Health Technology Assessment 2011; Vol. 15: No. 16
ISSN 1366-5278

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C Carroll, D Papaioannou, A Rees and E Kaltenthaler

April 2011
10.3310/hta15160

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C Carroll,* D Papaioannou, A Rees and E Kaltenthaler

The University of Sheffield, School of Health and Related Research (ScHARR), Sheffield, UK

*Corresponding author

Declared competing interests of authors: none

Published April 2011
DOI: 10.3310/hta15160

This report should be referenced as follows:

Carroll C, Papaioannou D, Rees A, Kaltenthaler E. The clinical effectiveness and safety of prophylactic retinal interventions to reduce the risk of retinal detachment and subsequent vision loss in adults and children with Stickler syndrome: a systematic review. *Health Technol Assess* 2011;**15**(16).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/ Clinical Medicine.

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ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

The clinical effectiveness and safety of prophylactic retinal interventions to reduce the risk of retinal detachment and subsequent vision loss in adults and children with Stickler syndrome: a systematic review

C Carroll,* D Papaioannou, A Rees and E Kaltenthaler

The University of Sheffield, School of Health and Related Research (ScHARR), Sheffield, UK

*Corresponding author

Background: Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is an inherited progressive disorder of the collagen connective tissues. Manifestations include short-sightedness, cataracts, retinal problems leading to retinal detachment and possible blindness. This is principally the case among individuals with type 1 Stickler Syndrome. It is the most commonly identified inherited cause of retinal detachment in childhood. However, there is no consensus regarding best practice and no current guidelines on prophylactic interventions for this population.

Objectives: The aim of this systematic review was to assess the evidence for the clinical effectiveness and safety of primary prophylactic interventions for the prevention of retinal detachment in previously untreated eyes without retinal detachment in patients with Stickler syndrome. The primary outcome of interest was retinal detachment post prophylaxis.

Data sources: A systematic search was made of 11 databases of published and unpublished literature, which included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library. There was no restriction by language or date. The references of all included studies were checked for further relevant citations and authors of studies with potentially relevant data were also contacted.

Review methods: Two reviewers double-screened all titles and abstracts of the citations retrieved by the search to identify studies that satisfied the inclusion criteria. Both reviewers also independently extracted and quality assessed all included studies. A narrative synthesis was performed.

Results: The literature search identified 1444 unique citations, of which four studies satisfied the inclusion criteria. The two principal studies were both retrospective cohort studies with control groups in populations with type 1 Stickler syndrome. One study evaluated 360° cryotherapy ($n = 204$) and the other focal or circumferential laser treatment ($n = 22$). Both studies reported a statistically significant difference in the rate of retinal detachment per eye between the groups receiving prophylaxis and the controls. However, both studies were subject to a high risk of bias. The results of the two supporting studies of Wagner–Stickler patients were either relatively inconsistent or unreliable. No study reported any major or long-term complications associated with the interventions. Despite the weaknesses of the evidence, the rate of retinal detachment in the intervention groups, especially the cryotherapy group, was lower than the rate either experienced in the study

control groups or reported in other studies of untreated Stickler syndrome populations not exposed to prophylaxis.

Conclusions: Only 360° cryotherapy and focal and circumferential laser treatment have been evaluated for the type 1 Stickler syndrome population, and then only by a single retrospective, controlled, cohort study in each case. Both of these studies report a significant difference between intervention and control groups (principally no treatment) and no major or long-term side effects or complications. However, there is a high risk of bias within these two studies, so the relative effectiveness of either intervention is uncertain.

Future work: A service priority is to determine reliably the prevalence of Stickler syndrome, i.e. how many individuals have type 1 or type 2 Stickler syndrome, and their risk of retinal detachment and subsequent blindness. A non-randomised, prospective cohort comparison study, in which eligible participants are treated, followed-up and analysed in one of three study arms, for no treatment, laser therapy or cryotherapy, would potentially offer further certainty in terms of the relative efficacy of both prophylaxis versus no prophylaxis and cryotherapy versus laser therapy than is possible with the currently available data. Alternatively, continued follow-up and analysis of existing study data, and data collection from relevant sample populations, are required to assess the long-term risks of blindness, retinal detachment and prophylaxis.

Funding: This study was funded by the National Institute for Health Research Health Technology Assessment programme.

Contents

Glossary

Retina The membrane or interior surface at the back of the eyeball.

Retinal detachment A separation of the sensory retina from the retinal pigment epithelium, with an accumulation of vitreous fluid in the potential space between them.

Retinal pigment epithelium The pigmented cell layer just outside the neurosensory retina, which is firmly attached to the underlying choroid and overlying retinal visual cells.

Vitreous A transparent, colourless mass of soft, gelatinous material filling the eyeball behind the lens.

List of abbreviations

CI	confidence interval
DARE	Database of Abstracts of Reviews of Effects
df	degrees of freedom
GRT	giant retinal tear
HTA	Health Technology Assessment
NHS EED	NHS Economic Evaluation Database
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
RD	retinal detachment
RR	risk ratio
UKCRN	UK Clinical Trials Research Network

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 in the notes at the end of the table.

Executive summary

Background

Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is an inherited progressive disorder of the collagen connective tissues. It is indicated by a variety of symptoms, and can affect the formation of the eyes, ears, palate, jaw and joints. Manifestations include short-sightedness, cataracts, retinal problems leading to retinal detachment (RD) and possible blindness, hearing loss, facial abnormalities including cleft palate and joint problems. Diagnosis can be confirmed by genetic analysis. Stickler syndrome is genetically heterogeneous with at least five subgroups, some with a high risk of ocular complications, others with no ocular involvement at all. The majority of patients have type 1 Stickler syndrome (MIM 108300), which is caused by mutation in the single gene that encodes type II collagen and has ocular, auditory, oro-facial and skeletal manifestations. This gene is called *COL2A1*. Types 2 and 3 Stickler syndrome are caused by mutations in the genes encoding type XI collagen. Unlike type II collagen, there are three genes encoding type XI collagen and they are *COL11A1*, *COL11A2* and *COL2A1*. Type 2 Stickler syndrome (MIM 604841) is due to mutations in the *COL11A1* gene and has ocular, auditory, oro-facial and skeletal manifestations. The *COL11A2* gene (mutations of which are responsible for type 3 Stickler syndrome – MIM 104840) is not expressed in the eye, and therefore this group of patients do not suffer eye problems and are more properly referred to as sufferers of otospondylomegaepiphyseal dysplasia. These patients have no ocular involvement, so they are not considered by this review.

Stickler syndrome is the most commonly identified inherited cause of RD in childhood. RD is a separation of the sensory retina from the retinal pigment epithelium, with an accumulation of vitreous fluid in the potential space between them. The rate of RD, potentially leading to loss of vision, in patients with Stickler syndrome has been suggested to be as high as about 60% in one eye. Whereas RD can take place at any age, and the risk is life-long, the first RD has been reported to occur most commonly in adolescence or early adulthood, between the ages of 10 and 30 years. There is therefore a potential case for early prophylactic intervention in those subgroups of patients with Stickler syndrome at the highest risk. Stickler syndrome is a comparatively rare condition and there are few reported data on prevalence, but the most commonly reported figure is one case in 10,000 people based on data from the USA. This figure is of limited reliability, however, given difficulties in diagnosis. Potential interventions, all of which seek to secure the retina and prevent RD, include cryotherapy, laser therapy and scleral buckling. Current service provision in the UK consists of no treatment, with or without monitoring; prophylaxis using 360° cryotherapy; or prophylaxis using laser treatment. There is no consensus regarding best practice and no current guidelines on prophylactic interventions for this population either in the UK or elsewhere.

Objectives

Firstly, to evaluate the clinical effectiveness of prophylactic retinal interventions for the primary prevention of RD in children and adults with Stickler syndrome. Secondly, to evaluate the safety (establish the numbers and types of adverse events or complications) associated with these interventions. Finally, to identify key areas for future primary research.

Methods

A systematic review was performed of the evidence for the clinical effectiveness and safety of primary prophylactic interventions for the prevention of RD in previously untreated eyes without RD in patients with Stickler syndrome. The primary outcome of interest was RD post prophylaxis. A systematic search was made of 11 databases for published and unpublished literature by an information specialist. These databases included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, the Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library. There was no restriction by language, date or study design (other than the requirement that studies have a comparator group). Two reviewers double-screened all titles and abstracts of the citations retrieved by the search to identify studies that satisfied the inclusion criteria. Any disagreements were resolved by discussion or reference to the full paper. Both reviewers also independently extracted and quality assessed all included studies. The references of all included studies were also checked for further relevant citations. The authors of any studies with potential but unspecified Stickler syndrome patients within their study sample were also contacted to retrieve any additional, potentially relevant data on the efficacy of interventions in this population.

Results

The literature search identified 1444 unique citations, of which two studies satisfied the inclusion criteria. These studies were conducted in populations diagnosed with type 1 Stickler syndrome (and confirmed 'where possible' by genetic analysis) and constitute the principal evidence. Two further studies (three papers) conducted in patients with 'Wagner–Stickler' syndrome, an anachronistic term to describe a condition in which patients may have symptoms consistent with a diagnosis of Stickler syndrome (but unconfirmed by genetic analysis), were identified as possible supporting evidence. All of the included studies were identified from the search of the electronic databases.

The two Stickler syndrome studies were both retrospective cohort studies with control groups in populations diagnosed as having type 1 Stickler syndrome. One study evaluated the prophylactic efficacy of 360° cryotherapy on the post-oral retina (204 participants), and the other evaluated 360° circumferential laser treatment for eyes with extensive contiguous retinal lesions, where lesions were present in at least three quadrants of the retina, and focal laser treatment for eyes with small localised lesions of lattice degeneration or isolated breaks (22 participants). Participants in the control groups of both studies received either no prophylaxis or, in the case of an unknown number in the cryotherapy study, prophylactic interventions other than cryotherapy. Both studies either performed prophylaxis in individuals with no previous RD in either eye, or performed prophylaxis in the fellow eye of those with a previous RD in the primary eye. Each study also reported a statistically significant difference in the rate of RD per eye between the groups receiving prophylaxis (bilateral and unilateral combined) and the controls ($p < 0.0025$). Neither study reported any major or long-term adverse events or complications associated with the interventions.

However, both studies are affected by a high risk of bias. The study design (retrospective cohort study with controls) is inherently weaker than prospective and randomised controlled studies. It is also unclear in both studies whether possible participants had been excluded. The control group in the study of cryotherapy was substantially different from the intervention groups. A principal difference concerned the major confounding factor of age: the controls were much older (a mean age of 49 years compared with 21 and 36 years in the intervention groups). Given

that the risk of RD is life-long for this population, the control group was therefore inherently at greater risk of having experienced the primary outcome than the intervention groups. The duration of follow-up for the controls was also not reported, introducing further risk of bias into the comparison between the groups. The control group was also not homogeneous as participants were exposed either to no prophylaxis or to a single type of prophylaxis. In the study of laser treatment, the sample was small ($n = 22$) and from a single family, and no information was reported on the ages of the intervention and control groups. No mean duration of follow-up was reported for the intervention group, but the maximum follow-up was also much less than in the larger study (15 vs 33 years).

The two small studies of patients reported to have been diagnosed with Wagner–Stickler syndrome reported inconsistent results. These studies are not included as principal trials, but as supporting evidence only, because of the quality and relatively small amount of relevant published evidence. One study compared laser treatment with scleral buckling and a range of other interventions (including cryotherapy) as prophylaxis in the fellow eye of patients who had had an RD in the primary eye (22 participants). The smallest number of RDs was reported for the scleral buckling intervention. The second study compared focal laser treatment or cryotherapy with two scleral buckling interventions, and reported no RDs in either group at follow-up of a maximum of 8 years. Both studies were affected by a high risk of bias: diagnostic criteria were unreported in one case; the follow-ups were short; comparability between groups was not assessed, nor was an assessment possible with the reported data; the sample sizes were small, and the results in the second study were unexpected and are potentially unreliable (no incidence of the primary outcome in any eye within the follow-up period).

Discussion

This is the first systematic review of prophylactic interventions for RD in Stickler syndrome. The review performed a highly sensitive search of the published and unpublished literature to identify potentially relevant studies. The principal author also contacted corresponding authors of studies who may have had a relevant but unspecified subgroup of Stickler syndrome patients within their study sample exposed to interventions for the primary prophylaxis of RD. No restrictions of language or date (non-English language articles were included) were applied, and the screening, data extraction and quality assessment were all performed independently by two reviewers. This approach reduced the potential for publication, selection and extraction bias.

The review found only four studies that satisfied the inclusion criteria, and all studies were retrospective cohort studies with comparator groups, which are more vulnerable to bias than some other study designs. The two principal studies of individuals diagnosed with type 1 Stickler syndrome both found a reduced risk of RD for those exposed to prophylaxis. However, the data reported in these studies do not permit the generation of a reliable estimate of effect for either cryotherapy or laser therapy compared with no prophylaxis: the efficacy of these interventions is therefore uncertain. This is because both studies are subject to a high risk of bias, either as a result of the lack of comparability between the intervention and control groups, especially in terms of the confounding factors of age and length of follow-up, or because the study evaluated only a small sample from a single family pedigree. In the absence of any good-quality studies directly comparing the two interventions, the relative efficacy of the two interventions is also uncertain. Neither study reported any major or long-term complications associated with the interventions, but the actual incidence and duration of minor complications is unknown. Despite the risk of bias in both studies and the uncertainty surrounding the relative effect of cryotherapy and laser therapy in the primary prophylaxis of RD in type 1 Stickler syndrome, the rate of RD in the intervention groups of both studies was lower than the rate either experienced in the

study control groups or reported in other studies of untreated Stickler syndrome populations not exposed to prophylaxis. These included subgroups of Stickler syndrome individuals under the age of 20 or 30 years, potentially the most comparable data. The ongoing reporting of follow-up data for the intervention groups in the largest principal study should potentially address some of the comparability issues between the intervention and control groups, principally differences in the confounding factor of age, but other issues affecting the comparability of the control group remain.

Conclusions

Only 360° cryotherapy and focal or 360° circumferential laser treatment have been evaluated for the type 1 Stickler syndrome population, and only then by a single retrospective, controlled, cohort study in each case. Both of these studies reported a significant difference between intervention and control groups (principally no treatment) and no major or long-term side effects or complications. However, there is a high risk of bias within these two studies, so the relative effectiveness of either 360° cryotherapy or focal and circumferential laser treatment in comparison with no treatment is uncertain. There is also no head-to-head trial comparing the two interventions, so their relative effectiveness in comparison with each other is also uncertain. A more reliable estimate of the relative efficacy of these interventions compared with no prophylaxis in terms of the prevention of RD and the frequency of complications could be generated by a high-quality randomised controlled trial comparing cryotherapy and laser treatment with each other and no treatment. The trial would require good baseline comparability between the intervention and control groups of type 1 Stickler syndrome individuals in terms of age and presence of RD in the primary eye, and adequate allocation concealment, and have a minimum follow-up of 10 years to offer data for interim analysis, but could be ongoing, given the life-long risk of the primary outcome. However, given the rarity of the condition, such a trial might be impractical. A non-randomised, prospective cohort comparison study, in which eligible participants are treated, followed up and analysed in one of these three study arms, is more realistic and practical. Such a study would potentially offer greater certainty in terms of the relative efficacy of both prophylaxis versus no prophylaxis and cryotherapy versus laser therapy than is possible with the currently available data. A service priority is also to determine reliably the prevalence of Stickler syndrome, i.e. how many individuals have type 1 or type 2 Stickler syndrome, and the risk of RD and subsequent blindness. Genetic analysis is required to establish the presence and type of Stickler syndrome. In summary, continued follow-up and analysis of study data, and data collection from relevant sample populations, are required to assess the long-term risks of blindness, RD and prophylaxis.

