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Surgical interventions for degenerative lamellar macular holes (Protocol)

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[Intervention Protocol]

Surgical interventions for degenerative lamellar macular holes

Declan C Murphy[1], Jon Rees[2], David HW Steel[3]

[1]Institute of Genetic Medicine, Newcastle University, Newcastle, UK. [2]School of Psychology, University of Sunderland, Sunderland, UK. [3]Sunderland Eye Infirmary, Sunderland, UK

Contact address: Declan C Murphy, murphy.declan.1994@gmail.com.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effect of surgical interventions on postoperative visual and anatomical outcomes in people with a confirmed degenerative lamellar macular hole.

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BACKGROUND

Description of the condition

Lamellar macular holes (LMH) are small, partial-thickness defects of the macula, which affect 1.1% to 3.6% of the population, with a preponderance towards people aged 50 to 70 years of age (Frisina 2019a).

Although LMHs can occur secondary to a variety of ophthalmic disease processes, there are two forms of idiopathic LMHs that have been recently distinguished based on their appearance, associations, clinical course, and response to surgery: tractional lamellar macular holes (TLMH) and degenerative lamellar macular holes (DLMH; (Govetto 2016; Haritoglou 2019; Hubschman 2020)).

TLMHs are partial-thickness defects of the macula that are associated with a classical type of contractile hyper-reflective epiretinal membrane. They are often found with an intact ellipsoid layer, and typical foveoschisis at the level of the Henle fibre layer, which is sometimes associated with microcystoid spaces in the inner nuclear layer and parafoveal retinal thickening, which can all be visualised using ocular coherence tomography (OCT; (Figueroa 2019; Govetto 2016; Ko 2017; Pang 2015)). People affected by TLMHs tend to retain stable vision, without requiring intervention (Figueroa 2019; Govetto 2016; Haritoglou 2019; Ko 2017; Pang 2015); however, when managed with pars plana vitrectomy, and epiretinal membrane and internal limiting membrane peeling, vision can improve significantly (Figueroa 2019).

In contrast, DLMHs are a newly defined, but long recognised type of partial-thickness retinal defect with characteristic OCT features, which include irregular central foveal thinning, and a newly recognised type of epiretinal membrane, termed ‘lamellar hole epiretinal proliferation’ (Morescalchi 2019). Lamellar hole epiretinal proliferation differs from typical epiretinal membrane; it has a different appearance, and seems to be non-contractile (Morescalchi 2019). Although the exact pathogenesis of DLMHs is unclear, Lamellar hole epiretinal proliferation is thought to develop as a result of Müller cell-driven processes, which originate from the middle retinal layers during the formation of LMHs (Govetto 2016; Haritoglou 2019; Morescalchi 2019; Pang 2015; Theodossiadis 2009). The influence of lamellar hole epiretinal proliferation on the natural course of LMHs is unknown, and studies that have investigated its potential contribution to the disease process have produced contradictory results (dell'Omo 2017; Ko 2017; Lai 2016). DLMHs may progressively worsen, and are associated with outer retinal atrophy, a larger hole diameter, and disruption to the ellipsoid zone, which contribute to poorer vision (Essex 2018; Govetto 2016; Jenisch 2017; Morescalchi 2019; Pang 2015; Schumann 2015; Thompson 1996).

The exact pathophysiology underpinning the development of DLMHs is unknown, however, their occurrence usually follow posterior vitreous detachment, sometimes with the presence of a pseudo-operculum on the posterior hyaloid face, which suggests that partial avulsion of foveal tissue may be the causative mechanism (Frisina 2019a; Johnson 2005). Evidence from OCT scans suggests they may result from an abortive process of a full-thickness macular hole, where the inner wall of the fovea, or a superficial cyst becomes avulsed by traction from the vitreous, but leaves sufficient tissue for the outer retinal layers (Theodossiadis 2009). Although the term 'degenerative' may suggest a slow and progressive mechanism, leading to additional loss of retinal tissue, this issue remains largely speculative.

