COMBAT

Clinical- and cost-effectiveness, safety, and acceptability of **COMB**ined phacovitrectomy, versus sequenti**A**l vi**T**rectomy and cataract surgery, for the management of rhegmatogenous retinal detachment: A Randomised Equivalence Clinical Trial.

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PROTOCOL AUTHORISATION

Protocol Title	Clinical- and cost-effectiveness, safety, and acceptability of COMBined phacovitrectomy, versus sequentiAl viTrectomy and cataract surgery, for the management of rhegmatogenous retinal detachment: A Randomised Equivalence Clinical Trial
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A review of the protocol has been completed and is understood and approved by the following:

Noemi Lois		10 / 3 / 25
Chief Investigator Name	Signature	Date
Christina Campbell	Campbell	10 / 3 / 25
Statistician	Signature	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
AE	Adverse Event
AR	Adverse Reaction
AREDS	Age-Related Eye Disease Study
BCVA	Best-Corrected Visual Acuity
BEAVRS	British and Eire Association of Vitreo-Retinal Surgeons
BHSCT	Belfast Health and Social Care Trust
CFI	Comparative Fit Index
CFIR	Consolidated Framework for Implementation Research
CI	Chief Investigator
CORDS	The Classification for the Reporting of Complications in Retinal Detachment Surgical Trials'
CRF	Case Report Form
CS	Cortical Sclerosis
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDI	Equality, Diversity and Inclusion
EQ-5D-5L	EuroQol - Five Dimension - Five Level
ERIC	Expert Recommendations for Implementing Change
GCP	Good Clinical Practice
ETDRS	Early Treatment Diabetic Retinopathy Study
GLM	General Linear Models
GP	General Practitioner
HEAP	Health Economic Analyses Plan
HES	Hospital Eye Services
HRA	Health Research Authority
HTA	Health Technology Assessment
ICH	International Conference of Harmonisation
ICF	Informed Consent Form
ISF	Investigator Site File
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
LogMAR	Logarithm of the Minimum Angle of Resolution
LRT	Likelihood Ratio Test
MM	Millimetre(s)
ModRUM	Modular Resource Use Measure
MRC	Medical Research Council
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute for Health and Care Research
NS	Nuclear Sclerosis
OCT	Optical Coherence Tomography
PCO	Posterior Capsule Opacification
PI	Principal Investigator
PIL	Patient Information Leaflet
PIP	Pillar Integration Process
PPI	Participant and Public Involvement
PPIER	Patient and Public Involved in Eye Research
PSC	Posterior Subcapsular
PSS	Personal Social Services
PVR	Proliferative Vitreoretinopathy
PVR-C	Proliferative Vitreoretinopathy – Grade C
QALY	Quality Adjusted Life Years

QoL	Quality of Life
QUB	Queens University Belfast
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RMSEA	Root-Mean-Square Error of Approximation
RPE	Retinal Pigment Epithelium
RRD	Rhegmatogenous Retinal Detachment
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SEM	Structural Equation Modelling
SmPC	Summary of Product Characteristic
SOP	Standard Operating Procedure
SWAT	Study Within a Trial
TFA	Theoretical Framework of Acceptability
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
VFQ-UI	Visual Function Questionnaire Utility Index
YAG	Yttrium Aluminum Garnett

