
10	18	1	2	1	1	0
11	42	3	3	1	1	0
12	23	1	1	1	1	0
13	23	1	1	1	1	0
14	25	1	1	1	1	0
15	23	1	1	1	1	0
16	16	2	1	1	1	0
17	16	1	1	1	1	0
18	14	1	1	1	1	0
19	14	1	1	1	1	0
20	14	1	1	1	1	0

TABLE 111 *Six-monthly transition matrix between visual acuity states from month 42 onwards*

Current VA state	Next VA state					
	1	2	3	4	5	6
1a	875	2	1	1	1	0
1b	16	1	0	0	0	0
2	0	3	2	0	0	0
3	0	0	1	0	0	0
4	0	0	0	1	1	0
5	0	0	0	0	1	0
6	0	0	0	0	0	1

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Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts & The London Queen Mary's School of Medicine & Dentistry, London

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, Royal Marsden Hospital & Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Consultant in Public Health, South Manchester Primary Care Trust, Manchester

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust, Southampton

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Visiting Professor in Clinical Biochemistry, University of Oxford

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton, Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon PCT, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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