NETSCC, HTA

16th October 2009

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

HTA 09/23/01

Protocol

13 August July 2009

1. Title of the project:

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

2. Project lead

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

Dr Christopher Carroll, Research Fellow
ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA
Tel: 0114 22 20864
Email: c.carroll@sheffield.ac.uk

3. Plain English Summary

Stickler syndrome, also known as hereditary progressive arthro-ophthalmology, is an inherited progressive disorder of the collagen connective tissues (1;2). It is indicated by a variety of symptoms and can affect the formation of the eyes, ears, palate, jaw and joints (1-4). Signs and symptoms can include short-sightedness, retinal problems, cataracts, blindness, hearing loss, facial abnormalities including cleft palate and joint problems (1-4). Stickler syndrome is the most common identified, inherited cause of retinal detachment in childhood (1). The exact prevalence of Stickler syndrome is unknown due to variability in symptoms and under-diagnosis (2;4;5), but has been reported to be approximately 1 in 10,000 in the United States (4;6). 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 (1), 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) (7;8), and, in type 2, defects in the vitreous phenotype but mutation in the type XI collagen (COL11A1 gene) (9-11). 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 (6). '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 (6). 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 (6). The rate of retinal detachment, potentially leading to loss of vision, in patients with Stickler syndrome has been suggested to be as high as 60% (2). Type 1 Stickler syndrome has been found to have a higher risk of retinal detachment than type 2 (9;12;13). Whilst retinal detachment can occur at any age, it most commonly occurs in adolescence or early adulthood (2;4).

Prophylactic retinal interventions aim to reduce the risk of retinal detachment 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) (14;15). There is some evidence that prophylactic interventions may prevent retinal detachment in the Stickler syndrome population, thus reducing the risk of blindness (12). However, these prophylactic interventions are not without the possibility of unwanted side effects or adverse events (14).

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

4. Decision problem

4.1 Purpose of the decision to be made

The assessment will address the question "Can prophylactic surgery reduce the risk of retinal detachment and blindness in Stickler syndrome, especially in children?"

4.2 Clear definition of the intervention

Prophylactic retinal interventions aimed at preventing retinal detachment. 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 retinal detachment. This will be before retinal detachment 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 retinal detachment or in one eye only.

4.6 Key factors to be addressed

1. Evaluate the clinical effectiveness of prophylactic retinal interventions for prevention of retinal detachment amongst children and adults with Stickler syndrome.

2. Evaluate the safety of prophylactic retinal interventions for prevention of retinal detachment.

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 statement, formally QUOROM (16;17). 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 (18)).

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 retinal detachment, eg. Wagner-Stickler syndrome, Marfan syndrome

5.2 Interventions

Any intervention aimed at primary prevention of retinal detachment. 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 retinal detachments (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 retinal detachment
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 retinal detachment. 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**. The aim of the strategy is to identify all studies that report on interventions to prevent retinal detachment either in populations reported specifically to be comprised of 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)
- UK Clinical Trials Research Network (UKCRN) and the National Research Register archive (NRR)
- 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 randomised controlled trials will exist in this area. In the absence of randomised controlled trial 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 where 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 retinal detachment, but that do no 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 10.2**). Discrepancies will be resolved by discussion, and with reference to a third reviewer if necessary.

5.10 Quality assessment strategy

Due 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 (19), case/control studies (20) and case series or case studies (21). An example of the latter is included in **Appendix 10.3**.

Consideration of study quality will include the following study characteristics:

1. *Appropriateness of study design*
2. *Recruitment and selection (including inclusion and exclusion criteria)*
3. *Comparability of groups*
4. *Numbers followed- up*

5. *Is the length of follow-up appropriate*
6. *Is the outcome measure appropriate and valid*
7. *Consideration of confounding variables*
8. *Appropriateness of form of analysis*
9. *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, sub-group 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 healthcare interventions for the NHS R&D Health Technology Assessment 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: http://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 healthcare 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, 8 Bedford Square, London WC1E 7HT, UK

Mr Alistair Laidlaw, Consultant Ophthalmologist, St Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH

Mr Richard Sheard, Consultant Ophthalmologist, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF

Dr Martin Snead, Consultant Vitreoretinal Surgeon, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, 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 (NCG) to provide MDT 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. 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/ (17290)

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 (32125)

14 prophyla*.tw. (92101)

15 prevent*.tw. (658496)

16 prevent*.tw. (658496)

17 ameliorat*.tw. (32765)

18 or/15-17 (685228)

19 13 and 18 (1941)

20 4 or 19 (2187)

21 exp Retinal Detachment/ (14246)

22 exp Retinal Perforations/ (2927)

23 (retinal adj2 (detach* or tear* or break* or perforat*)).tw. (12260)

24 or/21-23 (19348)

25 20 and 24 (352)

Appendix 2: Data extraction forms

Table: Characteristics of included studies

Ref Man ID	**Study ref** Author, date, country	**Study design**	**Inclusion criteria** (incl. criteria for diagnosis)	**Exclusion criteria** (incl. number excluded)	**Intervention group and population characteristics** Number, age, gender, ethnicity, retinal status, co-morbidities, etc.	**Comparison group and population characteristics** Number, age, gender, ethnicity, retinal status, co-morbidities, etc.	**Prophylactic intervention** Description of technique and setting	**Control / comparison** (eg. no treatment)

Table: Study outcomes

Ref Man ID	**Study ref** 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. patients unilateral RD No. Patients bilateral RD **Secondary outcomes:** No patients with total vision loss No. patients with unilateral vision loss No patients with retinal tear/lesions Time to RD or tear / lesions	**Comparison group:** **Primary outcome**: No. patients unilateral RD No. Patients bilateral RD **Secondary outcomes:** No patients with total vision loss No. patients with unilateral vision loss No patients with retinal tear/lesions Time to RD or tear / lesions	**Adverse effects** Descriptions and frequency	**Notes**

Appendix 3

Critical Appraisal Guidelines for Single Case Studies (Atkins & Sampson, 2002)

Element Evaluation criteria
Way of thinking 1. Is a credible argument given for why a case study is appropriate?
2. Are the philosophical stance and perspective of the authors stated?
3. Is there evidence that any bias is taken into account when performing data analysis?
Way of controlling
4. Have the criteria for analysis been confirmed by an independent researcher?
5. Have any opportunities for various forms of triangulation been exploited?
6. Is the research process auditable?
7. Has relevant literature been used to support the selection of an appropriate theoretical framework to guide the research?
8. Does the study use appropriate theory to support the findings.
9. Does the study describe how the conclusions were arrived at and how they are justified by the
results?
10. Are assertions / conclusions made well grounded in the data?
Way of working 11. Are the criteria used to select the appropriate case and participants clearly described?
12. Does the study provide a clearly formulated question describing an important IS issue?
13. Are the approaches and techniques for data collection and analysis described in detail?
14. Is the conceptual framework for the research explicitly described?
Way of supporting
15. Does the study describe an orderly process for the collection of data?
16. Does the study describe and employ a systematic way to analyse the data?
17. Is the history and context of the research clearly described?
Way of communicating
18. Are the aims and objectives of the study clearly stated?
19. Are limitations to the study acknowledged and described?
20. Does the study suggest if and how the findings might be transferable to other settings?
21. Is sufficient detail given to allow readers to evaluate the potential transferability of the research
to other contexts?
22. Does the report identify questions or issues for future research?
23. Is the presentation of the research appropriate to the intended audience?
24. *Could this research potentially make a contribution to the work of IS practitioners?
25. *Does the research provide new insights into some aspect of IS work?
26. *Is the research presented in such a way that there is evidence of logical rigour throughout the
study?
27. *Does the study place the findings in the context of IS practice?
28. *Does the study place the findings in the context of IS research?
29. *Is the research process open to scrutiny?

Reference List

(1) Snead MP, Yates JR, Snead MP, Yates JR. Clinical and Molecular genetics of Stickler syndrome. [Review] [59 refs]. Journal of Medical Genetics 1999 May;36(5):353-9.