1. STUDY SUMMARY

Scientific title	Clinical- and cost-effectiveness, safety, and acceptability of **COMB**ined phacovitrectomy, versus sequenti**A**l vi**T**rectomy and cataract surgery, for the management of rhegmatogenous retinal detachment: A Randomised Equivalence Clinical Trial.
Public title	Treatment of retinal detachment in people who have not had cataract surgery and are not very short-sighted with either vitrectomy surgery alone or with vitrectomy and removal of the cataract at the same time.
Health condition(s) or problem(s) studied	Retinal detachment
Study Design	Pragmatic randomised equivalence trial.
Study Aim and Objectives	**Aim** To determine whether, in people with non-highly myopic phakic rhegmatogenous retinal detachment (RRD) (Population), phacovitrectomy (Intervention) is equivalent (equivalence margin +/- 7 Early Treatment Diabetic Retinopathy Study ETDRS letters) to vitrectomy and subsequent cataract surgery (phacoemulsification) if/when needed (Comparator) for improving vision following surgery (primary Outcome) but superior for other (secondary) outcomes (as listed in this protocol) in the 52 weeks (+/- 6 weeks) after surgery. **Objectives** To determine if, in people presenting with non-highly myopic phakic RRD, phacovitrectomy (i.e. removing the cataract and doing vitrectomy to repair the RRD) is as good or better as doing only the retinal detachment repair with vitrectomy and then, if and when the cataract develops, doing a phaco (i.e. cataract surgery) and to assess post-trial implementation strategies and scalability.
Study Intervention	**Intervention** Phacovitrectomy (i.e. cataract surgery combined with retinal detachment surgery). **Comparator** Vitrectomy only, first, and then, if and when a cataract develops, doing the cataract surgery (phacoemulsification). In both randomised groups, surgeries will be undertaken as per standard care. Vitrectomy using any gauge size (e.g. 23g, 25g, 27g) will be allowed as per standard care at each participating site.
Primary Outcome	Change in Best-Corrected Visual Acuity (BCVA) in the study eye from baseline to 52 weeks (+/- 6 weeks) after surgery (equivalence margin +/- 7 ETDRS letters).
Key Secondary Outcomes	At 52 weeks (+/- 6 weeks) after surgery for all outcomes except *: – *Primary anatomical success (proportion of eyes with an attached retina after one vitrectomy).* – *Final anatomical success (proportion of eyes with an attached retina after two or more vitrectomies).* – *Intraoperative complications (total number and by severity score).* – *Postoperative complications (total number and by severity score).* – *Number and type of surgeries performed.* – *Refractive error *(difference between aimed (sought) and obtained post-operative refraction at 12 weeks after surgery in the phaco-vitrectomy arm and 6-8 weeks post-cataract surgery,*

	if this takes place, as per standard of care, in the vitrectomy only arm). – *Proportion of participants with BCVA <69 letters* – *Proportion of participants with BCVA <34 letters.* – *Time to achieve 'best vision'.* – *Change in BCVA from baseline over time.* – *Health related quality of life using EuroQol-5 level (EQ-5D-5L).* – *Vision-specific quality of life using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25).* – *Participant's experience, and acceptability of treatments.* – *Use of health and social care services and non-health care.* – *Safety*
Key Inclusion and Exclusion Criteria	**Inclusion criteria** – *Adults ≥50 years of age* – *Non-highly myopic (< -6 diopters; ≤26.5 mm axial length) phakic RRD* – *Naive to previous vitreoretinal surgery* – *Pars plana vitrectomy is planned to repair their RRD.* **Exclusion criteria** – *Presence of a "formed/established cataract."* A "formed/established cataract" is defined as a cataract that, based on the Age-Related Eye Disease Study (AREDS) Research Group, is graded as nuclear sclerosis of ≥3 and/or if there is an anterior cortical cataract and/or a subcapsular posterior cataract involving the visual axis. – *Pseudophakia or aphakia.* – *High myopia (≥-6 diopters; >26.5 mm axial length).* – *Giant retinal tear (i.e. presence of one or more retinal tears of ≥3 clock hours in size)* – *Retinal dialysis* – *Inclusion in an investigational drug study* – *Declined consent for participation*
Countries of Recruitment	United Kingdom
Study Setting	Hospital Eye Services
Target Sample Size	276 participants
Study Duration	48 months

2. STUDY TEAM

Chief Investigator	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland *Details of co-applicants and co-investigators can be requested from* combat@nictu.hscni.net
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Sponsor's Reference	B25/03
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Contact for scientific queries	**Professor Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine Queen's University Belfast 97 Lisburn Road Belfast, BT9 7BL Northern Ireland Email: n.lois@qub.ac.uk

3. ROLES AND RESPONSIBILITIES

3.1. Funder

The National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme is providing the research costs for the COMBAT study (Reference NIHR161891).

The funder has no role in the study design, data acquisition, analysis and interpretation, or manuscript preparation.