The best method for managing people with LMHs (both TLMH and DLMH) is unknown. Although the integrity of the external limiting membrane seems important to improve visual function (Govetto 2016), the expected functional and anatomical outcomes following successful surgery remain unclear (Morescalchi 2019). Previously published studies have been inconsistent in how they define LMHs. Many do not differentiate DLMHs from TLMHs according to current criteria, as they were published before their development, and reported outcomes vary between studies (Androudi 2009; Casparis 2011; Frisina 2019b; Garretson 2008; Lee 2012). Therefore, comparing the effectiveness of surgery to manage LMHs has been difficult. Some surgeons are concerned that rather than improving outcomes, surgical intervention may contribute to adverse outcomes, because it can be challenging to separate the epimacular tissue from the DLMH’s internal limiting membrane, which could create macular hole defects (Haritoglou 2019). Therefore, surgeons tend to manage people with LMHs by observation to avoid potential surgery-related complications, and because LMHs (particularly TLMHs) seem to have a relatively stable anatomy, with largely unchanged visual function over time (Govetto 2016; Nava 2017).

Few studies have compared surgical outcomes in people with TLMHs and DLMHs (dell'Omo 2017; Figueroa 2019; Ko 2017; Lai 2016). Figueroa and colleagues suggested that following pars plana vitrectomy and internal limiting membrane peeling, vision improved significantly more for tractional LMH or macular pseudoholes than for DLMHs (Figueroa 2019). This may be because DLMHs are associated with worse preoperative visual acuity, and ellipsoid and external limiting membrane defects (dell'Omo 2017; Ko 2017; Lai 2016; Nava 2017; Schumann 2015). However, Bottoni and colleagues suggested that surgical intervention using pars plana vitrectomy and internal limiting membrane peeling of all perimacular membrane and lamellar hole epiretinal proliferation may be an effective treatment option for people with DLMH that is associated with worsening retinal anatomy and visual function (Bottoni 2013).

There may be a rationale to recommend surgical intervention for people with DLMHs that show evidence of functional or anatomical deterioration, or poor baseline vision that is causing significant disability, to stabilise the DLMH and prevent further visual deterioration.

Description of the intervention

Surgery is the most successful intervention for managing full-thickness macular holes; roughly 95% achieve complete hole closure following a single operation, and closure typically results in improved vision (Kelly 1991; Spiteri Cornish 2013; Steel 2020). Surgery usually involves pars plana vitrectomy and internal limiting membrane peeling. This can close the hole by reducing retinal compliance once the rigid internal limiting membrane is removed, and moving the retina, which surrounds the hole, centripetally, shortening the distance between the fovea and optic disc (Ishida 2014; Spiteri Cornish 2013; Steel 2020).

DLMHs have a more variable and unclear response to surgery (dell'Omo 2017; Figueroa 2019; Ko 2017; Lai 2016; Schumann 2015). Several published studies report improved postoperative visual

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function and retinal anatomy, some show no effect, and some highlight a potentially increased risk to developing complications, such as secondary macular hole formation (dell'Omo 2017; Figueroa 2019; Ko 2017; Lai 2016; Morescalchi 2019; Pang 2015; Schumann 2015).

The most effective surgical intervention to manage DLMHs is unclear. A variety of different surgical interventions have been attempted (AAO 2019; Figueroa 2019; Frisina 2019b; Gaudric 2013; Schumann 2015; Shiode 2018; Shiraga 2013). Most involve pars plana vitrectomy, with or without intravitreal tamponade by instilling gas or air. The methods by which the lamellar hole epiretinal proliferation and internal limiting membrane are managed, in an attempt to achieve DLMH closure, are of particular interest; some remove both the lamellar hole epiretinal proliferation and internal limiting membrane (Figueroa 2019; Gaudric 2013), some spare the perifoveal internal limiting membrane (Figueroa 2019), and others have incorporated novel methodologies to achieve DLMH closure, such as epiretinal membrane peel with inverted internal limiting membrane flap (AAO 2019), double inverted lamellar hole epiretinal proliferation with internal limiting membrane flap (Frisina 2019b), by embedding the lamellar hole epiretinal proliferation into the retinal cleavage (Shiraga 2013), or by embedding the lamellar hole epiretinal proliferation into the retinal cleavage, combined with internal limiting membrane inversion (Shiode 2018).