Chapter 1

Background

Description of health problem

Stickler syndrome, also known as hereditary progressive arthro-ophthalmopathy, is an inherited progressive disorder of the collagen connective tissues which was first described in 1965.[1–3] It is indicated by a variety of symptoms and can affect the formation of the eyes, ears, palate, jaw and joints.[1,2,4–9] Manifestations can include short-sightedness, cataracts, retinal problems leading to retinal detachment (RD) and possible blindness, hearing loss, facial abnormalities including cleft palate and joint problems.[1,2,8] Stickler syndrome is the most commonly identified, inherited cause of RD in childhood.[1] RD is a separation of the sensory retina from the retinal pigment epithelium, with an accumulation of vitreous fluid in the potential space between them.

There are no agreed diagnostic criteria for Stickler syndrome,[1] but diagnosis can be confirmed by genetic analysis. Stickler syndrome is genetically heterogeneous with at least five subgroups, some with a high risk of ocular complications, others with no ocular involvement at all. The majority of patients have type 1 Stickler syndrome (MIM 108300), which is caused by mutation in the single gene which encodes type II collagen and has ocular, auditory, oro-facial and skeletal manifestations.[10,11] This gene is called *COL2A1*. Types 2 and 3 Stickler syndrome are caused by mutations in the genes encoding type XI collagen.[6,12,13] Unlike type II collagen there are three genes encoding type XI collagen and they are *COL11A1*, *COL11A2* and *COL2A1*. Type 2 Stickler syndrome (MIM 604841) is due to mutations in the *COL11A1* gene and has ocular, auditory, oro-facial and skeletal manifestations.[6,12–14] The *COL11A2* gene (mutations of which are responsible for type 3 Stickler syndrome – MIM 104840) is not expressed in the eye and therefore this group of patients do not suffer eye problems and are more properly referred to as suffering from otospondylomegaepiphyseal dysplasia.[14] Given that these patients have no ocular involvement, they are not considered further in this review. Both type 1 and type 2 Stickler syndrome are autosomal dominant disorders, but recently a fourth recessive variety of Stickler syndrome has been identified due to mutations affecting both alleles of the gene encoding the α1 chain of type IX collagen (*COL9A1*) (MIM 120210). In other families, all known candidate genes have been excluded, so that there is at least a fifth genetic variation, and further heterogeneity remains to be resolved.

About 75% of people diagnosed with Stickler syndrome suffer from type 1. Types 1 and 2 both indicate 'full' Stickler syndrome.[11] 'Full' Stickler syndrome affects the eyes, joints and hearing; patients with type 1 have an increased incidence of cleft abnormalities and those with type 2 an increased incidence of deafness.[15] Type 2 may also have a reduced risk of RD.[2,5,6] There can be a great deal of variability in the number and type of systemic or non-ocular symptoms in Stickler syndrome patients.[2,8,16] A subgroup of individuals have been identified who have type 1 Stickler syndrome, confirmed by genetic analysis, but with no or very few systemic features.[17–20] In the absence of genetic testing, the diagnosis of Stickler syndrome can therefore be problematic. Diagnosis may also be delayed (e.g. until the first RD has occurred), especially in children, who may not report symptoms.[2,8,21,22] Clinical advice also suggests that a diagnosis of Stickler syndrome may not even be considered for adults experiencing an RD. Consequently, the number of individuals with Stickler syndrome may be higher than currently diagnosed or reported. No figures on prevalence are available for the UK, but it has been reported previously

to be approximately one case in 10,000 people for types 1 and 2 in the USA.[8,23] However, given the difficulties with diagnosis, this figure may not be reliable: for these reasons prevalence is estimated to be higher by the UK Genetic Testing Network (www.ukgtn.org).

The rate of RD, potentially leading to loss of vision, in patients with Stickler syndrome has been found in adults to be as high as 57%,[20] 60%[2] or 61%[8] in one eye or 40% in both eyes.[2] RD is 'a separation of the sensory retina from the retinal pigment epithelium, with an accumulation of fluid in the potential space between them'.[24] Whereas RD can occur at any age and the risk is life-long,[2,25,26] the first RD has been found to occur most commonly in adolescence or early adulthood, between the ages of 10 and 30 years.[2,27] For example, the mean age of those presenting with a first RD (and therefore being diagnosed as having Stickler syndrome) has been reported by one study to be between 21 and 25 years.[27] However, clinical advice also suggests that a diagnosis of Stickler's syndrome is not always considered for adults presenting with an RD, so the mean age of first RD may be higher still. Children may therefore be more likely to be diagnosed with Stickler syndrome but represent a different problem as they may be unlikely to report symptoms and so are diagnosed only after the first RD or other irreparable damage has occurred. Given the more likely diagnosis of Stickler syndrome in children, there is therefore a potential case for early prophylactic intervention in type 1 and type 2 Stickler syndrome patients, especially as the treatment of RD in this population is complex and difficult to manage: success rates for reattachment have been reported to be 78.57% (22/28 patients), but with an average time to redetachment of < 4 months in 73% of cases.[27] The risk of RD progressing to blindness, i.e. the loss of sight in both eyes, in Stickler syndrome is also uncertain as there are very little published data. A survey of members of Stickler syndrome support groups from the UK and the USA reported that 11% and 8% respectively were registered as legally blind (i.e. both eyes).[2] Sixteen per cent of the UK sample was also categorised as 'partially sighted', i.e. complete loss of sight in one eye and reduced vision in the fellow eye. However, this sample was composed of individuals diagnosed with various types of Stickler syndrome, and it is known that the risk of RD, and therefore blindness, is higher for those with type 1. The proportion of this published sample with type 1 is unknown. It is also unclear how many of this sample had suffered and been treated for an RD prior to blindness or how many who received treatment for RD were not classified as legally blind. The long-term success of RD surgery is therefore unknown for this population and the risk of subsequent blindness is uncertain.

Current service provision

Current service provision in the UK in terms of prophylaxis for RD in Stickler syndrome populations consists of no treatment, with or without monitoring; prophylaxis using 360° cryotherapy; or prophylaxis using laser treatment. In both cases the procedure forms a scar with the aim of increasing adhesion and reducing the likelihood of tears or holes leading to a detachment. There is currently a lack of certainty regarding best practice. There are no current guidelines on prophylactic interventions for this population either in the UK or elsewhere.

Description of technology under assessment

The technologies under assessment are primary prophylactic interventions to reduce the risk of RD in eyes that have not previously had a detachment, and, thus, to reduce the potential for loss of vision. The possible interventions include cryotherapy, laser photocoagulation and scleral buckling. Cryotherapy uses intense cold, applied via a freezing probe at the peripheral retina throughout 360°, to destroy choroidal and retinal tissue in order to form a chorioretinal scar. The scar increases adhesion between the neurosensory retina and the retinal pigment epithelium.[28]

Different areas of the eye can be treated in this way: at the post-oral retina and at the equator. Laser photocoagulation involves applying multiple small laser burns to the peripheral retina throughout 360° to create a chorioretinal scar and thus increase retinal adhesion. As with cryotherapy, this treatment can be applied to different areas of the eye.[29] Scleral buckling involves the application of a 360° silicone band around the eyeball at the equator or over affected areas. However, these prophylactic interventions are not without the possibility of unwanted side effects or adverse events, such as discomfort, lid swelling or epiphora.

A possible relevant subgroup for primary prophylactic intervention may be children, because the risk of a first RD has been reported to be highest in Stickler syndrome populations between the ages of 10 and 30 years: the percentage of individuals with Stickler syndrome experiencing RD increases from 8% (aged 0–9 years) to 26% (aged 10–19 years) to 61% (aged 20–29 years), then it levels out (57%–65% for those aged ≥ 30 years).[2] Given that children are also arguably the most likely to be diagnosed with Stickler syndrome, albeit perhaps only after an RD has already occurred, it therefore makes sense to perform prophylaxis at an earlier rather than a later age. There are currently no data publicly available on the current levels of use of each or any of these technologies in the NHS.

Chapter 2

Definition of the decision problem

Decision problem

The assessment will address the question 'Can prophylactic surgery reduce the risk of RD and blindness in Stickler syndrome, especially in children?'.

Overall aims and objectives of assessment

- To evaluate the clinical effectiveness of prophylactic retinal interventions for the primary prevention of RD in children and adults with Stickler syndrome.
- To evaluate the safety (numbers of types of adverse events or complications) of interventions for the primary prevention of RD.
- To identify key areas for primary research.

It is not the aim of this assessment to evaluate the relative effectiveness of interventions using indirect comparison methods.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

A review of the evidence for clinical effectiveness has been undertaken systematically following the general principles recommended in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[29] English- and non-English-language studies were included (where translation is available) and there was no limit by date.

Identification of studies

A comprehensive search was undertaken in October 2009 to identify, systematically, both clinical effectiveness and adverse events literature pertaining to prophylactic retinal interventions to prevent RD in populations reported specifically to comprise participants with Stickler syndrome or populations that may include participants with Stickler syndrome. This search was performed by an information specialist (AR). Searches were not restricted by language or publication date. The MEDLINE search strategy is reported in *Appendix 1*.

The following electronic databases and online conference proceedings were searched from inception for published and unpublished research evidence:

- MEDLINE (Ovid) 1950–October 2009
- MEDLINE in process (Ovid) October 2009
- EMBASE 1980–October 2009
- Cumulative Index to Nursing and Allied Health Literature (via EBSCO) 1982–October 2009
- The Cochrane Library including the following databases 1991–October 2009: Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) and NHS Economic Evaluation Database (NHS EED)
- Biological Abstracts [via Thomson Reuters (formerly ISI) Web of Science®] 1969–October 2009
- Science Citation Index (via ISI Web of Science) 1900–October 2009
- UK Clinical Trials Research Network (UKCRN) and the National Research Register archive up to October 2009
- Current Controlled Trials up to October 2009
- Clinical Trials.gov up to October 2009
- Annual Meeting of the Association for Research in Vision and Ophthalmology up to 2009.

All citations were imported into REFERENCE MANAGER, version 12, software (Thomson Reuters, New York, NY, USA) and duplicates were deleted (AR). Titles and abstracts of all unique citations were then double-screened by two reviewers (CC and DP) using the inclusion criteria outlined below. Any disagreements concerning possible inclusion were resolved by discussion between the reviewers or with reference to the full paper itself. The full papers of all potentially relevant citations were retrieved so that an in-depth assessment concerning inclusion could be made. Again, both reviewers independently screened full papers for relevance and any disagreements concerning possible inclusion were resolved by discussion. In the event that published papers did not report potentially relevant data, corresponding authors were contacted by letter. If relevant data were made available by this route, they were included in the analysis.

Inclusion and exclusion criteria

Population

Children (up to the age of 18 years) and adults diagnosed with type 1 or type 2 Stickler syndrome or 'Wagner–Stickler' syndrome with non-ocular features. There are no universally agreed diagnostic criteria for Stickler syndrome, but it is expected that study participants would demonstrate the presence of a typical vitreous phenotype (type 1 or 2) and/or *COL2A1*/*COL11A1* mutation. Criteria of diagnosis were recorded. The protocol originally stated that individuals with Wagner–Stickler syndrome were to be excluded (see *Appendix 6*). It is recognised that Wagner and Stickler syndromes are quite distinct genetically, and in terms of systemic features.[10,17,19,30,31] For example, Wagner syndrome is accepted to have only ocular abnormalities and no other systemic features.[10,17,19,30] However, Stickler syndrome has a highly variable degree of systemic features (a subgroup has been identified with no or very few systemic features).[17–20] The differences between the two syndromes have become clinically apparent only in recent years, so, despite the previously 'confusing' nomenclature of 'Wagner–Stickler' syndrome,[17] studies of this population have also been included in this review if their study samples exhibit non-ocular symptoms (i.e. consistent with Stickler syndrome). This is because there is little published research evaluating primary prophylaxis in populations specifically diagnosed with Stickler syndrome, and study samples diagnosed with Wagner–Stickler syndrome may be composed of individuals diagnosed with Stickler syndrome, in part at least. Clinical advice was divided on the relevance of including these studies, but the majority opinion was that they offered some interesting supporting but not pivotal information, as long as the issues regarding the reported diagnosis of these populations in these studies were highlighted. Any studies of Wagner–Stickler patients with non-ocular symptoms have therefore not been presented as pivotal evidence but are alluded to as supporting evidence only. Children form a possible relevant subgroup, as the risk of RD, although life-long, has been reported to be highest between the ages of 10 and 30 years in Stickler syndrome populations. Individuals with conditions or syndromes other than Stickler syndrome or Wagner–Stickler syndrome with non-ocular features, but who have a predisposition to RD, e.g. retinopathy of prematurity or Marfan syndrome, were excluded.

Interventions

Any intervention aimed at the primary prevention of RD. Interventions must involve surgical procedures or settings, such as the use of a sterile environment or anaesthesia.

Comparators

No prophylactic treatment (there is no defined usual care for this population).

Settings

Secondary care.

Outcomes

Primary outcome

Retinal detachment in the eye(s) exposed to prophylactic intervention.

Secondary outcomes

1. Adverse events relating to the intervention.
2. Blindness (by self-assessment, or being registered or legally blind).
3. Time to RD.
4. Presence and type of lesions or retinal tears (as these may constitute a precursor for RD).

Study design

Any study design with a control or comparator group.

Data extraction strategy

Data were extracted independently from all included studies by two reviewers (CC and DP) using a data extraction form developed for this review and piloted on two studies (see *Appendix 2*). Any discrepancies between extractions were resolved by discussion and referral to the full paper.

Quality assessment strategy

Assessment of study quality was undertaken using an appropriate study design checklist, in this case the Critical Appraisal Skills Programme checklist for cohort studies.[32] A copy of the full checklist is included in *Appendix 3*. The critical appraisal of study quality was again conducted for each study independently by two reviewers (CC and DP) and any discrepancies resolved by discussion. The aim of the quality assessment process was to address issues regarding the appropriate recruitment of the sample, controlling for possible confounders (including comparability of groups), the length of follow-up, and the preciseness and external validity of the results. Studies were not excluded on the basis of their assessed quality. The purpose of this appraisal was to assess both the internal validity of the included studies and the potential risk of bias across studies included in the review.

Methods of analysis/synthesis

Data were tabulated and, given the small number of studies identified (two pivotal studies[33,34] and two supporting studies[36–38]) and the heterogeneity of the evaluated interventions, a narrative synthesis rather than a meta-analysis was performed. The relative risk or risk ratio (RR) measure of relative effect was not reported in any of the published papers and also has not been reported in the main body of this report. This is because of the high risk of bias found in both studies[33,34] (see *Quality assessment* below), especially concerning the comparability of treatment and control groups, which would adversely affect the reliability and validity of any such estimates of effect.[35] The between-group differences reported in the published papers are therefore the only statistical results reported here.

Results

Quantity and quality of research available

The search of electronic databases identified 1444 unique citations. One hundred and twenty-two full papers were retrieved after double-screening to determine whether they were relevant to this review. After double-screening of the full papers, only two studies explicitly satisfied all of the inclusion criteria: Ang *et al.*[33] and Leiba *et al.*[34] A further two studies (three papers)[36–38] were identified as being of potential relevance as supporting studies because the study population had Wagner–Stickler syndrome. The diagnostic criteria described in these two studies included non-ocular features, and so were possibly consistent with a diagnosis of Stickler rather than Wagner syndrome. No additional relevant papers were identified from either reference tracking (two potential papers were unattainable, but appeared to concern Wagner syndrome patients only)[39,40] or contact with expert advisors.

Seventy full papers were double-screened and excluded because they clearly failed to satisfy one or more of the criteria relating to the population, intervention or outcomes (these studies are listed in *Appendix 4*). The full papers of three citations were not available for screening.[41–43] A total of 44 further papers were excluded because they evaluated primary prophylactic surgical interventions for RD but did not provide sufficient details to be certain that there were no Stickler syndrome patients within the study population. These studies are listed in *Appendix 5*. Eight of these studies stated that a family history of RD was either an indication for prophylactic intervention or a characteristic of the study population.[44–51] Details of the screening and inclusion process are provided in the PRISMA flow diagram (*Figure 1*).