(2) Stickler GB, Hughes W, Houchin P. Clinical features of hereditary progressive arthro-ophthalmopathy (Stickler syndrome): a survey. Genetics in Medicine 2001;3(3):192-6.

(3) Popkin JS, Polomeno RC. Stickler's syndrome (hereditary progressive arthro-opthalmopathy). Candian Medical Association Journal 1974;111:1071-6.

(4) Nowak CB, Nowak CB. Genetics and hearing loss: a review of Stickler syndrome. [Review] [60 refs]. Journal of Communication Disorders 1998 Sep;31(5):437-53.

(5) Lansford M, Lansford M. Focus on the physical assessment of the infant with Stickler syndrome. [Review] [23 refs]. Advances in Neonatal Care 2008 Dec;8(6):308-14.

(6) Hughes W. Stickler Syndrome: What is it? And how can we help? An introduction to the condition and the support group (for patients, carers and families). 2006. Report No.: Stickler Syndrome Support Group (SSSG).

(7) Snead MP, Payne SJ, Barton DE, Yates JR, al-Imara L, Pope FM, et al. Stickler syndrome: correlation between vitreoretinal phenotypes and linkage to COL 2A1. Eye 1994;8(Pt 6):609-14.

(8) Snead MP, Yates JR, Pope FM, Temple IK, Scott JD, Snead MP, et al. Masked confirmation of linkage between type 1 congenital vitreous anomaly and COL 2A1 in Stickler syndrome. Graefes Archive for Clinical & Experimental Ophthalmology 1996 Nov;234(11):720-1.

(9) Annunen S et al. Splicing mutations of 54-bp exons in the COL11A1 gene cause Marshall syndrome, but other mutations cause overlapping Marshall/Stickler phenotypes. Am J Hum Genet 1999;65:974-83.

(10) Martin S.Richards. Stickler syndrome: Further mutations in COL11A1 and evidence for additional locus heterogeneity. European Journal of Human Genetics 1999;7(7):807-14.

(11) Richards AJ, Yates JR, Williams R, Payne SJ, Pope FM, Scott JD, et al. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in alpha 1 (XI) collagen. Human Molecular Genetics 1996 Sep;5(9):1339-43.

(12) Ang A, Poulson AV, Goodburn SF, Richards AJ, Scott JD, Snead MP. Retinal Detachment and Prophylaxis in Type 1 Stickler Syndrome. Ophthalmology 2008;115(1):164-8.

(13) Poulson AV, Hooymans JM, Richards AJ, Bearcroft P, Murthy R, Baguley DM, et al. Clinical features of type 2 Stickler syndrome. Journal of Medical Genetics 2004 Aug;41(8):e107.

(14) Ang GS, Townend J, Lois N. Interventions for prevention of giant retinal tear in the fellow eye. Cochrane Database of Systematic Reviews 2009;Issue 2.

(15) Hudson JR, Kanski JJ, Elkington AR. Prophylactic encirclement. British Journal of Ophthalmology 1973;57:531-6.

(16) Moher D., Liberati A., Tetzlaff J., Altman D., PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009;151(4):1-16.

(17) CONSORT. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement flow diagram. http://www consort-statement org/index aspx?o=1346 2007Available from: URL: http://www.consort-statement.org/index.aspx?o=1346

(18) Stickler GB, Belau PG, Farrell FJ, Jones JD, Pugh DG, Steinberg AG, et al. Hereditary progressive arthro-ophthalmopathy. Mayo clinic proceedings 1965;40(6):433-55.

(19) Critical Appraisal Skills Programme. 12 questions to help you make sense of a cohort study. CASP; 2004.

(20) Critical Appraisal Skills Programme. 11 questions to help you make sense of a case control study. England: Public Health Resource Unit; 2006.

(21) Atkins C, Sampson J. Critical Appraisal Guidelines for Single Case Study Research. Proceedings of ECIS 2002. The Xth European Conference on Information Systems, Gdansk, 6-8 June. 2002.