How the intervention might work

The mechanisms by which peeling the internal limiting membrane, or lamellar hole epiretinal proliferation, or both, encourages DLMH closure is not clear, especially, because lamellar hole epiretinal proliferation causes minimal contraction, so mechanisms that close macular holes are unlikely to play such a significant role in postoperative outcomes (Govetto 2016; Haritoglou 2019; Morescalchi 2019; Pang 2015; Theodossiadis 2009). Theories include: by inlaying the lamellar hole epiretinal proliferation and the internal limiting membrane, cytokines may be released and glial cells activated, to encourage normal healing processes; lamellar hole epiretinal proliferation may be an aberrant healing response, so, once removed by peeling, may help to restore the normal retinal anatomy; and finally, although lamellar hole epiretinal proliferation has less contractile characteristics than other epiretinal membranes, there is often a component of typical epiretinal membrane present, so epiretinal membrane and internal limiting membrane removal may improve retinal compliance and restore the anatomical integrity of the retina.

Why it is important to do this review

This Cochrane Review aims to synthesise current evidence, obtained from randomised controlled trials to determine the effect of surgical intervention on postoperative functional (e.g. visual function) and anatomical (e.g. central retinal thickness) outcomes for people affected by DLMHs.

This topic is important because DLMHs can progress over time, and are associated with deteriorating visual function, however, we do not understand the most appropriate way to manage these patients (Haritoglou 2019). A conservative approach is most commonly adopted by clinicians because of concerns related to intraoperative and postoperative adverse events; on the other hand, delaying intervention may, unnecessary, risk visual disability (Pang 2015).

This review will improve our understanding of the value of surgery in managing DLMHs, and either inform future clinical practices, or suggest the most appropriate investigative approaches required for future research.

OBJECTIVES

To assess the effect of surgical interventions on postoperative visual and anatomical outcomes in people with a confirmed degenerative lamellar macular hole.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCT) only in this review. Study status will not affect study inclusion.

Types of participants

The following criteria will determine inclusion:

- Studies involving participants with a confirmed diagnosis of degenerative lamellar macular hole (DLMH), evidenced on ocular coherence tomography (OCT; (Hubschman 2020)). For a confirmed diagnosis to be made, the following criteria must be fulfilled:
  - a defect with irregular foveal inner surface contours;
  - presence of epiretinal proliferation;
  - no full-thickness defect in the macula.

The following criteria will determine participant exclusion:

- non-degenerative lamellar macular holes (e.g. tractional, secondary, non-specified or unclear diagnosis);
- other diseases that can mimic foveal disease (e.g. macular telangiectasia (MacTel));
- significant comorbid ocular pathology (e.g. visually significant cataract, age-related macular degeneration, glaucoma, diabetic retinopathy, or retinal vascular diseases);
- previous vitrectomy.

No restrictions will be made based on geographical location, the study setting, or participant-specific characteristics (e.g. age and sex).

Types of interventions

We will consider studies that involve one or more surgical intervention(s), alone or in combination, in at least one arm of a RCT for inclusion. Surgical interventions can include pars plana vitrectomy and:

- detachment and removal of the posterior hyaloid;
- peeling of the internal limiting membrane;
- peeling of epiretinal tissues (either classic epiretinal membrane or lamellar hole epiretinal proliferation);
- inlay or creation of a flap of lamellar hole epiretinal proliferation or internal limiting membrane;
- foveal-sparing internal limiting membrane peel;
- filling of the vitreous cavity with gas or air.

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The control arm of the RCT can include at least one (or any combination) of the following:

- other surgical interventions (as detailed above);
- non-surgical interventions;
- sham procedures;
- observation.

Types of outcome measures

We will not exclude studies on the basis of reporting of outcomes.

We plan to collect data on change between preoperative and postoperative measurements. If data are only reported as a final value, we will collect these data and include them in statistical analyses. If an outcome is reported both as change and final value, we will preferentially use values describing the change before and after an intervention.

Primary outcomes

Change in BCVA from baseline (before surgery) to 6-month follow-up

We will collect data detailing BCVA, regardless of the measurement chart used (e.g. logMAR, Early Treatment Diabetic Retinopathy Study (ETDRS) letters, Snellen measures). We will only pool data if measurements can be converted to a logMAR score.

We will consider a 0.2 logMAR change in vision as clinically significant.

Secondary outcomes

Secondary outcome measures will be divided into the following three categories.