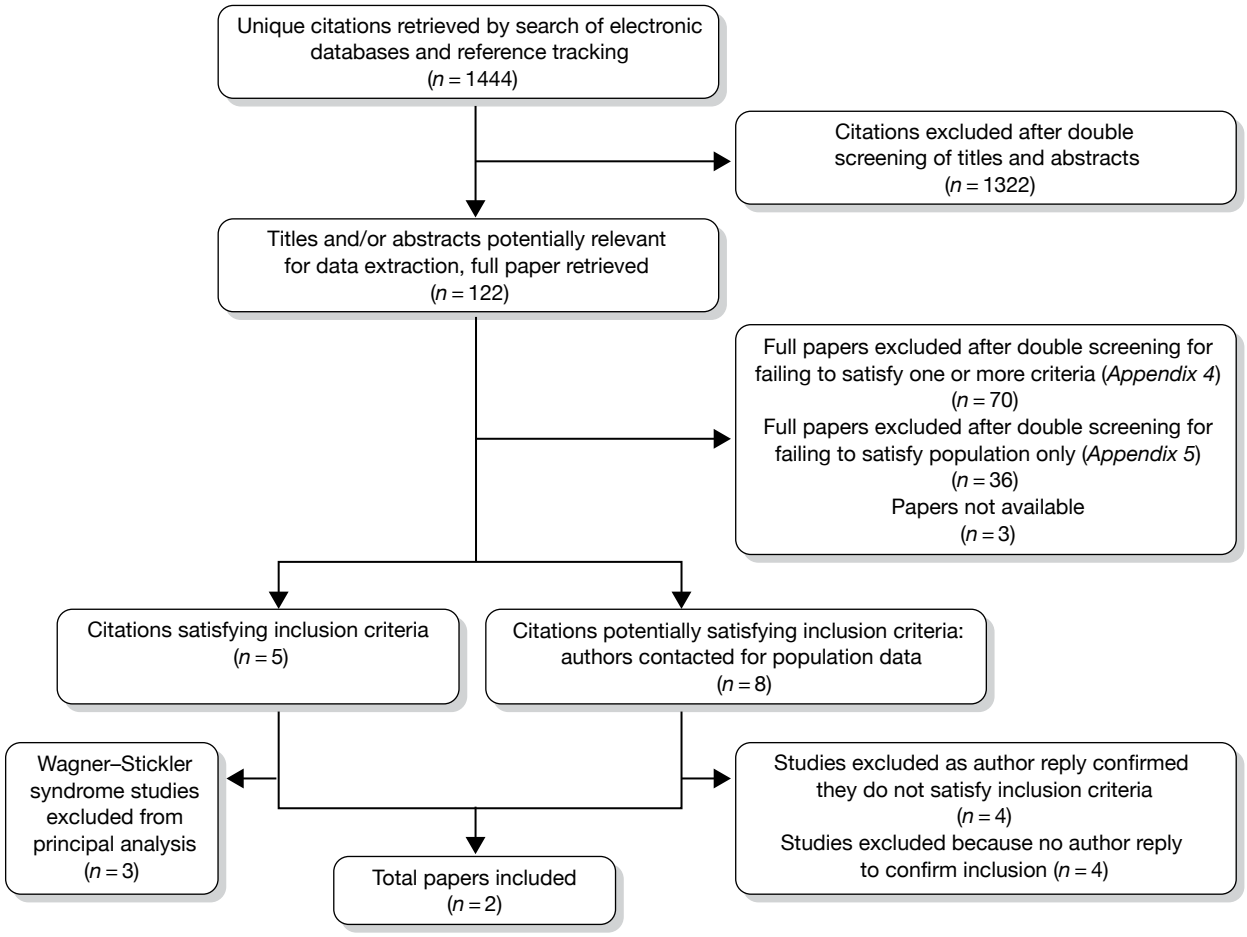

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

The reviewers therefore contacted the authors of these eight papers[44–51] to ascertain whether there were any Stickler syndrome patients in their study sample (November 2009) and the results of any intervention for this subgroup. However, at the time of this report, only four authors had communicated with the review team, and all reported either that there was no known Stickler syndrome patients in their samples[45–47] or that the data were no longer available to determine whether or not Stickler patients had been included.[48] The total number of studies therefore included in the principal analysis was two controlled cohort studies of prophylactic surgical interventions in type 1 Stickler syndrome populations. Details of two studies (three papers)[36–38] of cohorts with comparator groups evaluating prophylactic surgical interventions in 'Wagner–Stickler' syndrome populations are also summarised as supporting evidence.

Summary of studies

Two studies were identified that assessed primary prophylactic surgical interventions in populations diagnosed with type 1 Stickler syndrome (*Table 1*).[33,34] The diagnostic criteria applied in both studies were consistent with Stickler syndrome. In both studies, the diagnosis was confirmed 'where possible' with genetic analysis, but this does not appear to have been applied to all participants.

In the Ang *et al.* study,[33] the intervention was 360° cryotherapy on the post-oral retina to prevent progression to RD of the posterior flap of giant retinal tears (GRTs). The study by Leiba *et al.*[34] evaluated circumferential or focal laser treatment. The circumferential treatment consisted of confluent laser burns 360° around the peripheral retina, with four to eight laser burns applied

TABLE 1 Study characteristics

Study	Study design	Population, age and gender	Diagnostic criteria	Inclusion criteria	Intervention (*n* = patients)	Control (*n* = patients)	Follow-up
Ang *et al.* 2008[33] UK	Retrospective cohort study with controls	Type 1 Stickler syndrome patients with GRTs and RD in one eye or no eye (*n* = 204) Age range 2–92 years Gender: 109 male; 95 female	Mutation analysis, where possible, with gene *COL2A1*, plus congenital vitreous anomaly and any three of myopia with onset before age 6 years; RRD or paravascular pigmented LD; joint hypermobility with an abnormal Beighton score with or without radiological evidence of joint degeneration; audiometric confirmation of hearing defect; midline clefting	Diagnostic criteria or individuals with type 1 previously seen or still under active management of Addenbrooke's Hospital, Cambridge, UK	Bilateral and unilateral surgical prophylaxis 'Standard prophylaxis': 360° cryotherapy on the post-oral retina Group 1: bilateral, i.e. both eyes (*n* = 62) Group 2: unilateral, fellow eye only (*n* = 31)	Group 3: No prophylaxis or 'non-standard prophylaxis', which included 'treating isolated areas of lattice more posteriorly or using laser retinopexy' (*n* = 111)	Group 1: range 1–27 years (mean 11.5 years) Group 2: range 1–33 years (mean 15.5 years) Group 3: 'data on the timing of events were either unreliable or missing'
Leiba *et al.* 1996[34] Israel	Not reported; appears to be retrospective cohort study with controls	A family group of type 1 Stickler Syndrome patients with ocular abnormalities (*n* = 22) Age range: NR Gender: 11 male; 11 female	High myopia, retinal degeneration, midface hypoplasia and retrognathia; definite history of family members. Diagnosis was confirmed by mutation analysis on gene *COL2A1*	*Intervention group* Diagnostic criteria and (1) ocular abnormalities: extensive peripheral retinal degeneration, i.e. at least 5 continuous hours of LD with or without retinal breaks; or (2) isolated foci of LD with one or more of the risk factors for RD: family member with inherited vitreoretinal disease; previous RD in fellow eye; family history of RD; myopia *Control group* Diagnostic criteria only	Bilateral and unilateral surgical prophylaxis (*n* = 6) Circumferential laser treatment for eyes with extensive contiguous retinal lesions where lesions were present in at least three quadrants of the retina Focal laser treatment for eyes with small localised lesions of LD or isolated breaks	No prophylaxis (*n* = NR; reviewers calculate *n* = 16)	Range: 1–15 years

LD, lattice degeneration; NR, not reported; RRD, rhegmatogenous retinal detachment.

circumferentially at the junction between the posterior border of the lesions and the unaffected retina. In the focal treatment, small localised lesions of lattice degeneration or isolated breaks were encircled by three to six rows of laser burns. The Ang *et al.*[33] study was conducted in the UK and the Leiba *et al.*[34] study in Israel. Both studies employed retrospective case review of data from a cohort exposed to the intervention and a cohort of controls. In both studies, bilateral and unilateral prophylaxis was performed. In the Leiba *et al.*[34] study, the control group does not appear to have received any specific form of prophylaxis. However, in the study by Ang *et al.*,[33] an unknown number of procedures of laser retinopexy or 'treating isolated areas of lattice more posteriorly' may have been performed on members of the control group. The length of follow-up for the intervention groups ranged from 1 to 33 years in the Ang *et al.*[33] study and from 1 to 15 years in the Leiba *et al.*[34] study. There was no reported length of follow-up for the controls in either study.

Quality assessment

Both the Ang *et al.*[33] and Leiba *et al.*[34] studies recruited relevant populations diagnosed with type 1 Stickler syndrome, although confirmatory genetic analysis appears to have been used only 'where possible' in the study by Ang *et al.*[33] Therefore, the diagnosis was made by clinical criteria only, and not confirmed by mutation analysis, for an unknown number of participants in the intervention and control groups in the Ang *et al.*[33] study. However, the clinical examination used in this study, i.e. to identify the relevant membranous vitreous phenotype, has been shown to have a high degree of sensitivity in predicting the results of genetic analysis.[30] Neither study justified the size of the sample (204 in Ang *et al.*[33] and 22 in Leiba *et al.*[34]) or considered its implications in analysis, although the Ang *et al.*[33] study does evaluate the largest published sample of any study of prophylactic interventions in Stickler syndrome or other potentially relevant populations. The intervention and outcome (RD) appear to be measured accurately in both studies (although an unknown number of participants in the control group in the Ang *et al.*[33] study may have been exposed to some form of prophylaxis). It is unclear in both studies whether possible participants had been excluded.

The risk of RD is life-long,[2] so the longer the follow-up, the better. The Ang *et al.*[33] study had a mean follow-up for both intervention groups of between 11 and 15 years, which is substantial. However, there is no reported follow-up for the control group. The follow-up of the intervention group in the Leiba *et al.*[34] study was as much as 15 years, but was also as little as 1 year, which may not be long enough to demonstrate effectiveness reliably. However, the follow-up for three patients in the intervention group (6 of the 10 eyes) was between 8 and 15 years, which is more reliable. The length of follow-up for the control group was not reported. Neither Ang *et al.*[33] nor Leiba *et al.*[34] reported the relative risk [or confidence intervals (CIs)] of experiencing the outcome when exposed to the intervention compared with the control. Both studies reported only whether there was a significant difference in rates of RD between the intervention and control groups. There was therefore no estimate of effect. Also, Leiba *et al.*[34] did not report the test used to determine a statistically significant difference between the two groups. The external validity of the Ang *et al.*[33] study was good in comparison with Leiba *et al.*:[34] the population and setting were highly applicable to the decision problem, being type 1 Stickler syndrome patients, compared with Leiba *et al.*'s[34] consideration of a single family group of individuals with type 1 Stickler syndrome.

The results of both studies are subject to a high risk of bias. Both were retrospective cohort studies and so were limited by the bias inherent in that design.[52] The study reported by Ang *et al.*[33] had a number of strengths, including sample size, length of follow-up for the intervention groups and the reporting of data on the principal confounding factor of age. However, the control group presents a number of major problems. It does not represent a homogeneous group in terms of being exposed either to a single comparator intervention or to no intervention at all: an unknown number in the sample appear to have received some sort of prophylaxis that was not cryotherapy. The study correctly reports the potential confounding factor of age, but does not control for this in the results or analysis. The rate of RD in the control group is high in comparison with the intervention groups and is also higher than reported elsewhere for other Stickler syndrome populations not exposed to prophylaxis (but unconfirmed as type 1 only, and therefore potentially not at the highest risk of RD, unlike most if not all of the type 1 individuals in the Ang *et al.*[33] study): 73% per patient compared with 57%–61% per patient reported in surveys.[2,8,20] There is also a substantial difference between the intervention groups and the control group in terms of 'follow-up': the former has a maximum of 33 years with a mean of between 11 and 15 years, while there is no reported 'follow-up' at all for the latter, the controls. This further adversely affects the reliability of any comparison of event data between intervention and control

groups. Also, the mean age of the controls was 49 years (range 5–92 years), the mean age of the bilateral prophylaxis group was 21 years (3–61 years) and the mean age of the unilateral group was 36 years (2–75 years). Given that age and, consequently, follow-up are both recognised to be important confounders, i.e. the likelihood of RD increases over time, with age, then the likelihood of the control group having experienced the outcome is inherently much higher than for the intervention groups. The relative effect of the intervention on the outcome of RD may therefore have been exaggerated when compared with the control group based on the event data reported in this study. It is also unclear whether the study was sufficiently powerful to generate a reliable effect size for the primary outcome. The risk of bias in this study was therefore high.

Leiba *et al.*[34] considered the potential confounding factors of age at first RD and the presence or absence of RD in the primary eye. Differences between intervention and control groups were not reported, although only those participants who were considered eligible for treatment actually received prophylaxis; the control group may therefore have had a different (possibly higher) level of risk of RD. The control group in the Leiba *et al.*[34] study is homogeneous as the subjects all appear to have received no form of prophylaxis at all. However, this study had more weaknesses than Ang *et al.*:[33] the reported follow-up was shorter (a minimum of 1 year and a maximum of 15 years); the sample was much smaller and narrower (i.e. from a single pedigree); and the mean age of the intervention and control groups was not reported, although the data reported enable the comparison to be made that 9/10 individuals in the control group experienced an RD before the age of 30 years, and 5/6 patients exposed to prophylaxis received the treatment before 30 years of age. The risk of bias in this study was therefore also high.

Assessment of effectiveness

No estimates of effect were reported in the published papers or calculated by the authors of this report (owing to the high risk of bias in the two studies[33,34]). The papers themselves appear to test for and report only between-group differences (see *Table 2*). The Ang *et al.*[33] study reported a statistically significant difference between groups both for eyes [$\chi^2 = 119.2$, degrees of freedom (df) = 1, $p < 0.001$] and for patients ($\chi^2 = 37$, df = 1, $p < 0.001$), and the Leiba *et al.*[34] study reported a statistically significant difference between intervention and control groups for RD ($p < 0.0025$), but the test used was not reported and it is unclear whether this was for eyes or patients. Relative estimates of effect (relative risks), calculated by the authors of this report and based on the event data reported by these studies, are not reported in the main body of the report because their validity is affected by the high risk of bias within the included studies. However, these relative risks are reported in *Appendix 8*.

Neither study reported details of any retinal tears or lesions which did not lead either to an RD or to further surgery. Only Leiba *et al.*[34] reported data on blindness due to RD: the intervention group had only one RD and no resulting blindness; 10 members of the control group experienced RD in one or both eyes (18 eyes), and 16 of these 18 eyes proceeded to blindness post RD surgery (time to failure not reported). Only two eyes had not re-detached by the time of the study (duration of follow-up not reported).

Subgroups: children

Only Leiba *et al.*[34] performed a subgroup analysis based on age. The study reported that 0/6 eyes treated prophylactically in children aged ≤ 13 years detached compared with 1/4 eyes treated prophylactically in children aged ≥ 13 years. The findings of this study may also indicate an increase in the likelihood of RD in adolescence and young adulthood. In the control group, who did not receive any prophylaxis, the retina detached in 6/13 (46%) eyes in children aged ≤ 13 years, but detached in 9/15 (60%) in adolescents and adults aged ≥ 13 years. However, this sample is very small.