3.2. Contributorship

The Chief Investigator (CI) conceived the study. The CI planned the study design, which was finalised with input from all co-investigators, including the COMBAT Participant and Public Involvement (PPI) Group. The statisticians determined the sample size and planned the data analysis, with input from the CI and co-investigators. The statisticians will oversee the primary statistical analysis of the trial. The health economists planned and will conduct the cost-effectiveness evaluation. Experts on qualitative research and implementation science designed and will undertake and analyse the evaluation of participant experience and acceptability and implementation strategies. The CI is the grant holder and will oversee the management and conduct of the study.

3.3. Sponsor

Queen's University Belfast (QUB) will act as Sponsor and the CI will take overall responsibility for the conduct of the study. Separate agreements will be put in place between the Sponsor and each organisation that will undertake Sponsor-delegated duties in relation to the management of the study. The Sponsor will have no role in the collection, analysis, and interpretation of data, writing of the reports, or decisions to submit reports for publication.

3.4. Trial Oversight Committees

Trial Management Group (TMG)

A Trial Management Group (TMG) will be established and chaired by the CI. It will comprise the CI and representatives from the Northern Ireland Clinical Trials Unit (NICTU), and any other co-investigators who provide trial specific expertise as required at the time, including the chair of the COMBAT PPI. The TMG will meet face to face or online on a monthly basis and communicate between times via telephone or online meetings and emails, as needed. The roles and responsibilities of the TMG will be detailed in the TMG Charter. Meetings will be formally minuted and a list of actions recorded and stored in the Trial Master File (TMF). All day-to-day activity will be managed by the Trial Manager/Trial Co-ordinator, in consultation with the CI as needed, providing a streamlined approach for handling enquiries regarding the study and disseminating communications.

Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be convened to provide oversight with respect to the conduct of the study on behalf of the Funder and Sponsor. The minimum quoracy for any TSC meeting to conduct business is 67% (two thirds) of the appointed independent membership. The TSC will have an independent chair. The TSC will include the CI, at least one public member and others with clinical expertise relevant to the study. Membership, role of the TSC and frequency of meetings will be listed in the TSC Charter. The TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants. Meetings will be formally minuted and the minutes will be stored in the TMF. Observers may be invited to attend TSC meetings, such as the Sponsor or Funder representatives or the Trial Manager to provide input on behalf of the NICTU.

Data Monitoring and Ethics Committee (DMEC)

An independent Data Monitoring and Ethics Committee (DMEC) will be convened, comprising two independent clinicians with experience in undertaking clinical trials and an independent statistician. The DMEC's overarching responsibility is to safeguard the interests of study participants, in particular with regard to safety, and assist and advise the TSC so as to protect the validity and credibility of the study. The membership, the role of the DMEC and the frequency of meetings will be listed in the DMEC Charter. The DMEC will meet to agree conduct and remit, which will be detailed in the DMEC Charter. Meetings will be formally minuted and the minutes will be stored in the TMF. Following recommendations from the DMEC, the TSC will decide what actions, if any, are required. It will be the

responsibility of the DMEC to inform the Sponsor if concerns exist about participant safety, following which the Sponsor will take appropriate action. If a trial extension and/or funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

User Involvement

Trial conception and design: The best friend of the CI developed a RRD and underwent vitrectomy in Spain. Soon after, she developed a cataract. She found it difficult to have to go through surgery again to get this removed and said that the combined procedure (phacovitrectomy) had not been offered to her at the time of vitrectomy. The CI decided to explore this further and established the COMBAT PPI group to determine if this was an issue for people in the United Kingdom (UK), to gather the views of more people with RRD, and, if appropriate, to plan a trial. The COMBAT PPI group was formed with help from the Patient and Public Involved in Eye Research (PPIER) Group of St Paul's Eye Unit in Liverpool and, specifically, with the Retinal Surgery group, created in 2019. This group has 34 members (the majority of whom have had a RRD). The group is diverse in age, sex, ethnicity, disability, and socio-economic background, reflecting the diverse community served. The group voiced that people with RRD are unable to make an informed decision about whether to have vitrectomy alone or phacovitrectomy because of the lack of evidence about potential harms and benefits of each surgical approach. They believed that, given this lack of evidence, a randomised trial was very much needed. The COMBAT PPI Group provided input to the study design, including outcomes to be investigated, to the "participant experience" evaluation plan, and to the lay abstract for the study.