1. Functional outcomes

- change in BCVA from baseline to 3-month or 12-month follow-up, or both.
- the length of time to reach driving-standard vision from baseline.
- change in the extent of metamorphopsia experienced by participants from baseline to 3-month, 6-month, or 12-month follow-up, or a combination. Metamorphopsia can be assessed using any validated methodology, such as the D chart, M chart, and patient-reported measures (McGowan 2016; Patel 2019; Wada 2017).
- change in retinal sensitivity (in decibels) in participants from baseline to 3-month, 6-month, or 12-month follow-up, or a combination. Retinal sensitivity can be measured using any validated methodology, such as microperimetry or visual fields (Donati 2019; Kim 2014; Laishram 2017).

2. Anatomical outcomes

- change in central retinal thickness (CRT; in microns) from baseline to 3-month, 6-month, 12-month follow-up, or a combination. We will consider a 50 micron change as clinically significant.
- change in ellipsoid and external limiting membrane defects from baseline to 3-month, 6-month, 12-month follow-up, or a combination. We will consider a 50 micron change as clinically significant.
- changes recorded in outer retinal thickness at the fovea (in microns) from baseline to 3-month, 6-month, 12-month follow-up, or a combination

3. Participant-specific outcomes

- vision-reported quality of life (VRQOL) at 3-month, 6-month, 12-month follow-up, or a combination, using any validated tool.

Adverse effects

- we will compare the frequency of all complications between all study arms, regardless of the intervention.

When a surgical intervention is performed in at least one study arm, we will present the frequency of intraoperative complications. In trials with two surgical arms, we will analyse and compare complications, based on the CONSORT extension for harm criteria guidelines and consensus documents (Ioannidis 2004; Moher 2010). Early postoperative complications are defined as those occurring within one-month follow-up, late postoperative complications, as those occurring after one-month follow-up. Examples of postoperative complications include: reduced vision (> 0.2 logMAR), cataract formation, retinal detachment, endophthalmitis, vitreous haemorrhage, and the formation of surgically-induced macular holes.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials and controlled clinical trials. There will be no restrictions to language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue; Appendix 1);
- MEDLINE Ovid (1946 to present; Appendix 2);
- Embase Ovid (1980 to present; Appendix 3);
- Scopus SciVerse (1970 to present; Appendix 4);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; Appendix 5);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; Appendix 6);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp; Appendix 7).

Searching other resources

We will search the reference lists of included trials to identify any other eligible trials or relevant systematic reviews and meta-analyses which our search strategy may miss.

If full texts are unavailable, we will contact the corresponding author directly, by email, or telephone, or both, and request the full text of the published article. If, after one month, the corresponding author has not provided the full text, we will exclude the study and document the reason for exclusion.

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Data collection and analysis

Selection of studies

Two review authors (DCM and DHS) will assess all titles and abstracts retrieved from the search strategy to determine their eligibility for inclusion in the review, based on predefined inclusion and exclusion criteria, using an online review management software (Covidence). Following the initial assessment, we will obtain the full text of studies that show potential for inclusion, and the same two review authors will independently review them. If there are disagreements about which studies are eligible, they will consult a third review author (JR), until we reach consensus. We will specify the reasons for exclusion. We will summarise the details of this process and the reasons for article exclusion in a flow chart, designed in accordance with the PRISMA statement (Liberati 2009).

For potentially eligible studies identified on trials registers, we will contact the chief investigator of the trial directly, by email or telephone, or both, to request the published data if the study has a recorded expected completion date of more than two years in the past. We will document the study as ongoing if its expected completion date is within two years in the past, or is in the future.

Data extraction and management

We will use a data extraction sheet to extract information from included studies and to summarise their details. Two review authors (DCM and DHS) will trial the sheet on the first two eligible articles, to ensure it is robust, and to make any necessary amendments before they review all of the articles. If data appear to be missing from the published article of a trial, we will contact the corresponding author directly, by email or telephone, or both, and request the data.

We will collect and record outcome data in Review Manager 5 (Review Manager 2014). We will extract data from the included studies on the following variables (Table 1).