Safety

None of the studies reported any serious or long-term adverse events or complications associated with cryotherapy, focal or circumferential laser treatment or scleral buckling. Only minor and temporary complications were reported by any of the studies. For cryotherapy, Ang *et al.*[33] reported transient epiphora, lid swelling and temporary accommodative paresis, but no cases of choroidal haemorrhage, macular pucker or unexplained loss of vision. However, the study did not report the number of patients experiencing any complications, so the proportion of patients experiencing these or any other complications, and the duration of any side effects, is unknown. Leiba *et al.*[34] reported that there were no ocular complications associated with the laser prophylaxis performed and visual acuity was unaffected.

Supporting studies

There are two studies (three papers), by Monin *et al.*[36,37] and Fritsch *et al.*,[38] reporting evaluations of primary prophylactic interventions in populations diagnosed as having 'Wagner–Stickler' syndrome (*Tables 3* and *4*). Both studies reported that all participants in their sample had 'Wagner–Stickler' syndrome, although the diagnostic criteria were not reported in the study by Monin *et al.*[36,37] However, in this study by Monin *et al.*, as well as being diagnosed with Wagner–Stickler syndrome, a number of participants had either a 'family history' of RD or 'systemic abnormalities (cleft palate)' in addition to ocular abnormalities stated as being consistent with Wagner or Stickler syndrome.[36] In the study by Fritsch *et al.*,[38] in addition to ocular abnormalities, all participants had non-ocular symptoms, which may be suggestive of Stickler rather than Wagner syndrome. However, neither chromosome nor genetic analysis was performed in either study to clarify diagnosis. It therefore cannot be stated categorically that the populations in these studies had Stickler syndrome. However, the reported, published diagnosis of Wagner–Stickler syndrome for these patients, and the greater consistency of symptoms with

TABLE 2 Reported outcomes

Study	Intervention vs control, *N* (eyes)	RD post bilateral and unilateral prophylaxis, *n*/*N* (eyes)	RD post bilateral prophylaxis	RD post unilateral prophylaxis	Time to treatment failure	Blindness[a]	Location of tears, lesions etc. likely to have caused RD. Other tears and lesions
Ang *et al.* 2008[33] UK	360° cryotherapy (*N* = 155) vs no prophylaxis (*N* = 222)	7/155 vs 134/222 Difference between groups based on eyes: $\chi^2 = 119.2$, df = 1, $p < 0.001$	4/124 vs 134/222 No analysis reported	3/31 vs 134/222 No analysis reported	Group 1: range 2 months to 15 years (mean 7.7 years) Group 2: range 49 months to 15 years (mean 11.6 years)	NR	*RDs in treated area* Group 1: 3/4; group 2: 1/3 *RDs posterior to treated area* Group1: 1/4; group 2: 2/3 Group 1: three posterior holes requiring top-up retinopexy Other tears or lesions: NR
Leiba *et al.* 1996[34] Israel	Circumferential (*N* = 4) and focal (*N* = 6) laser treatment vs no prophylaxis (*N* = 34)	1/10 vs 15/34[b] Difference between groups: $p < 0.0025$ (test not reported)	1/8 vs 15 or 18/34 No analysis reported	0/2 vs 15/34[b] No analysis reported	5 years	0/10 vs 16/34[c]	One RD occurred 'owing to a new lesion' in an untreated area of the eye Three eyes required new focal laser treatment because they developed new lesions (location and type NR)

NR, not reported.
a Definition of blindness: hand movement to light perception.
b These figures are reported in Tables III and IV and the text in p. 705 in the Leiba *et al.*[34] study: a figure of 18 RDs is reported on p. 704.
c Reported numbers across outcomes for RD (pp. 704–5) and blindness (p. 702) are not consistent.

TABLE 3 Study characteristics (Wagner–Stickler syndrome)

Study	Study design	Population, age and gender	Diagnostic criteria	Inclusion criteria	Intervention (*n* = patients)	Control	Follow-up
Monin *et al.* 1994[36] and 1993[37] France	Retrospective cohort study with controls	Wagner–Stickler patients (*n* = 22) Age: NR 16 male, 6 female	NR Some participants have a 'family history' of RD or 'systemic abnormalities (cleft palate)'	RD in first eye and had not received any prophylaxis in the fellow eye	Unilateral surgical prophylaxis Group 1: argon laser photocoagulation with a 'barrage circulaire large' or a 'plaque' posterior to the 'equateur' (*n* = 10) Group 2: Encircling scleral buckling (*n* = 8) (1993)	'Other treatments' (*n* = 4) 1 = cryotherapy; 1 = focal laser photocoagulation; 1 = circular laser photocoagulation; 1 = vitrectomy	Range: 3–67 months
Fritsch *et al.* 1989[38] France	Cohort study without controls	Wagner–Stickler patients (*n* = 26) Age = NR Gender = NR	1. Ocular lesions typical of Wagner–Stickler 2. Typical non-ocular symptoms, e.g. facial dysmorphia, cleft-palate and arthropathy 3. Family history	Diagnostic criteria (1), (2) and (3) or (1) and (2) only; RD in one eye (*n* = 7) or no RD (*n* = 19)	Bilateral and unilateral surgical prophylaxis Exact numbers for each intervention NR: Focal laser treatment or cryotherapy for patients without RD (*n* = 22; bilateral = 19; unilateral = 3);	Unilateral prophylaxis: Scleral buckling (*n* = 2) Focal laser treatment plus scleral buckling (*n* = 2)	Range: 2–8 years

NR, not reported.

TABLE 4 Reported outcomes (Wagner–Stickler syndrome)

Study	Intervention vs control, *n* = eyes	RD post bilateral and unilateral prophylaxis, *n*/*N* (eyes)	RD post bilateral prophylaxis	RD post unilateral prophylaxis	Time-to-treatment failure	Location of tears, lesions, etc. likely to have caused RD. Other tears and lesions
Monin *et al.* 1994[36] and 1993[37] France	ALP (*N* = 10) vs encircling scleral buckling (*N* = 8) vs various other interventions (*N* = 4)	N/A	N/A	5/10 vs 0/7[b] vs 4/4 No analysis reported	Group 1: 3–24 months (mean 12 months) Group 2: N/A Group 3: 18–67 months	NR
Fritsch *et al.* 1989[38] France	Various interventions (*N* = 45) No control	0/45	0/38	0/7	N/A	Three eyes required additional treatment in the monitoring period because they developed new lesions

ALP, argon laser photocoagulation; N/A, not applicable; NR, not reported.

a This patient received focal laser treatment in both eyes and experienced RD in one eye only after 5 years, the fellow eye had not detached after 9 years.

b One lost to follow-up. Fuller details of these scleral buckling data are from Monin *et al.* 1993.[37]

Stickler rather than Wagner syndrome, suggest that there are reasons to consider that these studies may provide possible relevant supporting evidence to this review. They have therefore been included, but are not considered as principal evidence.

In the Monin *et al.*[36,37] study, only participants who had already experienced RD in the primary eye were included; prophylaxis was performed on the fellow eye (i.e. the eye that had not experienced a detachment). The study was conducted in France. There were three intervention groups, each exposed to different forms of primary prophylaxis: argon laser photocoagulation; scleral buckling; and a group exposed to four different interventions: focal cryotherapy, focal or circular laser photocoagulation, or vitrectomy. No group was designated as the primary intervention group or as controls. This study employed retrospective case review of data from cohorts exposed to the various interventions. Follow-up was reported to range from 3 to 67 months. In the study by Fritsch *et al.*,[38] participants received either bilateral or unilateral prophylaxis. This was a cohort study conducted in France. It is unclear whether the study was prospective or retrospective. Groups in the cohort were exposed to one of the following interventions: focal laser treatment or cryotherapy, and scleral buckling or focal laser treatment with scleral buckling. Follow-up was reported to range from 2 to 8 years.

Monin *et al.*[36,37] reported that scleral buckling appeared to be effective as none of the seven participants exposed to this unilateral intervention in the fellow eye had experienced an RD at follow-up (9 months to 3 years) (*Table 4*).[37] However, 5 of 10 individuals exposed to unilateral argon laser photocoagulation had an RD in the fellow eye in the follow-up period, as did all four individuals exposed to cryotherapy, focal or circular laser photocoagulation, or vitrectomy. The mean age at first RD was 8 years in the laser group failures, 11 years for the laser group 'successes' and 16 years for the successful scleral buckling group participants. The age at first RD may therefore be a confounding factor. In the Fritsch *et al.*[38] study, none of the individuals exposed to cryotherapy (number unknown), focal laser treatment (number unknown), scleral buckling ($n = 2$) or focal laser treatment with scleral buckling ($n = 2$) experienced an RD. Monin *et al.*[36,37] reported lid swelling and chemosis immediately post operation for scleral buckling, as well as a single case of longer-term sero-haemorrhagic choroid detachment, which spontaneously resolved. The Fritsch *et al.*[38] study did not report any complications with any intervention.

Both the Monin *et al.*[36,37] and Fritsch *et al.*[38] studies had a high risk of bias. They appear to be retrospective cohort studies and had very small samples (22 and 26 respectively); it is unclear if some possible participants had been excluded and the diagnosis itself may be flawed. There is no justification of the sample size in either study. In the absence of clearly reported diagnostic or treatment criteria, it is not possible to determine whether the populations in the treatment groups in the study by Monin *et al.*[36,37] are in fact all the same. Fritsch *et al.*[38] was a cohort study with comparator groups, but did not report the exact number of participants exposed to either focal laser treatment or cryotherapy in the principal group. The effect of each of the reported interventions therefore could not be determined. Neither Monin *et al.*[36,37] nor Fritsch *et al.*[38] reported any differences between groups. The follow-up in both studies (maximum 8 years) is almost certainly insufficient to demonstrate effect. Neither study performed any analysis on the results or calculated an estimate of effect. Fritsch *et al.*[38] reported that no participant experienced the outcome of interest. This seems unlikely given the population and length of follow-up (up to 8 years): Monin *et al.*[36,37] evaluated similar interventions in a similar population over a shorter length of time and reported a high incidence of RD in two of the three intervention groups. The external validity of both studies is limited because the populations were diagnosed as Wagner–Stickler syndrome rather than Stickler syndrome (although reported symptoms suggest a majority may have had Stickler syndrome) and neither was conducted in the UK, and techniques may differ by location.

Chapter 4

Assessment of factors relevant to the NHS and other parties

Stickler patients may present to the NHS in one of three ways. Firstly, individuals may present with an RD in the primary eye and it is noted that they have systemic features consistent with Stickler syndrome, e.g. cleft lip or joint abnormalities.[8,27] Secondly, they may be referred to a consultant ophthalmologist (Hospital Eye Service) on account of poor vision, high myopia or amblyopia ('lazy eye') and are found also to have other ocular and systemic features that are consistent with Stickler syndrome. Given the issues with diagnosis outlined above, molecular genetic analysis would be required to confirm the presence and type of Stickler syndrome. It has been reported that the efficiency of mutation detection after vitreoretinal assessment is 96.5% for the membranous phenotype *COL2A1*.[53] Currently, the cost of diagnostic genetic testing is reported to be approximately £1000 (East Anglian Medical Genetics Service, Addenbrooke's Hospital, Cambridge, UK, 1 July 2010). Finally, family members of an individual (index case) diagnosed with Stickler syndrome could be approached and offered molecular genetic analysis to confirm the presence and type of Stickler syndrome (pre-symptomatic tests £162 for sequence of one exon: East Anglian Medical Genetics Service, 1 July 2010). An assessment of ocular and non-ocular features of Stickler syndrome would also need to be made for these individuals, and the risk of RD determined. All groups for whom mutation of the relevant genes has been detected may also benefit from genetic counselling.[8,19,54] Published figures estimate the lifetime costs associated with congenital visual loss in childhood or adolescence to be up to £257,000 per person, with 61% of this cost attributable to productivity losses.[55] In the event that a form of prophylaxis was found to be definitely relatively more effective than others (though no particular treatment is demonstrably and certainly more effective based on current published evidence), then that form of prophylaxis could be offered to these groups.

In order to quantify or assess the implications for the NHS, more reliable estimates or data are needed on the prevalence of Stickler syndrome in the UK, the risk of blindness in individuals diagnosed with type 1 and type 2 Stickler syndrome, i.e. those types at highest risk of RD, with and without treatment for RD, and the efficacy of prophylaxis. If these elements are established, then there may also be a case for screening programmes in order to identify individuals both with and without a recognised family history (i.e. a new mutation) before they present with an RD.

Chapter 5

Discussion

Statement of principal findings

Two studies were identified that assessed the effectiveness of interventions for the primary prophylaxis of RD in type 1 Stickler syndrome populations.[33,34] Both studies were retrospective cohort studies. The study by Ang *et al.*[33] evaluated the efficacy of 360° cryotherapy for the prevention of GRTs progressing to RD. The intervention was applied to both eyes or one eye only, i.e. as bilateral or unilateral prophylaxis, and compared with either no prophylaxis or, for some controls, alternative but unknown forms of prophylaxis. This study had 204 participants. The Leiba *et al.*[34] study evaluated focal and 360° circumferential laser treatment in bilateral or unilateral prophylaxis compared with no prophylaxis. This study had only 22 participants, from a single family group. The primary outcome in both studies was the incidence of RD in eyes without any prior RD and receiving prophylaxis. Both studies reported a significant difference between the number of RDs in the intervention and control groups. The reduction in the risk of RD was statistically significant for cryotherapy prophylaxis compared with non-cryotherapy prophylaxis or no prophylaxis both for individuals with no previous RD and for those with an RD in the primary eye.

There was clinical heterogeneity between these two studies,[33,34] so their results could not be combined statistically to offer a potentially more robust and precise estimate of effect. Both studies included only patients diagnosed as having type 1 Stickler syndrome, but all participants in the intervention groups in the study by Ang *et al.*[33] had GRTs, while none of the participants exposed to the intervention in the study by Leiba *et al.*[34] had any GRTs. The indications for prophylaxis were therefore different in the two studies. The interventions being evaluated were also different – 360° cryotherapy alone[33] or focal or circumferential laser treatment[34] as was the control – no prophylaxis or prophylaxis other than cryotherapy[33] – or no prophylaxis.[34] Both studies had reasonable follow-up of the intervention groups. Although the risk of RD is life-long, all reported RDs occurred in < 6 years in the Leiba *et al.*[34] and Monin *et al.*[36,37] studies, and at a mean of 7.7 years for the bilateral prophylaxis population in the Ang *et al.*[33] study; so, follow-up of up to 15 or 33 years, which was achieved for some participants in the Leiba *et al.*[34] and Ang *et al.*[33] studies respectively, may potentially capture a sizeable number of RDs subsequent to prophylaxis. However, longer follow-up would offer much more reliable results. According to the studies by Ang *et al.*[33] and Leiba *et al.*,[34] neither 360° cryotherapy nor focal or circumferential laser treatment appears to be associated with major or long-term complications. However, the number of patients experiencing minor or temporary complications or side effects was not reported in either study.

There is a high risk of bias within both studies. The lack of comparability between the intervention and control groups is the principal source of bias affecting the reliability and validity of the findings of the study by Ang *et al.*[33] The control group is different from the intervention groups. It is substantially older than the intervention groups (mean age of 49 years compared with 21 or 36 years) and, given that the risk of RD is life-long,[2,8] these controls were therefore inherently much more likely to have experienced the outcome of interest (RD). The study acknowledges the problem of the lack of comparability, stating that the control group offered 'a useful estimate of the prevalence of RD' without cryotherapy. However, the percentage of patients

with RD in either eye in the control group is also higher than the figure commonly cited in the literature for rates of RD in Stickler syndrome populations not exposed to prophylaxis (73% vs a rate of 57% in 165 members of a family with Stickler syndrome,[20] and 60% or 61% in two studies sampling individuals in Stickler syndrome support groups in either the UK and North America[2] or the UK only[8]). As noted above, these surveys are not explicitly limited to individuals with type 1 Stickler syndrome, who are at the highest risk of RD, only individuals principally diagnosed by ophthalmologists or geneticists as having Stickler syndrome. There may also be a risk of misdiagnosis, but this has never been quantified. The sampling of both the controls in the Ang *et al.*[33] study and the participants in the surveys is at risk of bias, so neither figure is a reliable estimate of prevalence of RD in untreated Stickler syndrome populations. However, these studies offer the only currently reported relevant comparative data on this outcome within this population.