Preparation of participant facing materials: The participant information leaflet (PIL), consent form, and posters for the trial were prepared with active input from the COMBAT PPI Group. Posters will be placed in Eye Casualty facilities and clinical rooms to raise awareness of the COMBAT study among staff and to prompt staff to inform potentially eligible participants about the study.

Trial recruitment: Researchers and the COMBAT PPI Group will work together to ensure a range of strategies are used to recruit a diverse group of participants into the study.

Retention of participants in the trial: The COMBAT PPI Group's input will be sought to ensure adequate measures are in place to maximise retention of participants. In this regard, when designing the study, researchers and the PPI Group carefully planned the evaluations and follow-up of participants as close to standard practice and in as simple and convenient manner as possible, to facilitate retention and completion of all visits.

Interpretation of trial results, dissemination, and implementation: The results of the COMBAT study will be interpreted with input from the COMBAT PPI Group. The TMG will consult with the PPI Group to identify strategies for dissemination and implementation of trial results. The implementation strategy developed in COMBAT will support the implementation of the findings into practice.

Identification of areas of future research: The COMBAT PPI Group will help the researchers to identify new areas of research, based on the findings of COMBAT.

4. BACKGROUND AND RATIONALE

4.1. Background Information

Rhegmatogenous retinal detachment (RRD) is the separation of the retina from the wall of the eye, where it is normally attached. It affects 10-18 people per 100,000 per year (1,2). Thus, in the UK, with a population of around 68 million (3) there are 6700-12,000 RRD per year.

RRD can lead to permanent central and peripheral vision loss (i.e. total blindness) if not treated in a timely manner. Vitrectomy is the most common surgery done for RRD (4,5). Retinal reattachment following one vitrectomy occurs in 80-88% of eyes, with 59-67% gaining vision above 0.3 LogMAR, which is the vision required to fulfil UK driving standards (4,5).

Data from the British and Eire Association of Vitreo-Retinal Surgeons (BEAVRS) showed that most patients with RRD are phakic; this means that they still have their natural lens (i.e. have not had cataract surgery) (5). Data from the BEAVRS database (unpublished, but accessible to the COMBAT

research group) showed that of 8436 vitrectomies done in non-high myopic phakic eyes out of 13,900 vitrectomies performed at several sites in the UK, only 10% combined vitrectomy with cataract surgery (called phacovitrectomy) at the time of the RRD repair. Of 664 phakic eyes with at least 12 months follow-up in which combined surgery was not performed at the time of RRD surgery, 320 (48%) were recorded to have a cataract or to have had it already removed within three months of the original vitrectomy. Only 20% of these eyes had their own clear natural lens at 12 months following vitrectomy. Therefore, phacovitrectomy is done in a minority of patients at the time of RRD repair; and many patients have either a cataract present or undergo separate cataract surgery soon after the RRD surgery.

Previous studies have shown the potential benefits of doing combined RRD and cataract surgery (6,7). If the cataract is removed when the RRD is repaired, the view of the back of the eye may be clearer, because the surgeon will see through the clear artificial lens. Furthermore, the purpose of the vitrectomy is to remove the vitreous, which is a gel-like structure that fills the back of the eye. The vitreous is involved in the occurrence of the RRD and, given that the vitreous is also present around the posterior part of the lens of the eye, removing the lens allows a more thorough removal of the vitreous. This has the potential to improve the anatomical outcome of the vitrectomy (i.e. reattachment of the retina) and reduce the number of surgeries required because there would be less need for reoperations (repeated vitrectomies) if the first vitrectomy fails to put the retina back in place. Phacovitrectomy would also obviate the need to do the cataract surgery at a later time following the vitrectomy. Adding a phaco to the vitrectomy will add approximately 8 minutes to the surgical time (7) but could save 6000 cataract surgeries per year to the NHS. Reducing the number of surgeries might benefit both patients and the NHS by reducing hospital admissions and clinical appointments, thereby reducing NHS costs, and increasing capacity to deal with more patients. Moreover, when cataract surgery is done after vitrectomy, the vitreous is no longer present and there is less support to the lens. This may make the cataract surgery more difficult and increase the risk of intraoperative complications (8).