- Primary author
- Title
- Country where the study was conducted
- Healthcare setting
- Sources of funding
- Potential author conflicts of interest
- Publication status
- Year article was published
- Study-specific eligibility criteria
- RCT trial design (e.g. parallel group, within-person, cluster, cross-over)
- Randomisation timing (the point at which participants were randomised into different arms)
- Randomisation method (e.g. simple randomisation, block randomisation, stratified randomisation)
- Number of participants randomised to each arm
- Number of participants per arm included in the statistical analysis
- Number of participants lost per group and reasons explained (e.g. lost to follow-up, removal of consent following initial enrolment)
- Baseline participant data (e.g. BCVA, metamorphopsia, phakic status, OCT measurements)
- Type of intervention(s) in each RCT arm
- Trial outcomes with definitions: primary outcomes, secondary outcomes, and adverse outcomes
- Outcome comparisons by group: primary, secondary, and adverse outcomes
- Confounding variables (e.g. phakic status)
- Sources of bias (e.g. masking)
- Quality of evidence (in accordance with GRADE approach Schünemann 2013)

Outcome data

For trials with multiple arms, we will only collect data relating to the interventions outlined in our predefined eligibility criteria.

Assessment of risk of bias in included studies

Two review authors (DCM and DHS) will independently assess the risk of bias in each included RCT, referring to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6 (Higgins 2011). They will review each study according to the six domains detailed in the assessment tool. They will specifically evaluate the completeness of data and the extent of masking (blinding). The extent of bias in selection, performance, detection, attrition and outcome reporting will all be assessed (Higgins 2011).

Following thorough evaluation, we will grade each domain as low risk of bias, high risk of bias or unclear risk of bias. When the extent of bias is unclear, we will contact the chief investigator of ongoing trials or the corresponding author of published trials by email or telephone or both to obtain the information necessary to inform an accurate assessment.

Measures of treatment effect

We will report risk ratios (RR) with 95% confidence intervals (CI) for dichotomous variables. Where possible, we will assess whether or not continuous data are skewed (Altman 1996). We will compare normally distributed continuous data using the mean difference (MD) with 95% CIs. TIme-to-event data will be analysed using the hazard ratio. We may need to calculate the hazard ratio using data on observed and expected events, depending on how the data are reported in the studies.

We will collect data detailing BCVA, regardless of the measurement chart used (e.g. logMAR, ETDRS letters, Snellen measures). We will only pool data if measurements can be converted to logMAR score. For continuous variables measured on different scales, we will use standard mean difference (SMD) for comparisons. The size of an effect relative to its variability can be expressed using SMD. For scales that point in opposite directions (one increases, another decreases), we will mathematically manipulate the data to ensure that all scales point in the same direction.

Unit of analysis issues

The eye with a DLMH will be considered the unit of analysis, rather than the individual participant. Included studies may randomise to one or both eyes.

If participants show evidence of DLMHs in both eyes, both will be included and reported in the review.

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If the trial randomised by participant and included both eyes, each receiving the same intervention, we will consider that outcomes in both eyes are likely to be similar. We will analyse as 'clustered data', and make adjustments for within-person correlations.

If the trial randomised according to each individual eye, we will analyse the data as paired data.

If there is uncertainty about the methodology used for selection, we will contact the corresponding trial investigator or corresponding author and ask for clarification.

In participants with both eyes affected, we will review the interventions performed per eye in detail, to determine if a confounding cross-over effect may be possible. This is unlikely for surgical interventions, but may occur in those undergoing non-surgical therapies.

Dealing with missing data

We expect that some trial reports will contain missing data because it is a common scenario in clinical trials (Dziura 2013). We will determine the reasons for participant exclusion and loss to follow-up after randomisation because they may introduce bias into the trial. Where data that are important for the analysis are missing, we will contact the study's corresponding author and request the data. Where possible, we will perform an intention-to-treat (ITT) analysis, using imputed data completed by the trial investigator. However, we will not impute missing data ourselves. If ITT analysis is not possible, we will perform a complete case analysis, based on the assumption that data are missing at random. We will assess how reasonable this assumption is for each included trial, based on factors such as exclusion criteria, and the extent to which participants are lost to follow-up.