By contrast, members of the intervention group receiving bilateral prophylaxis in the Ang *et al.*[33] study, with a mean age of 21 years, will have been the least likely to experience the outcome by the age of intervention or follow-up, as the risk of RD is reported to increase in young adulthood up to 30 years of age[2] and if the primary eye has already experienced a detachment.[50,56–58] Given the life-long risk of RD in individuals with Stickler syndrome, age is a major confounding factor in any comparison of primary prophylaxis for RD, and should be controlled. Ang *et al.*[33] also recognise that a substantially increased rate of RD beyond the existing follow-up period might potentially negate the findings of the study.[21] A higher rate of RD beyond the study duration is possible, given that the mean age of the group receiving bilateral prophylaxis was 21 years; and it has been reported elsewhere that the first RD occurred between the mean ages of 21 and 25 years in a group of Stickler syndrome patients presenting over a 40-year period.[27]

The data for the control group in the Ang *et al.*[33] study are also cross-sectional, i.e. they are reported only for a single point in time (the time of the study's data collection), unlike the data for the intervention groups. The intervention groups have a baseline (the time of the exposure to the intervention) and an end point (the time of the study's data collection). The control group has not been exposed to an intervention and so lacks the 'baseline'; there is therefore no reported length of follow-up. This therefore also introduces further risk of bias into any comparison between the intervention and control groups. The generation of a potentially more comparable control group, from within the Ang *et al.*[33] controls, may be possible if age at first RD was known, i.e. those who had not experienced an RD by the mean age at which the bilateral prophylaxis group were exposed to the intervention (10 years), and those who had experienced RD in only one eye by the mean age at which the unilateral prophylaxis group were exposed to the intervention (21 years). This would offer a baseline for comparability between groups: the age of the controls at the time of data collection would represent the follow-up, and the incidence of RD (including if there was bilateral RD) would be more comparable to any reported incidence in the intervention groups. However, it is stated in the study by Ang *et al.*[33] that 'data on the timing of events [in the control group] were either unreliable or missing' and the confounding factors of age and heterogeneity in the exposure of controls to prophylaxis would remain. This lack of comparability between the intervention and control groups therefore introduces a high risk of bias into this study; consequently, there is considerable uncertainty regarding the relative efficacy of this intervention.

The reliability of any estimate of the relative effect of the intervention would be further adversely affected by heterogeneity in the control group in terms of the comparator intervention as some subjects were exposed to no intervention at all and an unknown number received some form of some prophylaxis. Finally, it is also unclear whether the study would be powerful enough to generate a reliable estimate of effect.

The study by Leiba *et al.*[34] was smaller and shorter. It considered only 22 individuals from a single family, and the follow-up of the intervention group was as little as 1 year and a maximum of only 15 years, which overall may not be long enough to reliably demonstrate effectiveness. There was no power calculation, so it is uncertain whether this small study would be powerful enough to generate a reliable estimate of effect. Leiba *et al.*[34] also failed to report differences between intervention and control groups, including the potential major confounding factor of age, and only those participants who were considered eligible for treatment actually received prophylaxis, so the relative likelihood of the control group experiencing RD is unknown.

Despite the high risk of bias in both studies, the rate of RD in the intervention groups is lower than the rate experienced in the study control groups. The rate of RD is 4/124 (3%) per eye and 4/62 (6%) per patient in those exposed to bilateral cryotherapy prophylaxis, and 3/31 (10%) per eye and per patient in those exposed to unilateral cryotherapy prophylaxis. This compares with 134/222 (60%) per eye in the study control group or, excluding those who experienced bilateral RD, 28/116 (24%).[33] The rate of RD is 1/8 (13%) in those exposed to bilateral laser prophylaxis and 0/2 in those exposed to unilateral laser prophylaxis, compared with 15/34 (44%) in the untreated control group.[34] The rates reported for the intervention groups are also lower than the 57%, 60% or 61% reported for rates of RD in surveys of Stickler syndrome populations not exposed to prophylaxis.[2,8,20] These studies do not report a mean age for these figures but, again, it is likely to be higher than the mean age reported for the intervention groups in the study by Ang *et al.*,[33] so there exists the same problem of comparability. Also, the rates of RD in the largest study sample increased from 26% to 61% from the 10–19 years to the 20–29 years age group.[2] This again highlights a problem with the mean age of 21 years for the bilateral prophylaxis group in the Ang *et al.*[33] study, as this group is likely to be at inherently lower risk of having experienced a first RD. However, in the two surveys sampling a similar population base, the percentage of patients experiencing RD was 16% ($n = 27/164$) in those < 20 years of age[2] and 20% ($n = 15/74$) for those < 16 years of age,[8] which are both higher than the rates reported for the bilateral and unilateral prophylaxis intervention groups with mean ages of 21 or 36 years in the study by Ang *et al.*:[33] 6% and 10% respectively.

The incidence of first RD appears to rise substantially after the age of 20 years in both of these surveys (from ≤ 26% to 60% or 61%).[2,8] Therefore, the ongoing reporting of rates of RD in the intervention groups of the study by Ang *et al.*[33] would permit a further, more robust evaluation of the relative efficacy of cryotherapy in the primary prophylaxis of RD in type 1 Stickler syndrome. This is because both the mean age of the intervention groups (currently a major confounder introducing a risk of bias into the study results) and the duration of follow-up (a second important confounder) would increase with the consequence that the risk of bias would be reduced. However, the problems with the study's control group would remain.

Two further studies were identified that assessed the effectiveness of interventions for primary prophylaxis of RD in populations designated as 'Wagner–Stickler' syndrome, but in which some or all of the participants had systemic features that may be consistent with Stickler syndrome.[36–38] Both were small cohort studies with a number of comparable intervention groups. Neither study reported significant differences between the number of RDs in the intervention groups. Monin *et al.*[36,37] reported 5/10 RDs in the argon laser photocoagulation group, 0/7 in the scleral buckling group and 4/4 in the group exposed to cryotherapy, focal or circumferential laser treatment, or vitrectomy. Fritsch *et al.*[38] reported no RDs in any group. However, there is a high risk of bias within both studies: neither was definitely conducted on a majority of Stickler syndrome individuals; neither controlled for confounding factors such as age; neither had follow-up of > 8 years for any individual; neither had large samples; and the numbers exposed to specific interventions were not reported in the principal intervention group in the study of Fritsch *et al.*[38]

In the absence of head-to-head studies of the stated interventions in this population, there may be scope for undertaking a form of indirect comparison. It is unfortunate that there are insufficient data to make a robust comparison between individual techniques. Further research is required to produce a definitive conclusion on the most effective clinical approach. Nevertheless, there may also be value in quantifying the uncertainty regarding the relative effectiveness of each intervention, if only to use it as a basis for designing a prospective randomised controlled trial (RCT) comparing potential interventions (J Stevens, Lecturer and Director of the Centre for Bayesian Statistics in Health Economics, March 2010, personal communication).

Strengths and limitations of the assessment

Strengths

- There is no other published review of primary prophylactic interventions for RD in either Stickler syndrome or Wagner–Stickler syndrome individuals.
- The literature search: a sensitive search was performed to identify published and unpublished comparative studies that satisfied the inclusion criteria. No formal assessment of publication bias has been made for this review, but the effect of any such bias is likely to be minimal given the absence of any date or language limits on the search, the inclusion of non-English-language journal articles, and the inclusion of supporting studies reporting inconsistent results for the interventions, including no effect.[36,59] The likelihood of a relevant study having been missed is therefore low.
- Authors of papers were contacted if a family history of RD was cited as a characteristic of study participants being exposed to primary prophylactic interventions for RD, but without any specific reference to Stickler syndrome. The aim was to identify any additional relevant data on Stickler syndrome subgroups in studies that did not otherwise specify that participants did or did not have this condition. No further data were forthcoming.
- The review process: all titles and abstracts of citations retrieved by the search of electronic databases were screened independently for inclusion and exclusion by two reviewers; and all data extraction and quality assessment of included studies were performed independently by two reviewers, and any discrepancies identified and resolved.
- The identification of two principal studies satisfying the inclusion criteria with populations diagnosed with type 1 Stickler syndrome patients (the subtype at highest risk of RD) and confirmed 'where possible' by genetic analysis.

Weaknesses

- The absence of any relevant studies with a robust comparative design to limit the risk of bias, e.g. RCTs. The only pivotal studies identified were retrospective cohort studies.
- The absence of any good-quality studies or data with which to answer the research question.
- The small number of relevant studies identified: two principal studies of type 1 Stickler syndrome individuals,[33,34] and two supporting studies of 'Wagner–Stickler' syndrome individuals,[36–38] with issues surrounding this diagnosis.
- Despite efforts to identify all published and unpublished research satisfying the inclusion criteria, publication bias as a result of the non-publication of studies of any of the various prophylactic interventions but which demonstrate no effect cannot entirely be discounted.

Uncertainties

The review identified only two principal studies that satisfied the inclusion criteria,[33,34] and the risk of bias in both studies is high. The study designs used (retrospective cohorts with comparator groups) are inherently at greater risk of bias than alternative study designs, such as randomised

or prospective controlled trials.[52] These two studies also had major weaknesses in the conduct of the study, including major differences between the intervention and control groups in terms of potential confounding factors, a possible lack of power, limited follow-up and, in one case, a small and narrow sample. The data reported by these studies therefore cannot generate a robust or reliable estimate of the effect for 360° cryotherapy or focal or circumferential laser treatment compared with no intervention as primary prophylaxis for RD in type 1 Stickler syndrome.

It is likely that future trials with greater comparability between treatment groups, longer follow-up, and a lower risk of bias, would not only enable the calculation of a valid and reliable estimate of effect, but also generate a reliable estimate of the relative risk of RD when exposed to either another primary prophylactic intervention or no intervention at all. The ongoing reporting of data from the intervention groups in the Ang *et al.*[33] study should partially address some of these issues. In the absence of good-quality trials comparing interventions within Stickler syndrome populations, or sufficient data to permit a robust indirect comparison, it is also uncertain which if any of the interventions of cryotherapy or focal or circumferential laser treatment is relatively the most effective.

It is uncertain whether other primary prophylactic interventions may be potentially effective in reducing rates of RD in this population. Scleral buckling, for example, has not been evaluated in confirmed type 1 Stickler syndrome populations, but Monin *et al.*[36,37] reported positive results for this technique in an intervention arm of a study of 'Wagner–Stickler' individuals. However, the number of participants in this group was very small ($n = 7$) and the follow-up was very short (3 years). The risk of bias in the studies of 'Wagner–Stickler' populations was also high, preventing reliable conclusions being drawn from the efficacy results relating to a range of different prophylactic interventions.

There appear to be few major or long-term complications or adverse events associated with 360° cryotherapy or focal or circumferential laser treatment, but the number of individuals likely to experience either minor or major short-term complications is uncertain. The clinical advice elicited for this report suggests that cryotherapy is likely to produce greater pain and swelling than laser therapy.

The interventions evaluated by the principal studies of Stickler syndrome individuals are 360° cryotherapy on the post-oral retina by Ang *et al.*[33] and focal or circumferential laser treatment by Leiba *et al.*[34] The efficacy of both interventions in different areas of the eye, such as 360° cryotherapy at the posterior border of the vitreous base[60] and at the equator, has not been assessed in type 1 Stickler syndrome populations. The evidence identified by this review also does not permit a conclusion to be drawn on whether there is an optimal intervention for particular indications, i.e. whether cryotherapy and/or focal or circumferential laser treatment are likely to be effective in Stickler syndrome populations presenting with indications for treatment different from those evaluated in the studies. Prophylactic cryotherapy has been evaluated only in type 1 Stickler syndrome patients with GRTs, and focal and circumferential laser treatment only in type 1 Stickler syndrome individuals with lattice degeneration with or without retinal breaks, or isolated foci of lattice degeneration with at least one of the following: myopia, previous RD and a family history of RD or vitreoretinal disease.

It is uncertain what the optimal indications are for prophylaxis in Stickler syndrome populations, that is if any such optimal indications exist, e.g. GRTs or other retinal lesions, lattice degeneration or high myopia. It is also unclear whether there are indications for which one or both of the interventions should not be used. Clinical advice suggests that the choice of intervention is currently determined by the clinician's preference only. The optimal age for treatment is also uncertain. It has been suggested that early intervention, in childhood, may be advisable given

that the first RD has been found to occur more frequently in the 10–30 years age group, and that children may not be able to report symptoms until it is too late.[21] Leiba *et al.*[34] performed a subgroup analysis based on age and found a smaller number of postprophylaxis RDs in children or adolescents aged ≤ 13 years old compared with those aged > 13 years. However, this sample was very small ($n = 11$).

It is uncertain how effective the interventions are at preventing or reducing the presence or type of retinal tears or lesions (possible precursors of RDs) in untreated areas of the eye. These data are reported by only one study for the intervention groups and not for the control group.[33] It is therefore also uncertain how frequently an intervention may need to be performed, given that neither procedure appears to prevent all tears or lesions that may lead to detachment. It has also been suggested that cryotherapy may cause or accelerate the development of new tears or lesions.[50,61] Supplementary prophylactic intervention (or 'top-up retinopexy') may need to be used to treat such tears or breaks that occur posterior to the treated area or secondary to GRTs.[33]

Other relevant factors

None reported.

Chapter 6

Conclusions

Implications for service provision

Only 360° cryotherapy[33] and focal and circumferential laser[34] treatment have been evaluated for the type 1 Stickler syndrome population, and by only a single retrospective, controlled, cohort study in each case. Both of these studies do report a significant difference between intervention and control groups (principally no treatment) and no major or long-term side effects or complications. However, there is a high risk of bias within both studies, so the relative effectiveness of either 360° cryotherapy or focal and circumferential laser treatment in comparison with no treatment is uncertain. There is also no head-to-head trial comparing the two interventions, so their relative effectiveness in comparison with each other is also uncertain. It is necessary to determine whether or not an individual has type 1 or type 2 Stickler syndrome, as this determines the risk of RD and therefore possible eligibility for any form of prophylaxis. Genetic analysis is required to establish the presence and type of Stickler syndrome. The groups for whom this may be necessary are described in *Chapter 4*. Continued follow-up and analysis of study data, and data collection from relevant sample populations, are required to assess the long-term risks of blindness, RD and prophylaxis. Therefore, given the uncertainties found by this report regarding the relative efficacy of the evaluated interventions, the implications for existing service provision are very limited, especially as continued follow-up and analysis of data being generated from existing services is a recommendation of this report.

Suggested research priorities

As a result of the high risk of bias in the studies included in this report, more reliable data may be generated from two sources. Firstly, the ongoing reporting and analysis of data from the study by Ang *et al.*[33] could potentially offer more reliable findings, but will still be affected by the risk of bias inherent in the design and control group of this study, unless the latter in particular was addressed.

Secondly, a new study could be undertaken that addresses the current uncertainties in the evidence base. Given that there are uncertainties concerning both the efficacy of cryotherapy and laser therapy compared with no treatment, and also uncertainty regarding the relative efficacy of the two principal, evaluated interventions, then a three-armed study comparing all of these options is to be recommended. A prospective RCT comparing the current treatment options would obviously offer the optimal study design for controlling for the effect of the principal confounding variables of age, comparable follow-up between groups, RD in the primary eye, and pathology and/or indications for treatment, as these factors should be present in comparable or equal numbers across groups.