However, some studies have suggested that postoperative inflammation (9), accumulation of fluid in the centre of the retina (called cystoid macular oedema) (10), epiretinal membrane formation (10), and posterior synechiae (adherence of the iris to the intraocular lens) (11) may be more frequent after phacovitrectomy. Calculation of the required artificial intraocular lens, which is used at the time of cataract surgery to replace the natural lens of the eye, may be less accurate when doing combined phacovitrectomy in eyes where the macula (i.e. the central retina) is detached (10). This is because the calculation of the intraocular lens requires measuring the length of the eye and this measurement is less accurate if the macula is detached. However, errors appear to depend on the technique used for this calculation (12). A less accurate measure of the intraocular lens would mean people may need glasses to improve their vision following surgery.

4.2. Rationale for the Study

Previous studies comparing vitrectomy with phacovitrectomy in people with RRD have been mostly retrospective and small, with numerous methodological weaknesses. None have addressed patient reported outcomes, patient views and acceptability for one surgery over the other, or costs.

Two systematic reviews of phacovitrectomy versus vitrectomy and subsequent cataract surgery have been published recently (13,14). Farahvash et al. (13) included studies in which vitrectomy or phacovitrectomy were used for a variety of retinal disorders, including RRD, macular hole, epiretinal membrane, and others. They included six retrospective before and after studies and one prospective study on RRD but no randomised trials. Results for the RRD group were not given separately. The Mirshahi et al. review (14) included studies specifically comparing surgeries in people with RRD. The review included five retrospective before and after studies, one study defined as a “quasi randomised” and one randomised trial. Only one of the studies included in the review by Mirshahi et al. was in the Farahvash et al. review. The randomised trial in Mirshahi et al. review [Mora et al. (15)] was a small poorly reported study with 59 patients (59 eyes) randomised to vitrectomy alone (n=29) or phacovitrectomy (n=30). Although not clearly stated, the trial seems to have been a non-inferiority trial with a non-inferiority margin of 10% or less between groups for the primary outcome (retinal reattachment with a single surgery at 6 months). However, a 10% difference in single surgery success on retinal re-attachment seems clinically important. The authors stated that, accepting a 5% type 1 error and 80% power, a sample size of 50 eyes would be needed to detect differences between groups in the primary outcome (15). Secondary outcomes included final best-corrected visual acuity (BCVA), intraocular pressure, central macular thickness, and progression of cataract in the vitrectomy only group. Mora et al. stated that all outcomes (primary and secondary) were assessed at 1 week

and 1, 3 and 6 months after surgery but do not report if patients and outcome assessors were masked to treatment allocation. The trial found no differences in any of the outcomes at six months post-surgery except progression of cataract in the vitrectomy group. Patient reported outcomes and patient experience and acceptability, intra and post-operative complications and costs were not systematically evaluated.

Authors of both recent systematic reviews (13,14) called for randomised trials to determine the best surgical approach for people with phakic RRD. COMBAT is such a trial and the need for it has been confirmed by the COMBAT PPI group who noted that people with RRD are currently unable to make an informed decision about whether to have vitrectomy alone or phacovitrectomy because of the lack of evidence about potential harms and benefits of each surgical approach. They confirmed that patients with RRD should be agreeable to joining COMBAT because both treatments have potential advantages and disadvantages. When they had their RRD, none of the patients in the COMBAT PPI group were offered a choice between having the surgeries at the same time or separately, with no discussion of the potential differences. COMBAT should provide the evidence to inform these discussions in the future.

4.3. Rationale for the Intervention

The intervention will be phacovitrectomy (i.e. phaco to remove the cataract and insert an intraocular lens and vitrectomy to repair the retinal detachment). This is performed routinely throughout the UK to treat people with a idiopathic macular hole. However, it is not the standard procedure for people with phakic, non-highly myopic RRD.

4.4. Rationale for the Comparator

The comparator in COMBAT is the current standard care (i.e. the performance of vitrectomy without concomitant cataract extraction) for most patients in the UK for whom vitrectomy is planned for the repair of the phakic, non-highly myopic retinal detachment, as shown by data from the BEAVRS database.