Assessment of heterogeneity

We will perform a thorough assessment of heterogeneity, using a multi-faceted approach. We will assess heterogeneity secondary to methodological and clinical variability by evaluating the characteristics of each trial. We will assess participant characteristics and the interventions performed in each study. This will inform the extent to which studies can be considered similar, so results can be sensibly pooled for analysis (Higgins 2002). We will calculate the I^2, an estimate of the percentage of variability in effect sizes arising from trial heterogeneity rather than chance, to summarise heterogeneity in included RCTs (Higgins 2002). We will consider that I^2 values less than 25% indicate a low level of heterogeneity, over 50% indicates substantial heterogeneity, and 75% indicates very high heterogeneity (Higgins 2002).

We will use the Chi^2 test to assess statistical heterogeneity; a P value < 0.010 will indicate statistically significant heterogeneity. Where high risk of heterogeneity is evident, we will explore the underlying causes. We will use forest plots to determine how consistent results are in different studies, including the direction and size of effects (Schünemann 2008).

Assessment of reporting biases

Biases in reporting can occur when results are presented in a particular format to influence research findings. Publication bias is an example, one in which the outcomes of a study influence the probability that a finding is published. One consequence of this is reported effects of an intervention may be larger in smaller-sized RCTs than in larger studies (Joober 2012).

Estimates of individual studies according to their study size and subsequent precision of their reported findings can be diagrammatically represented by a funnel plot (Sterne 2011). If we include a sufficient number of studies (N = 10), we will construct funnel plots. Asymmetry in such a funnel plot may indicate small study effects and potential publication bias.

The risk of selective outcome reporting will be assessed as part of the risk of bias assessment tool detailed above (Higgins 2011).

Data synthesis

We will pool data using a random-effects model in Review Manager 5 (Review Manager 2014). If there are fewer than three trials in a comparison, we will use a fixed-effect model, because it provides a more robust estimate of effect when there are limited data available, compared with a random-effects model. If inconsistencies between individual study results are significant enough to render a pooled result an inappropriate method to summarise individual trial results (e.g. I^2 > 50% and P < 0.10), we will describe the pattern of the individual trial results instead.

If we find statistical heterogeneity, but all effect estimates are in the same direction so that a pooled estimate would be appropriate, we may report trial results as pooled data. If it is not possible to perform a meta-analysis, due to clinical or methodological heterogeneity, we will combine the details of included studies in a narrative synthesis, according to the type of comparator and outcome measures.

Subgroup analysis and investigation of heterogeneity

If we find heterogeneity, and there are enough trials available, we will analyse the effect of the interventions according to specific subgroups. Subgroups will include age, the presence of a classic epiretinal membrane, and the presence of an external limiting membrane defect.

Sensitivity analysis

Sensitivity analysis allows one to assess the robustness of results after considering the inclusion of trials at high risk of bias, and examining the effects of using fixed-effect and random-effects models.

If possible, we will perform a sensitivity analysis to examine the effects of masking, the methods used to randomise participants, concealment of allocation groups, the use of fixed-effect and random-effects models, and attrition bias. Once we have collected the details of the specific characteristics of individual trials, we may consider additional sensitivity analyses, depending on our review of the data.

Summary of findings and assessment of the certainty of the evidence

Two review authors (DCM and DHS) will use the GRADE approach to independently examine and classify the certainty of the evidence for each outcome as high, moderate, low, or very low (Schünemann 2013). If disagreements between the two review authors occur, they will consult the third review author (JR); discussions between all three review authors will reach consensus.

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We will present the most important outcomes in a separate 'Summary of findings' table for each comparison. The tables will include information about the magnitudes of relative and absolute effects of the interventions examined, the available evidence and the quality of the evidence (Schünemann 2019a). Quality of evidence will be based on five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias (Schünemann 2019b). We will include the following outcomes in each table:

- change in BCVA from baseline to 6-month follow-up;
- change in metamorphopsia from baseline to 6-month follow-up;
- change in anatomical outcomes (CRT, ellipsoid and external limiting membrane defects, and outer retinal thickness at the fovea) from baseline to 6-month follow-up based on information obtained from OCT;
- vision-related quality of life; and
- adverse outcomes.

These outcomes are considered most important because they detail key patient-specific information about vision, quality of life and adverse outcomes. Outcomes which detail anatomical changes are also important because differences in outer retinal anatomy may improve our understanding of how DLMHs form and the mechanisms at play following surgical interventions.