However, as such a trial would be both costly and impractical, given the rarity of the condition and the likely number of centres involved, and also given that such strong opinions are held within the ophthalmology community on the prophylactic efficacy or otherwise of the two interventions,[21] some referring clinicians are unlikely to accept the randomisation of eligible patients under their care to a study arm, and either a treatment or no treatment that they

consider to be ineffective or around which there is too much uncertainty. Consequently, despite being inherently at a greater risk of bias than an RCT, a potential priority for research might be a prospective cohort comparison study, comparing three cohorts exposed to cryotherapy, laser therapy and no treatment with participants satisfying specific inclusion criteria on diagnosis, age and pathology. Relevant referring clinicians could then enter eligible patients into the study arm of their choice. Individuals exposed to bilateral or unilateral prophylaxis (i.e. having already experienced an RD in the primary eye) would be entered into the study and would be analysed separately, given the possible non-independence of eyes from the same person. These data could be used to supplement the ongoing report of data from the Ang *et al.*[33] retrospective study. The primary outcome is RD.

Participants would then be followed over time until a difference between treatments, or between treatment and no treatment, became apparent through interim analysis of available data (e.g. at 5, 10 and 15 years), when the study could be discontinued. Alternatively, the study could also be discontinued if no such difference was demonstrated through such interim analysis of available data. In both cases, an appropriate 'stopping rule' which was deemed clinically and statistically robust would need to be determined, i.e. what constitutes a clinically meaningful difference between groups and a sufficiently meaningful length of follow-up. The relative effect of the treatments or the non-treatment would be determined by a calculation of the RR using the dichotomised data of there being either an event (RD) or no event at a single point in time (e.g. 5, 10 and 15 years).

The resulting study may lack power, especially if it was discontinued early, as the sample size may be small. For the purpose of providing context only, the following power calculations are presented to give an idea of possible sample sizes, and their power, required by such a study. Using a sample size formula for binary data (i.e. the risk of having or not having an RD),[62] 98 participants (196 eyes) exposed to bilateral prophylaxis in each arm could detect a reduction in the relative risk of RD from 20% in one group to 10% in the other groups at 80% power and 5% ($\alpha = 0.05$) two-sided level of significance. Given the rarity of the condition, and potential problems with recruiting to the study, 80% power is preferred to 90% power, as the latter would require a larger number of participants in each arm to detect this difference in the reduction of the relative risk of RD between arms (i.e. 131 participants, 262 eyes). Clinical advice has suggested that this reduction in the relative risk of an RD would be clinically important: the figure of 20% being similar to the rates of RD in individuals up to 20 years of age reported in two surveys,[2,8] the age group most likely to present for prophylaxis. These figures are for bilateral prophylaxis only; for 80% power, unilateral prophylaxis would require 196 participants in each arm.

Given that a majority of the likely participants might be children or adolescents, there would be ethical issues surrounding consent and participation in any such study. Also, while it should be noted that the studies evaluating the interventions reported no major or long-term adverse events or complications, the frequency of minor complications is unknown and further studies would need to take into account the potential complications of both laser therapy and cryotherapy and include these in the patient information sheet and ethics application. Clinical advice also suggests that there is a need to identify reliable prevalence data on type 1 or type 2 Stickler syndrome, as this would provide a context for assessing the implications of the efficacy of any form of prophylaxis.

Acknowledgements

Dr Jennifer Evans, Lecturer and member of Cochrane Eyes and Vision Group (CEVG), London School of Hygiene and Tropical Medicine, London, UK.

Mr Alistair Laidlaw, Consultant Ophthalmologist, St Thomas' Hospital, London, UK.

Mr Richard Sheard, Consultant Ophthalmologist, Royal Hallamshire Hospital, Sheffield, UK.

Dr Martin Snead, Consultant Vitreoretinal Surgeon, Addenbrooke's Hospital, Cambridge, UK.

Gill Rooney provided administrative support in preparing and formatting the report.

Contributions of authors

Christopher Carroll acted as Principal Investigator for this assessment, he also designed, co-ordinated and wrote the review. Christopher Carroll and Angie Rees designed the searches, and Angie Rees undertook the searches. Christopher Carroll and Diana Papaioannou screened search results, assessed the quality of included papers, extracted data from papers and undertook analysis of and interpreted the data. Eva Kaltenthaler read and approved the review.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the nine departments in the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical and cost-effectiveness of health-care interventions for the National Institute of Health Research HTA programme on behalf of a range of policy-makers, including the National Institute of Health and Clinical Excellence. ScHARR-TAG is part of a wider collaboration of six units from other regions. The other units are the Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen HTA Group, University of Aberdeen; Liverpool Reviews & Implementation Group, University of Liverpool; Peninsular Technology Assessment Group, University of Exeter; NHS Centre for Reviews and Dissemination, University of York; and West Midlands Health Technology Assessment Collaboration, University of Birmingham.

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Appendix 1

Literature search strategies

Example Search Strategy: Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1950 to Present)

1. stickler.mp. (256)
2. progressive arthro-opthalmopathol*.tw. (0)
3. progressive arthroopthalmopath*.tw. (0)
4. or/1-3 (256)
5. exp cryotherapy/ (17,686)
6. exp Light Coagulation/ (9473)
7. exp laser coagulation/ (4980)
8. exp Scleral Buckling/ (2085)
9. cryotherap*.tw. (4115)
10. ((laser or light) adj2 (coagulat* or photocoagulat*)).tw. (4771)
11. (scleral* adj2 (buckl* or encircl*)).tw. (1437)
12. encircling band.tw. (110)
13. or/5-12 (34,143)
14. prophyla*.tw. (97,339)
15. prevent*.tw. (704,485)
16. ameliorat*.tw. (35,737)
17. or/14-16 (805,028)
18. 13 and 17 (2425)
19. 4 or 18 (2677)
20. exp RD/ (14,335)
21. exp retinal perforations/ (2955)
22. (retinal adj2 (detach* or tear* or break* or perforat*)).tw. (12,624)
23. or/20-22 (16,095)
24. 23 and 19 (427)

Appendix 2

Data abstraction tables

Characteristics of included studies

Reference Manager ID	Study reference Author, date, country	Study design	Diagnostic criteria	Inclusion criteria (including criteria for diagnosis)	Exclusion criteria (including number excluded)	Intervention group and population characteristics Number, age, gender, ethnicity, retinal status, comorbidities, etc.	Comparison group and population characteristics Number, age, gender, ethnicity, retinal status, comorbidities, etc.	Prophylactic intervention Description of technique and setting	Control/comparison (e.g. no treatment)

Study outcomes

Reference Manager ID	Study reference Author, date	Study duration/ follow-up	Measurement details How, by whom	Intervention group: No. enrolled No. included in analysis No. excluded, withdrew	Comparison group: No. enrolled No. included in analysis No. excluded, withdrew	Intervention group Primary outcome: No. eyes (patients) unilateral RD No. eyes (patients) bilateral RD Secondary outcomes: No with total vision loss No. with unilateral vision loss No with retinal tear/ lesions Time to RD or tear/ lesions	Comparison group Primary outcome: No. eyes (patients) unilateral RD No. eyes (patients) bilateral RD Secondary outcomes: No with total vision loss No. with unilateral vision loss No with retinal tear/ lesions Time to RD or tear/ lesions	Adverse effects Descriptions and frequency	Notes and new references

Appendix 3

Quality assessment

CRITICAL APPRAISAL SKILLS PROGRAMME

making sense of evidence
12 questions to help you make sense of a cohort study

General comments

Three broad issues need to be considered when appraising a cohort study:

- Are the results of the study valid?
- What are the results?
- Will the results help locally?

The 12 questions on the following pages are designed to help you think about these issues systematically.

The first two questions are screening questions and can be answered quickly. If the answer to those two is 'yes', it is worth proceeding with the remaining questions.

There is a fair degree of overlap between several of the questions.

You are asked to record a 'yes', 'no' or 'can't tell' to most of the questions.

A number of italicised hints are given after each question. These are designed to remind you why the question is important. There will not be time in the small groups to answer them all in detail!

A/ Are the results of the study valid?

Screening Questions

1 Did the study address a clearly focused issue? *HINT: A question can be focused in terms of:* *- the population studied* *- the risk factors studied* *- the outcomes considered* *- is it clear whether the study tried to detect a beneficial or harmful effect?*	**Yes** ☐	**Can't tell** ☐	**No** ☐
2 Did the authors use an appropriate method to answer their question? *HINT: Consider* *- Is a cohort study a good way of answering the question under the circumstances?* *-Did it address the study question?*	**Yes** ☐	**Can't tell** ☐	**No** ☐

Is it worth continuing?

Detailed Questions

3 Was the cohort recruited in an acceptable way? *HINT: We are looking for selection bias which might compromise the generalisability of the findings:* *- Was the cohort representative of a defined population?* *- Was there something special about the cohort?* *- Was everybody included who should have been included?*	**Yes** ☐	**Can't tell** ☐	**No** ☐

4. Was the exposure accurately measured to minimise bias? *HINT: We are looking for measurement or classification bias:* *- Did they use subjective or objective measurements?* *- Do the measures truly reflect what you want them to (have they been validated)?* *- Were all the subjects classified into exposure groups using the same procedure?*	**Yes** ☐	**Can't tell** ☐	**No** ☐
5. Was the outcome accurately measured to minimise bias? *HINT: We are looking for measurement or classification bias:* *- Did they use subjective or objective measurements?* *- Do the measures truly reflect what you want them to (have they been validated)?* *- Has a reliable system been established for detecting all the cases (for measuring disease occurrence)?* *- Were the measurement methods similar in the different groups?* *- Were the subjects and/or the outcome assessor blinded to exposure (does this matter)?*	**Yes** ☐	**Can't tell** ☐	**No** ☐
6. A. Have the authors identified all important confounding factors? List the ones you think might be important, that the authors missed. **B. Have they taken account of the confounding factors in the design and/or analysis?** *HINT:* *- Look for restriction in design, and techniques eg modelling, stratified-, regression-, or sensitivity analysis to correct, control or adjust for confounding factors*	**Yes** ☐ **Yes** ☐ **List:**	**Can't tell** ☐ **Can't tell** ☐	**No** ☐ **No** ☐

7. A. Was the follow up of subjects complete enough?	**Yes** ☐	**Can't tell** ☐	**No** ☐
B. Was the follow up of subjects long enough? *HINT:* *- The good or bad effects should have had long enough to reveal themselves* *-The persons that are lost to follow-up may have different outcomes than those available for assessment* *- In an open or dynamic cohort, was there anything special about the outcome of the people leaving, or the exposure of the people entering the cohort?*	**Yes** ☐	**Can't tell** ☐	**No** ☐

B/ What are the results?

8. What are the results of this study? *HINT:* *- What are the bottom line results?* *- Have they reported the rate or the proportion between the exposed/unexposed, the ratio/the rate difference?* *- How strong is the association between exposure and outcome (RR,)?* *- What is the absolute risk reduction* (ARR)?	**9. How precise are the results?** **How precise is the estimate of the risk?** *HINT:* *- Sise of the confidence intervals*

10. Do you believe the results? HINT: - Big effect is hard to ignore! - Can it be due to bias, chance or confounding? - Are the design and methods of this study sufficiently flawed to make the results unreliable? - Consider Bradford Hills criteria (eg time sequence, dose-response gradient, biological plausibility, consistency).	**Yes** ☐	**Can't tell** ☐	**No** ☐

Is it worth continuing?

C/ Will the results help me locally?

11. Can the results be applied to the local population? *HINT: Consider whether* *- The subjects covered in the study could be sufficiently different from your population to cause concern.* *- Your local setting is likely to differ much from that of the study* *- Can you quantify the local benefits and harms?*	**Yes** ☐	**Can't tell** ☐	**No** ☐
12. Do the results of this study fit with other available evidence?	**Yes** ☐	**Can't tell** ☐	**No** ☐

One observational study rarely provides sufficiently robust evidence to recommend changes to clinical practice or within health policy decision making. However, for certain questions observational studies provide the only evidence. Recommendations from observational studies are always stronger when supported by other evidence.

Appendix 4

List of studies excluded because they clearly failed to satisfy one or more of the designated population, intervention or outcome criteria

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6. Avitabile T, Longo A, Lentini G, Reibaldi A. Retinal detachment after silicone oil removal is prevented by 360 degrees laser treatment. *Br J Ophthalmol* 2008;**92**:1479–82.
7. Baron A, Michel G, Baron A, Michel G. Preventive cryotherapy of retinal detachment. *Bull Soc Ophtalmol Fr* 1972;**72**:635.
8. Belda J, Ruiz-Moreno J, Perez-Santonja J, Alio J. Scleral buckle and corneal ectasia after LASIK. *Ophthalmology* 2002;**109**:1950–1.
9. Bergamini F. Laser photocoagulation of the peripheral fundus lesions. *Ann Ottalmol Clin Ocul* 1995;**121**:717–19.
10. Binder S, Riss B. Prophylactic treatment of retinal detachment. *Klin Monbl Augenheilkd* 1981;**179**:78–80.
11. Bochkareva A, Ivanishko I. Use of photocoagulation for preventing and treating traumatic retinal detachments. *Vestn Oftalmol* 1981;**1**:17–19.
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21. Chabot J, Bouchet G. Use of the Essel laser photocoagulator in prevention of retinal detachment on localized alterations or holes. *Bull Soc Ophtalmol Fr* 1970;**70**:797–808.

22. Chang T. Prophylactic scleral buckle for prevention of retinal detachment following vitrectomy for macular hole. *Br J Ophthalmol* 1999;**83**:944–8.

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30. Goezinne F, La Heij EC, Berendschot TT, Gast ST, Liem AT, Lundqvist IL, *et al.* Low redetachment rate due to encircling scleral buckle in giant retinal tears treated with vitrectomy and silicone oil. *Retina* 2008;**28**:485–92.

31. Gross-Jendroska M, Owens S, Flaxel C, Guymer R, Bird A. Treatment to fellow eyes of unilateral retinal pigment epithelial tears with prophylactic laser. *Invest Ophthalmol Vis Sci* 1996;**37**(3).

32. Han DPL. Laser photocoagulation in the acute retinal necrosis syndrome. *Arch Ophthalmol* 1987;**105**:1051–4.

33. Haut J, Van Effeenterre G, Monin C, Fleury P. Analysis of 8 cases of retinal detachment occurring shortly after argon laser photocoagulation for prevention of retinal detachment. *Bull Soc Ophtalmol Fr* 1981;**81**:65–9.

34. Haut J, Allagui M, Lepvrier N, Morel C. Preventive surgical scleral buckling of retinal detachment after severe ocular injuries. *Journal Francais d'Opthalmologie* 1993;**16**:668–72.

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37. Hudson JR, Kanski JJ. Prevention of aphakic retinal detachment by circumferential cryotherapy. *Mod Probl Ophthalmol* 1977;**18**:530–7.

38. Hudson J. The prevention of retinal detachment. *Isr J Med Sci* 1972;**8**:1410–14.

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40. Izumi N, Sugimoto M, Matsubara H, Kuze M, Uji Y. Long-term outcome after photocoagulation for Coats disease in infants and children. *Rinsho Ganka* 2005;**59**:61–4.

41. Jin D-LD. Preventive photocoagulation treatment of retinal degeneration and tear before LASIK. *International Journal of Ophthalmology* 2009;**9**:1175–6.

42. John J. Significance of preventive photocoagulation. *Cesk Oftalmol* 1978;**34**:45–50.

43. Johnson D, Nieto J, Ip M. Retinal detachment due to an outer retinal tear following laser prophylaxis for retinoschisis. *Arch Ophthalmol* 2008;**126**:1775–6.

44. Kaluzny J. Complications following laser coagulation used in prevention and treatment of retinal detachment. *Klin Oczna* 1973;**43**:523–527.

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46. Kazahaya M. Prophylaxis of retinal detachment. *Semin Ophthalmol* 1995;**10**:79–86.