We will develop a separate 'Summary of findings' table for the following comparisons:

Primary comparison:

- surgery (of any type) versus observation;

Secondary comparisons

- surgery with peri-DLMH internal limiting membrane peel and/or LMEP preservation versus complete internal limiting membrane peeling, and;
- surgery with peeling of any type versus surgery with adjuvants (e.g. platelets, blood etc.).

For the comparison 'surgery (of any type)', all surgical interventions will be pooled. Similarly, 'surgery with peeling of any type' will be derived by combining all surgical interventions which have involved an intra-operative membrane peel.

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ADDITIONAL TABLES

Table 1. Study characteristics

Mandatory items		Optional items
Methods		
Study design	• **Parallel-group RCT** *i.e. people randomised to treatment* • **Within-person RCT** *i.e. eyes randomised to treatment* • **Cluster-RCT** *i.e. communities randomised to treatment* • **Cross-over RCT**	Reasons for no follow-up: exclusions after randomisation; losses to follow-up; number randomised/analysed Specified method for how missing data was handled. Evidence of

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Table 1. Study characteristics *(Continued)*

		an initial power calculation performed and cohort sample size. Unusual study design/issues
Eyes *or* Unit of randomisation/unit of analysis	• **One eye included in study**: the eye showing evidence of a DLMH as defined by inclusion criteria • **Two eyes included in study, both eyes received same treatment:** both must show evidence of DLMH and treatment received should be randomised using with individual eyes as units of randomisation/analysis • **Two eyes included in study, eyes received different treatments:** both must show evidence of DLMH and treatment received should be randomised	
Participants		
Country		setting; ethnic group; equivalence of baseline characteristics (Y/N)
Total number of participants	Information collected to describe the participants should have been collected for the total number initially enrolled in the study, not only for those who were fully followed-up.	
Number (%) of men and women		
Average age and age range		
Inclusion criteria	As specified in inclusion and exclusion criteria section of protocol	
Exclusion criteria	As specified in inclusion and exclusion criteria section of protocol	
Interventions		
Intervention (N =) Comparator (N =)	• Number of people randomised to each group • Name of surgical or non-surgical intervention • Method of randomisation	
Outcomes		
Primary and secondary outcomes *as defined in study reports*	• Any or all specified primary, secondary, or adverse outcomes reported (Y/N); length of follow-up and intervals at which outcomes were assessed	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Reported subgroup analyses (Y/N) Were trial investigators contacted?

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Table 1. Study characteristics *(Continued)*

Sources of funding	As reported in published articles. If not published, will be requested from chief investigator of trial.
Declaration of interest	As reported in published articles. If not published, will be requested from chief investigator of trial.
Included in trials registry	Y/N, including registration number if available

DLMH: deep lamellar macular hole

APPENDICES

Appendix 1. CENTRAL search strategy

#1 degenerative near/2 lamellar
#2 lamellar near/2 (macula* or hole*)
#3 macular lamellar hole*
#4 partial thickness near/2 (macula* or hole*)
#5 DLMH* or LMH* or PTMH* or PTH*
#6 pseudohole*
#7 fovea* near/2 defect*
#8 non near/1 full near/1 thick* near/1 macula*
#9 (atypical or dens*) near/2 ERM*
#10 (atypical or dens*) near/2 epiretinal membrane
#11 AERM
#12 degenerative adj2 (membrane or epiretinal or ERM*)
#13 (epiretinal or ERM*) near/5 macula* pigment*
#14 epiretinal proliferation
#15LHEP
#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 MeSH descriptor: [Vitrectomy] this term only
#18 PPV*
#19 vitrectom*
#20 cortical near/2 vitreous
#21 MeSH descriptor: [Epiretinal Membrane] this term only
#22 internal near/2 limit* near/2 membrane*
#23 ILM or FSILM
#24 fovea* near/2 spar*
#25 peel* or inlay or flap or flap
#26 MeSH descriptor: [Endotamponade] this term only
#27 gas or air
#28 tamponade*
#29 MeSH descriptor: [Sulfur Hexafluoride] explode all trees
#30 sulfur hexafluoride*
#31 hexafluoroethane*
#32 perfluoropropane*
#33 octafluoropropane*
#34 SF6 or C2F6 or C3F8
#35 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36 #16 and #35

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.