47. Kikuchi M, Iwaki M, Fukao R, Okinami S. Treatment of cytomegalovirus retinitis with ganciclovir and laser photocoagulation. *Nippon Ganka Kiyo* 1991;**42**:2350–6.

48. Kosmides P, Ladas I, Koulios P, Dadoush G, Nicolaidou S, Liarikos S, *et al.* Prophylactic laser photocoagulation following ganciclovir treatment of CMV retinitis. IXth International Conference on AIDS in affiliation with the IVth STD World Congress, 1993, Berlin.

49. Kovacevic D. Long-term results of argon laser retinal photocoagulation for retinal ruptures. *Acta Med Croatica* 2006;**60**:149–52.

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54. Morris R, Kuhn F, Witherspoon CD, Mester V. Prophylactic scleral buckle for prevention of retinal detachment following vitrectomy for macular hole. *Br J Ophthalmol* 2000;**84**:673.

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58. Rauber M, Mester U. Incidence and prophylaxis of retinal detachment following pars plana vitrectomy. *Ophthalmologe* 2006;**103**:673–6.

59. Robertson D, Norton E. Cause of failure in prophylactic treatment of retinal breaks. *Mod Probl Ophthalmol* 1974;**12**:74–80.

60. Robertson D. 360 degrees prophylactic cryoretinopexy. A clinical and experimental study. *Arch Ophthalmol* 1979;**97**:2130–4.

61. Sakaue E. A report of three cases with retinal detachment following prophylactic photocoagulation. *Nippon Ganka Kiyo* 1970;**21**:395–403.

62. Sanderson P. To push? Or not to push?: Second stage management in a patient with Stickler syndrome at risk of retinal detachment. *J Obstet Gynaecol* 2009;**29**:61–2.

63. Saracco J, Estachy G, Gastaud P, Maymard I. Prophylactic treatment of aphakic retinal detachment by argon laser photocoagulation. Study on 600 cases. *Ophthalmologica* 1980;**181**:142–8.

64. Schimkat M, Althaus C, Sundmacher R. Prophylactic argon-laser coagulation for rhegmatogenous retinal detachment in AIDS-patients with cytomegalovirus-retinitis. *Invest Ophthalmol Vis Sci* 1996;**37**:1711.

65. Schroeder W. Retinal detachment after prophylactic coagulation. *Ophthalmologe* 1996;**93**:144–8.

66. Stein R, Pinchas A, Treister G. Prevention of retinal detachment by a circumferential barrage prior to lens extraction in high-myopic eyes. *Ophthalmologica* 1972;**165**:125–36.

67. Sternberg J. Photocoagulation to prevent retinal detachment in acute retinal necrosis. *Ophthalmology* 1988;**95**:1389–93.

68. Vallat M, Detre J, Van Coppenolle F, Goudoud M. Limitations of argon laser photocoagulation in the preventive treatment of retinal detachment. *Bull Soc Ophtalmol Fr* 1986;**86**:1307–11.

69. Vallat M, Barthe J, Mathon C, Fritsch D, Van Coppenolle F, Detre J, *et al.* Prevention of retinal detachment. Whom to treat? *Ophtalmologie* 1989;**3**:297–8.

70. Yoshizumi M, Kreiger A, Sharp D. Massive peri-retinal proliferation following prophylactic treatment of retinal breaks. *Trans Ophthalmol Soc N Z* 1983;**35**:33–6.

Appendix 5

List of studies excluded on basis of lack of details on population alone

Studies evaluating primary prophylaxis interventions for RD, but with insufficient details on population to exclude categorically as including no Stickler syndrome patients.

*Indicates papers stating that a family history of RD was a characteristic of the population or an indication for treatment. The authors of these papers were contacted to ascertain if their sample included any Stickler or Wagner–Stickler syndrome patients.

1. Abujamra S. Prophylactic argon laser photocoagulation. *Rev Bras Oftalmol* 1984;**43**:204–10.
2. Avitabile T, Bonfiglio V, Reibaldi M, Torrisi B, Reibaldi A, Avitabile T, *et al.* Prophylactic treatment of the fellow eye of patients with retinal detachment: a retrospective study. *Graefes Arch Clin Exp Ophthalmol* 2004;**242**:191–6.
3. *Boen-Tan T. *Analysis of prophylactic laser coagulation of retinal defects and degenerations performed in patients of the Free University of Amsterdam during the period from* 1982 to July 1986. *Doc Ophthalmol* 1987;**67**:83–8.
4. Boguszakova J. Prophylactic use of the argon laser in the patients with imminent retinal detachments. *Cesk Oftalmol* 1984;**40**:272–5.
5. *Boniuk I, Okun E, Johnston GP, Arribas N, Boniuk I, Okun E, *et al.* Xenon photocoagulation vs. cryotherapy in the prevention of retinal detachment. *Mod Probl Ophthalmol* 1974;**12**:81–92.
6. *Chignell A, Shilling J. Prophylaxis of retinal detachment. *Br J Ophthalmol* 1973;**57**:291–8.
7. Constantinides G, Francois P, Madelain F. Prevention of retinal detachment. *Bull Soc Ophtalmol Fr* 1973;**73**:1213–16.
8. Eliseeva R, Makarskaia N, Malashenkova E, Moiseeva I, Nesterov S, *et al.* Importance of photocoagulation in the prevention of retinal detachment. *Vestn Oftalmol* 1978;**4**:52–7.
9. Folk J. Prophylactic treatment to the fellow eye of patients with phakic lattice retinal detachment: Analysis of failures and risks of treatment. *Retina* 1990;**10**:165–9.
10. Franchuk A, Linnik L, Pukhlik E, Ganichenko I, Rasskazova N. Degree of the risk of occurrence of bilateral retinal detachment and the role of laser coagulation in its prevention (late observations). *Oftalmol Zh* 1981;**36**:67–70.
11. *Freeman H. Fellow eyes of giant retinal breaks. *Trans Am Ophthalmol Soc* 1978;**76**:343–82.
12. Girard P. Long-term follow-up of the unaffected eye following retinal detachment: Study of 1,148 cases. *Journal Francais d'Ophtalmologie* 1982;**5**:681–5.
13. Glasspool M, Kanski J. Prophylaxis in giant tears. *Trans Ophthalmol Soc U K* 1973;**93**:363–71.
14. Haut J, Monin C, ner-Nedey S, Van Effenterre G. Prevention of bilateralization of idiopathic retinal detachment by treatment with argon laser. *Journal Francais d'Opthalmologie* 1987;**10**:717–22.

15. Haut J, Monin C, ner-Nedy S, Van Effenterre G, Lacotte J. Value of the preventive treatment of the 2d eye when the 1st has developed retinal detachment. *Bull Soc Ophtalmol Fr* 1987;**87**:1055–6.

16. Haut J. Prophylactic treatment of retinal detachment of the fellow eye. Results of 5 years follow-up of 109 eyes. *J Fr Ophtalmol* 1991;**14**:397–404.

17. Karel I. Argon laser photocoagulation in prevention of retinal detachment (author's transl). *Klin Oczna* 1981;**83**:213–15.

18. Karel I. Argon laser coagulation as prophylaxis of retinal detachment. *Cesk Oftalmol* 1980;**36**:1–6.

19. Kreissig I, Robert Y. Prevention, in the contralateral eye, of a giant tear ablation. *Klin Monbl Augenheilkd* 1983;**182**:121–4.

20. La T, Carelli F, Galassi F. Retinal detachment preventing treatment by argon-laser photocoagulation about retinal tears from one papillar diameter upwards statistical review 3 years. *Ann Ottalmol Clin Ocul* 1986;**112**:289–93.

21. Laatikainen L. The fellow eye in patients with unilateral RD: Findings and prophylactic treatment. *Acta Ophthalmol* 1985;**63**:546–51.

22. Labrune P, Theron HP, Massin M. Argon laser in the prevention of retinal detachment. *Arch Ophtalmol Rev Gen Ophtalmol* 1975;**35**:725–34.

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Appendix 6

Protocol

Can prophylactic surgery reduce the risk of RD and blindness in Stickler syndrome, especially in children?

HTA 09/23/01

13 August July 2009

Title of the project

The clinical effectiveness and safety of prophylactic retinal interventions to reduce the risk of RD and subsequent vision loss in adults and children with Stickler syndrome

Project lead

The University of Sheffield, School of Health and Related Research (ScHARR)

Dr Christopher Carroll, Research Fellow

ScHARR, University of Sheffield, Sheffield, UK

Plain English summary (all references omitted)

Stickler syndrome, also known as hereditary progressive arthro-ophthalmology, is an inherited progressive disorder of the collagen connective tissues. It is indicated by a variety of symptoms and can affect the formation of the eyes, ears, palate, jaw and joints. Signs and symptoms can include short-sightedness, retinal problems, cataracts, blindness, hearing loss, facial abnormalities, including cleft palate, and joint problems. Stickler syndrome is the most common identified, inherited cause of RD in childhood. The exact prevalence of Stickler syndrome is unknown owing to variability in symptoms and under-diagnosis, but has been reported to be approximately 1 in 10,000 in the USA. The actual prevalence of Stickler syndrome may therefore be higher. No figures on prevalence are available for the UK.

There are no agreed diagnostic criteria for Stickler syndrome, but two principal types of Stickler syndrome have been identified. In type 1 Stickler syndrome there appear to be defects in the vitreous phenotype and a mutation in the type II collagen (*COL2A1* gene), and, in type 2, defects in the vitreous phenotype but mutation in the type XI collagen (*COL11A1* gene). Type 1 is responsible for Stickler syndrome in about 75% of people diagnosed with the condition. Types 1 and 2 both indicate 'full' Stickler syndrome. 'Full' Stickler syndrome affects the eyes, joints and hearing; patients with type 1 have an increased incidence of cleft abnormalities, and those with type 2 an increased incidence of deafness. The genes responsible for a third type of Stickler syndrome, which also affects the eyes, joints, hearing and mid-line clefting of lip and palate, have yet to be identified. The rate of RD, potentially leading to loss of vision, in patients with Stickler syndrome has been suggested to be as high as 60%. Type 1 Stickler syndrome has been found to have a higher risk of RD than type 2. Whereas RD can occur at any age, it most commonly occurs in adolescence or early adulthood.

Prophylactic retinal interventions aim to reduce the risk of RD and thus the potential for loss of vision. Such interventions include cryotherapy (application of intense cold to create a scar that increases retinal adhesion), scleral buckling (use of a 360-degree silicone band around the eye ball) and laser photocoagulation (light energy from the laser is used to create a scar and thus increase retinal adhesion). There is some evidence that prophylactic interventions may prevent RD in the Stickler syndrome population, thus reducing the risk of blindness. However, these prophylactic interventions are not without the possibility of unwanted side effects or adverse events.

The aim of this review is to systematically evaluate and appraise the safety and clinical effectiveness of prophylactic retinal interventions in comparison with usual care (no treatment or routine care) for the primary prevention of RD in adults and children with Stickler syndrome.

Decision problem

4.1 Purpose of the decision to be made

The assessment will address the question 'Can prophylactic surgery reduce the risk of RD and blindness in Stickler syndrome, especially in children?'.

4.2 Clear definition of the intervention

Prophylactic retinal interventions aimed at preventing RD. This includes scleral buckling, cryotherapy and laser photocoagulation.

4.3 Place of the intervention in the treatment pathway(s)

This review will focus on the use of retinal interventions as primary prevention for RD. This will be before RD has occurred or if retinal attachment has occurred in one eye only and prophylactic treatment is administered to the non-affected eye.

4.4 Relevant comparators

No treatment/usual care.

4.5 Population and relevant sub-groups

The population for the assessment is children and adults with all types of Stickler syndrome, who have no history of RD or in one eye only.

4.6 Key factors to be addressed

1. Evaluate the clinical effectiveness of prophylactic retinal interventions for prevention of RD among children and adults with Stickler syndrome.
2. Evaluate the safety of prophylactic retinal interventions for prevention of RD.
3. Identify key areas for primary research.

5. Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, formally QUOROM (quality of reporting of meta-analyses). English and non-English language studies will be included (where translation is available), and there will be no limit by date (although Stickler syndrome was first described in 1965).

5.1 Population

5.1.1 Inclusion criteria

Children and adults diagnosed with Stickler syndrome (any type). There are no universally agreed diagnostic criteria for Stickler syndrome, but it is expected that study participants would demonstrate either the presence of a typical vitreous phenotype (type 1 or 2) and/or *COL2A1*/*COL11A1* mutation. Criteria of diagnosis will be recorded.

5.1.2 Exclusion criteria

Individuals with other syndromes leading to a predisposition to RD, e.g. Wagner–Stickler syndrome, Marfan syndrome.

5.2 Interventions

Any intervention aimed at primary prevention of RD. This includes:

1. cryotherapy
2. laser photocoagulation
3. scleral buckling.

5.3 Comparators

No treatment/usual care (there is no defined usual care for this population).

5.4 Settings

Secondary care.

5.5 Outcomes

5.5.1 Primary outcome

1. Number of RDs (RD) post prophylactic intervention: unilateral or bilateral.

5.5.2 Secondary outcomes

1. Adverse events relating to the intervention.
2. Blindness (by self-assessment, or being registered or legally blind).
3. Time to RD.
4. Number of lesions or retinal tears (a pre-cursor for RD).

5.6 Search strategy

The search strategy will comprise the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

5.6.1 Electronic searches

A comprehensive search will be undertaken to identify systematically both clinical effectiveness and adverse events literature pertaining to prophylactic retinal interventions to prevent RD. Search strategies will be used to identify relevant studies (as specified under the inclusion criteria, above) and systematic reviews/meta-analyses (for identification of additional studies). Searches will not be restricted by language or publication date. An example of the MEDLINE search strategy is shown in *Appendix 10.1* (on pp. 57). The aim of the strategy is to identify all studies that report on interventions to prevent RD in either populations reported specifically to comprise participants with Stickler syndrome or populations that may include participants with Stickler syndrome. Only data relating to participants with Stickler syndrome will be extracted

and analysed. Authors of studies that do not specify whether or not participants have Stickler syndrome will be contacted, and, if these data are available, they will be included in the analysis.

5.6.2 Databases

The following electronic databases will be searched from inception:

- MEDLINE (Ovid)
- MEDLINE in process (Ovid);
- EMBASE;
- The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, DARE, NHS EED and HTA databases;
- Science Citation Index (via ISI Web of Science)
- UKCRN and the National Research Register archive
- Current Controlled Trials
- Clinical Trials.gov.

In addition, relevant conference proceedings will be searched, for example: The proceedings of the Annual Meeting of the Association for Research in Vision and Ophthalmology.

5.7 Inclusion criteria

The inclusion criteria are as reported in 5.1–5.5 above. For the review of clinical effectiveness and safety, it is unlikely that RCTs will exist in this area. In the absence of RCT evidence, other study designs will be included. These include prospective and retrospective studies such as cohort studies and case–control studies, and case studies/series.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus, or with reference to a third reviewer when necessary.

5.8 Exclusion criteria

Reviews of primary studies will not be included in the analysis, but will be retained for discussion and identification of additional trials. The following publication types will be excluded from the review: animal models, preclinical and biological studies, narrative reviews, editorials, opinions and those in which insufficient methodological details are reported to allow critical appraisal of study quality. The authors of studies of mixed populations (i.e. individuals with Stickler syndrome combined with non-Stickler syndrome individuals), or unspecified populations undergoing prophylactic intervention for RD, but that do not present separate event data for individuals with Stickler syndrome, will be contacted to ascertain if there are any such data on patients in their sample. If these data are not available, then the study will be excluded and listed under 'excluded studies'. If these data are available, they will be included in the analysis.

5.9 Data extraction strategy

Data will be extracted independently from all studies by two reviewers using a standardised data extraction form (see *Appendix 2*). Discrepancies will be resolved by discussion, with reference to a third reviewer if necessary.

5.10 Quality assessment strategy

Owing to the likelihood of inclusion of non-RCT evidence, study quality assessment will be tailored according to the study's design. This will be undertaken by using an appropriate study design checklist for each study design. Likely study designs include cohort studies, case–control studies and case series or case studies. An example of the latter is included in *Appendix 3*.

Consideration of study quality will include the following study characteristics:

- appropriateness of study design
- recruitment and selection (including inclusion and exclusion criteria)
- comparability of groups
- numbers followed up
- is the length of follow-up appropriate?
- is the outcome measure appropriate and valid?
- consideration of confounding variables
- appropriateness of form of analysis
- validity of results.

Critical appraisal will be performed by two reviewers independently. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.11 Methods of analysis/synthesis

Data will be tabulated and, if appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses. However, it is anticipated that heterogeneity of study designs and interventions, and the type of data available, may mean that it is not appropriate to perform meta-analysis. The likely form of analysis will be narrative synthesis.

All preliminary analyses will be performed based on the intervention and primary outcome, with populations combined (regardless of age group or type of Stickler syndrome). If possible, subgroup analysis will also be performed on these data, according to age group (child or adult) and type of Stickler syndrome, to explore whether different treatment effects or adverse events are apparent in different groups. Where possible, analysis will be performed on secondary outcomes also, such as number of retinal tears.

5.12 Methods for estimating qualify of life

Quality of life will not be assessed in this report.

6. Report methods for synthesising evidence of cost-effectiveness

A review of cost effectiveness literature is not commissioned and therefore will not be undertaken for this review.

7. Expertise in this TAR team

TAR Centre

The ScHARR Technology Assessment Group (ScHARR-TAG) undertakes reviews of the effectiveness and cost-effectiveness of health-care interventions for the NHS R&D HTA programme on behalf of a range of policy-makers in a short timescale, including the National Institute for Health and Clinical Excellence. A list of our publications can be found at www.sheffield.ac.uk/scharr/sections/heds/collaborations/scharr-tag/reports.

Much of this work, together with our reviews for the international Cochrane Collaboration, underpins excellence in health care worldwide.

Team members' contributions

Christopher Carroll, Research Fellow, ScHARR, has extensive experience in systematic reviews of health technologies. CC will lead the project and undertake the systematic reviewing. He will co-ordinate the review process, protocol development, abstract assessment for eligibility, quality assessment of trials, data extraction, data entry, data analysis and review development of background information and clinical effectiveness.

Diana Papaioannou, Research Associate, ScHARR, has experience in systematic reviews of health technologies. DP will assist CC with the project and undertake the systematic reviewing. She will be involved in protocol development, abstract assessment for eligibility, quality assessment of trials, data extraction, data entry, data analysis and review development of background information and clinical effectiveness.

Angie Rees, Systematic Reviews Information Officer, ScHARR, has extensive experience of undertaking literature searches for the ScHARR Technology Assessment Group systematic reviews and other external projects. AR will be involved in the protocol development and she will develop the search strategy and undertake the electronic literature searches.

Gill Rooney, Project Administrator, will assist in the retrieval of papers and in preparing and formatting the report.

Clinical and expert advisors

Dr Jennifer Evans, Lecturer and member of Cochrane Eyes and Vision Group (CEVG), London School of Hygiene and Tropical Medicine, London, UK.

Mr Alistair Laidlaw, Consultant Ophthalmologist, St Thomas' Hospital, London, UK.

Mr Richard Sheard, Consultant Ophthalmologist, Royal Hallamshire Hospital, Sheffield, UK.

Dr Martin Snead, Consultant Vitreoretinal Surgeon, Addenbrooke's Hospital, Cambridge, UK.

8. Competing interests of authors

The authors do not have any competing interests.

Clinical advisors:

- Jennifer Evans: none
- Alistair Laidlaw: none
- Richard Sheard: none.

Martin Snead is the lead applicant of a bid to the National Commissioning Group to provide multi-disciplinary team service for patients and families with Stickler syndrome.

9. Timetable/milestones

The project is expected to run from 4 August 2009 to 31 March 2010.

Milestone	
Draft protocol	4 August 2009
Final protocol	14 August 2009
Start review	7 September 2009
Progress report	3 March 2010
Assessment report	31 March 2010

10. Protocol appendices

10.1 Appendix 1: Draft MEDLINE search strategy

Database: Ovid MEDLINE(R) <1950 to July Week 2 2009> Search strategy

1. stickler.mp. (248)
2. progressive arthro-opthalmopathol*.tw. (0)
3. progressive arthroopthalmopath*.tw. (0)
4. or/1-3 (248)
5. exp Cryotherapy/ (17,290)
6. exp Laser Coagulation/ (4910)
7. exp Light Coagulation/ (9394)
8. exp Scleral Buckling/ (2075)
9. cryotherap*.tw. (3926)
10. ((laser or light) adj2 (coagulat* or photocaogulat*)).tw. (1369)
11. (scleral adj2 (buckl* or encircl*)).tw. (1411)
12. encircling band.tw. (108)
13. or/5-12 (32,125)
14. prophyla*.tw. (92,101)
15. prevent*.tw. (658,496)
16. prevent*.tw. (658,496)
17. ameliorat*.tw. (32,765)
18. or/15-17 (685,228)
19. 13 and 18 (1941)
20. 4 or 19 (2187)
21. exp RD/ (14,246)
22. exp Retinal Perforations/ (2927)
23. (retinal adj2 (detach* or tear* or break* or perforat*)).tw. (12,260)
24. or/21-23 (19,348)
25. 20 and 24 (352)

Appendix 7

Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable, background; objectives; data sources; study eligibility criteria, participants and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2–7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known	8–10
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	12
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g. web address), and, if available, provide registration information including registration number	*Appendix 6*
Eligibility criteria	6	Specify study characteristics (e.g. PICOS, length of follow-up) and report characteristics (e.g. years considered, language, publication status) used as criteria for eligibility, giving rationale	14–16
Information sources	7	Describe all information sources (e.g. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	13–14
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	*Appendix 1*
Study selection	9	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	13–14
Data collection process	10	Describe method of data extraction from reports (e.g. piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	14
Data items	11	List and define all variables for which data were sought (e.g. PICOS, funding sources) and any assumptions and simplifications made	*Appendix 2*
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	15–16
Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means)	16
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis	16
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g. publication bias, selective reporting within studies)	16
Additional analyses	16	Describe methods of additional analyses (e.g. sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	16

Section/topic	#	Checklist item	Reported on page #
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	16–18
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g. study size, PICOS, follow-up period) and provide the citations	17,19,23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	19–21
Results of individual studies	20	For all outcomes considered (benefits or harms) present for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	21–22,24–28
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	21–22
Additional analysis	23	Give results of additional analyses, if done]e.g. sensitivity or subgroup analyses, meta-regression (see Item 16)]	22
DISCUSSION			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g. health-care providers, users and policy-makers)	29–35
Limitations	25	Discuss limitations at study and outcome level (e.g. risk of bias) and at review-level (e.g. incomplete retrieval of identified research, reporting bias)	30–38
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	30–41
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g. supply of data); role of funders for the systematic review	1–2

N/A, not applicable.
Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7):e1000097.
For more information visit www.prisma-statement.org

Appendix 8

Relative estimates of effect based on the published event data

The relative risk or RR measure of relative effect was not reported in any of the published papers, so has been generated for both fixed- and random-effects models by the authors of this report using REVMAN version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The primary outcome was the binary variable of RD or no RD at a single point in time (the one follow-up). The RR is the standard measure of effect used in HTA reports and is used in preference to the odds ratio because, for interventions such as prophylaxis that aim to reduce the chances of events, the odds ratio may be smaller than the RR and this may lead to an overestimation of the effect of the intervention. To calculate the RR, the risk of an event in the intervention group (i.e. the number of RDs in the intervention group, divided by the number of eyes in that group) is divided by the risk of the event in the control group (i.e. the number of RDs in the control group, divided by the number of eyes in that group). These calculations were performed on the data from the principal studies only. Separate analyses were conducted for participants who were exposed to bilateral prophylaxis (prophylaxis in both eyes of an individual) and unilateral prophylaxis (prophylaxis in only one eye of an individual who had already experienced an RD in the primary eye) and, where possible, for both sets of study participants combined. These relative risks were calculated using the event data provided in each of the published papers, but for which only chi-squared analyses or an equivalent had been performed to test for differences between groups (see *Chapter 3, Assessment of effectiveness*).

Based on the event data reported in the two studies, there was a statistically significant reduction in the risk of RD for those exposed to cryotherapy for bilateral prophylaxis compared with the controls (RR 0.05, 95% CI 0.02 to 0.14, $p < 0.0001$), as well as for unilateral prophylaxis (RR 0.16, 95% CI 0.05 to 0.47, $p = 0.0009$). There was also a reduction in the risk of RD for those exposed to laser treatment for bilateral prophylaxis compared with the controls (RR 0.28, 95% CI 0.04 to 1.84, $p = 0.19$), as well as for those exposed to unilateral prophylaxis (RR 0.13, 95% CI 0.01 to 1.90, $p = 0.45$), but neither was statistically significant (see table below), possibly because, given the small sample and small number of events in the intervention group (1/10), the study was underpowered or the effect was due to chance. The validity and reliability of these relative estimates of effect, generated using the event data reported for the intervention and control groups of these studies, must be considered in light of the high risk of bias within both studies, especially affecting the comparability between groups.

Relative risks

Study	Intervention vs control	RD post bilateral and unilateral prophylaxis *n*/*N* (eyes)	RD post bilateral prophylaxis	RD post unilateral prophylaxis
Ang *et al.* 2008[33] UK	360° cryotherapy (*N*=155) vs no prophylaxis (*N*=222)	7/155 vs 134/222 RR 0.07 (95% CI 0.04 to 0.16), $p<0.0001$	4/124 vs 134/222 RR 0.05 (95% CI 0.02 to 0.14), $p<0.0001$	3/31 vs 134/222 RR 0.16 (95% CI 0.05 to 0.47), $p=0.0009$
Leiba *et al.* 1996[34] Israel	Circumferential and focal laser treatment vs no prophylaxis	1/10 vs 15/34 RR 0.23 (0.03 to 1.51), $p=0.13$	1/8 vs 15/34 RR 0.28 (0.04 to 1.84), $p=0.19$	0/2 vs 15/34 RR 0.13 (0.01 to 1.90), $p=0.45$

RR, relative risk.
These RRs have been calculated by the reviewers using both random- and fixed-effects models. The RRs calculated were the same for both models.

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Consultant Senior Lecturer in Microbiology, Department of Pathology & Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mrs Una Rennard,
Public contributor

Dr Stuart Smellie,
Consultant in Clinical Pathology, Bishop Auckland General Hospital

Ms Jane Smith,
Consultant Ultrasound Practitioner, Leeds Teaching Hospital NHS Trust, Leeds

Dr Allison Streetly,
Programme Director, NHS Sickle Cell and Thalassaemia Screening Programme, King's College School of Medicine

Dr Alan J Williams,
Consultant Physician, General and Respiratory Medicine, The Royal Bournemouth Hospital

Observers

Dr Tim Elliott,
Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody,
Programme Manager, Medical Research Council

Professor Julietta Patrick,
Director, NHS Cancer Screening Programme, Sheffield

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy Research Programme, Department of Health

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Professor of Epidemiology, University of Warwick Medical School, Coventry

Dr Robert Cook,
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Senior Research Fellow, Peninsula Medical School (Primary Care)

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Public contributor

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Professor of Primary Care Medicine, Bute Medical School, University of St Andrews

Dr Russell Jago,
Senior Lecturer in Exercise, Nutrition and Health, Centre for Sport, Exercise and Health, University of Bristol

Dr Julie Mytton,
Consultant in Child Public Health, NHS Bristol

Professor Irwin Nazareth,
Professor of Primary Care and Director, Department of Primary Care and Population Sciences, University College London

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Assistant Director of Public Health, Derbyshire Country Primary Care Trust

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Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Dr Kenneth Robertson,
Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow

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Associate Director, Centre for Public Health Excellence, NICE

Professor Carol Tannahill,
Glasgow Centre for Population Health

Mrs Jean Thurston,
Public contributor

Professor David Weller,
Head, School of Clinical Science and Community Health, University of Edinburgh

Observers

Ms Christine McGuire,
Research & Development, Department of Health

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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Mr Jim Reece,
Public contributor

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Dr Pippa Tyrrell,
Senior Lecturer/Consultant, Salford Royal Foundation Hospitals' Trust and University of Manchester

Dr Sarah Tyson,
Senior Research Fellow & Associate Head of School, University of Salford

Dr Nefyn Williams,
Clinical Senior Lecturer, Cardiff University

Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy Research Programme, Department of Health

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Public contributor

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Public contributor

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Public contributor

Mr Seumas Eckford,
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Consultant Senior Lecturer, University of Bristol

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Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy Research Programme, Department of Health

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Public contributor

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Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre,
Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Dr James Gray,
Consultant Microbiologist, Department of Microbiology, Birmingham Children's Hospital NHS Foundation Trust

Ms Kylie Gyertson,
Oncology and Haematology Clinical Trials Manager, Guy's and St Thomas' NHS Foundation Trust London

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Dr Andrew Prentice,
Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

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Public contributor

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General Practitioner, Silver Lane Surgery, Leeds

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Public contributor

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General Practitioner, Senior Research Fellow, Pharmacy Practice and Medicines Management Group, Leeds University

Observers

Dr Kay Pattison,
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Mr Simon Reeve,
Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

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Programme Manager, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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Consultant Psychiatrist, Leicestershire Partnership NHS Trust

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Dr Karim Saad,
Consultant in Old Age Psychiatry, Coventry and Warwickshire Partnership Trust

Dr Lesley Stockton,
Lecturer, School of Health Sciences, University of Liverpool

Dr Simon Wright,
GP Partner, Walkden Medical Centre, Manchester

Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy Research Programme, Department of Health

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Life and Health, University of
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Consultant in Public Health, South
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Director, Molecular Medicine
Unit, St James's University
Hospital, Leeds

Dr Peter Moore,
Freelance Science Writer, Ashtead

Dr Andrew Mortimore,
Public Health Director,
Southampton City Primary Care
Trust

Dr Sue Moss,
Associate Director, Cancer
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Institute of Cancer Research,
Sutton

Professor Miranda Mugford,
Professor of Health Economics
and Group Co-ordinator,
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Professor Jim Neilson,
Head of School of Reproductive
& Developmental Medicine
and Professor of Obstetrics
and Gynaecology, University of
Liverpool

Mrs Julietta Patnick,
Director, NHS Cancer Screening
Programmes, Sheffield

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Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe, Stoke
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Professor William Rosenberg,
Professor of Hepatology and
Consultant Physician, University
of Southampton

Professor Peter Sandercock,
Professor of Medical Neurology,
Department of Clinical
Neurosciences, University of
Edinburgh

Dr Philip Shackley,
Senior Lecturer in Health
Economics, Sheffield Vascular
Institute, University of Sheffield

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St
James's University Hospital, Leeds

Dr Margaret Somerville,
Director of Public Health
Learning, Peninsula Medical
School, University of Plymouth

Professor Sarah Stewart-Brown,
Professor of Public Health,
Division of Health in the
Community, University of
Warwick, Coventry

Dr Nick Summerton,
GP Appraiser and Codirector,
Research Network, Yorkshire
Clinical Consultant, Primary Care
and Public Health, University of
Oxford

Professor Ala Szczepura,
Professor of Health Service
Research, Centre for Health
Services Studies, University of
Warwick, Coventry

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Medical Director, Medical
Department, Association of the
British Pharmaceutical Industry

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Consumer Member, Southern
Derbyshire Community Health
Council

Professor Martin Whittle,
Clinical Co-director, National
Co-ordinating Centre for Women's
and Children's Health, Lymington

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278