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5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. (degenerative adj2 lamellar).tw.
14. (lamellar adj2 (macula$ or hole$)).tw.
15. macular lamellar hole$.tw.
16. (partial thickness adj2 (macula$ or hole$)).tw.
17. (DLMH$ or LMH$ or PTMH$ or PTH$).tw.
18. pseudohole$.tw.
19. (fovea* adj2 defect$).tw.
20. (non adj1 full adj1 thick$ adj1 macula$).tw.
21. ((atypical or dens$) adj2 ERM$).tw.
22. ((atypical or dens$) adj2 epiretinal membrane).tw.
23. AERM.tw.
24. (degenerative adj2 (membrane or epiretinal or ERM$)).tw.
25. ((epiretinal or ERM$) adj5 macula$ pigment$).tw.
26. epiretinal proliferation.tw.
27. LHEP.tw.
28. or/13-27
29. vitrectomy/
30. PPV$.tw.
31. vitrectom$.tw.
32. (cortical adj2 vitreous).tw.
33. Epiretinal Membrane/
34. (internal adj2 limit$ adj2 membrane$).tw.
35. (ILM or FSILM).tw.
36. (fovea* adj2 spar$).tw.
37. (peel$ or inlay or flap or flaps).tw.
38. Endotamponade/
39. (gas or air).tw.
40. tamponade$.tw.
41. exp sulfur hexafluoride/
42. sulfur hexafluoride$.tw.
43. hexafluoroethane$.tw.
44. perfluoropropane$.tw.
45. octafluoropropane$.tw.
46. (SF6 or C2F6 or C3F8).tw.
47. or/29-46
48. 28 and 47
49. 12 and 48
50. (hyperparathyroidism or parathyroid$ or hydrocephalus or hemodialysis).ti.
51. 49 not 50

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9

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11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. (degenerative adj2 lamellar).tw.
34. (lamellar adj2 (macula$ or hole$)).tw.
35. macular lamellar hole$.tw.
36. (partial thickness adj2 (macula$ or hole$)).tw.
37. (DLMH$ or LMH$ or PTMH$ or PTH$).tw.
38. pseudohole$.tw.
39. (fovea* adj2 defect$).tw.
40. (non adj1 full adj1 thick$ adj1 macula$).tw.
41. ((atypical or dens$) adj2 ERM$).tw.
42. ((atypical or dens$) adj2 epiretinal membrane).tw.
43. AERM.tw.
44. (degenerative adj2 (membrane or epiretinal or ERM$)).tw.
45. ((epiretinal or ERM$) adj5 macula$ pigment$).tw.
46. epiretinal proliferation.tw.
47. LHEP.tw.
48. or/33-47
49. vitrectomy/
50. pars plana vitrectomy/
51. PPV$.tw.
52. vitrectom$.tw.
53. (cortical adj2 vitreous).tw.
54. epiretinal membrane/
55. (internal adj2 limit$ adj2 membrane$).tw.
56. (ILM or FSILM).tw.
57. (fovea* adj2 spar$).tw.
58. (peel$ or inlay or flap or flaps).tw.
59. endotamponade/
60. (gas or air).tw.
61. tamponade$.tw.
62. sulfur hexafluoride/
63. sulfur hexafluoride$.tw.
64. hexafluoroethane$.tw.
65. perfluoropropane$.tw.
66. octafluoropropane$.tw.
67. (SF6 or C2F6 or C3F8).tw.
68. or/49-66
69. 48 and 68
70. 32 and 69
71. (hyperparathyroidism or parathyroid$ or hydrocephalus or hemodialysis).ti.
72. 70 not 71

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Appendix 4. Scopus SciVerse search strategy

((TITLE-ABS-KEY (lamellar W/2 macular W/2 holes)) OR (degenerative W/2 lamellar)) AND (random)

Appendix 5. ISRCTN search strategy

" lamellar macular hole"

"degenerative lamellar"

Appendix 6. ClinicalTrials.gov search strategy

lamellar macular hole

degenerative lamellar

Appendix 7. WHO ICTRP search strategy

lamellar macular hole

degenerative lamellar

HISTORY

Protocol first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

DM wrote the first draft of the protocol with input from DS and JR.

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DM: none known
JR: none known
DS: I have acted as a consultant to a number of companies unrelated to the subject matter of this review.

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