5. STUDY AIM AND OBJECTIVES

5.1. Research Hypothesis

We hypothesise that combined phacovitrectomy will be preferred by patients because it will provide faster visual recovery and obviate the need for a second surgery (the cataract surgery) following RRD repair, and possibly reduce the number of reoperations related to failure to re-attach the retina. The COMBAT PPI Group have highlighted that obviating the need for further cataract surgery should have a positive impact on patients because of the stress and anxiety that occurs before surgical procedures. Phacovitrectomy may reduce the number of visits and admissions to hospital, reducing costs and pressures on the NHS and probably reducing costs to patients such as travel costs and time off work for attending hospital visits. These costs are especially problematic for patients with limited income and the self-employed. Phacovitrectomy may also reduce other health inequalities because if cataract surgery is required after RRD repair, long waiting times for this surgery in the NHS could adversely affect people with lower income who may be unable to achieve visual rehabilitation as quickly as those with higher income who can afford to have their cataracts removed privately.

5.2. Research Question and Study Aim

Research question: In people with non-highly myopic phakic RRD (Population) in whom vitrectomy is planned to repair their RRD, is phacovitrectomy (Intervention) equivalent (equivalence margin +/- 7 ETDRS letters) to vitrectomy and subsequent cataract surgery (phacoemulsification) if/when needed (Comparator) for improving vision following surgery (primary Outcome) but superior for other (secondary) outcomes (listed below) in the 52 weeks (+/- 6 weeks) after surgery.

Aim: To conduct a pragmatic randomised trial evaluating clinical and cost-effectiveness, safety and acceptability and patient experience of combined phacovitrectomy versus vitrectomy and subsequent cataract surgery (if/when needed) for non-highly myopic phakic RRD and to undertake a structured

analysis of strategies to implement the phacovitrectomy pathway, if this is shown to be as good or better than current standard care.

5.3. Study Objectives

In people presenting with a phakic, non-highly myopic RRD, the objectives of the COMBAT study are;

1. To determine if the clinical effectiveness of phacovitrectomy is equivalent (or superior) to that of vitrectomy and subsequent cataract surgery (if/when needed).
2. To compare the cost-effectiveness of phacovitrectomy with that of vitrectomy and subsequent cataract surgery (if/when needed) via an economic evaluation.
3. To evaluate the participant experience and acceptability of phacovitrectomy compared with vitrectomy and subsequent cataract surgery (if/when needed) via a mixed methods evaluation.
4. To evaluate the post-trial implementation and scalability of phacovitrectomy via a process evaluation.

6. STUDY DESIGN

6.1. Study Design

Pragmatic, allocation-concealed, single-masked (outcome assessors), multicentre, randomised (1:1), equivalence trial with an internal pilot to assess feasibility of recruitment.

6.2. Internal Pilot

The internal pilot will take place during the first nine months of recruitment, to assess feasibility of recruitment and determine if the study should continue to a full trial. The go/amend/stop criteria will be assessed nine months after the first site is open to recruitment. The target recruitment will be an average of 0.5 participants per month per open site. With the proposed staggered opening of sites, the recruitment target for the internal pilot is 63 participants, which would represent 23% of the required sample size for the full trial.

Table 1 shows the criteria for progression to the full trial: GREEN: Progress to full trial. AMBER: Discuss feasibility with the TSC and NIHR and develop a recovery plan to reach the recruitment target, including evaluating options to improve recruitment and considering number of eligible patients identified, percentage of these patients randomised and reasons for non-randomisation, site recruitment performance, and recruitment procedures. RED: Decision to progress with trial will be made by the TSC and NIHR.

Table 1 Traffic light system for progression criteria from internal pilot to main study

Criteria (% threshold)	Red (<50%)	Amber (50-99%)	Green (100%)
Average recruitment rate/site/month	<0.25	0.25-0.49	0.5
Number of sites opened	<12	12 - 23	24
Number of participants recruited	<31	31 - 62	63

6.3. Schematic Diagram

Figure 1 provides an overview of participant flow in the trial.

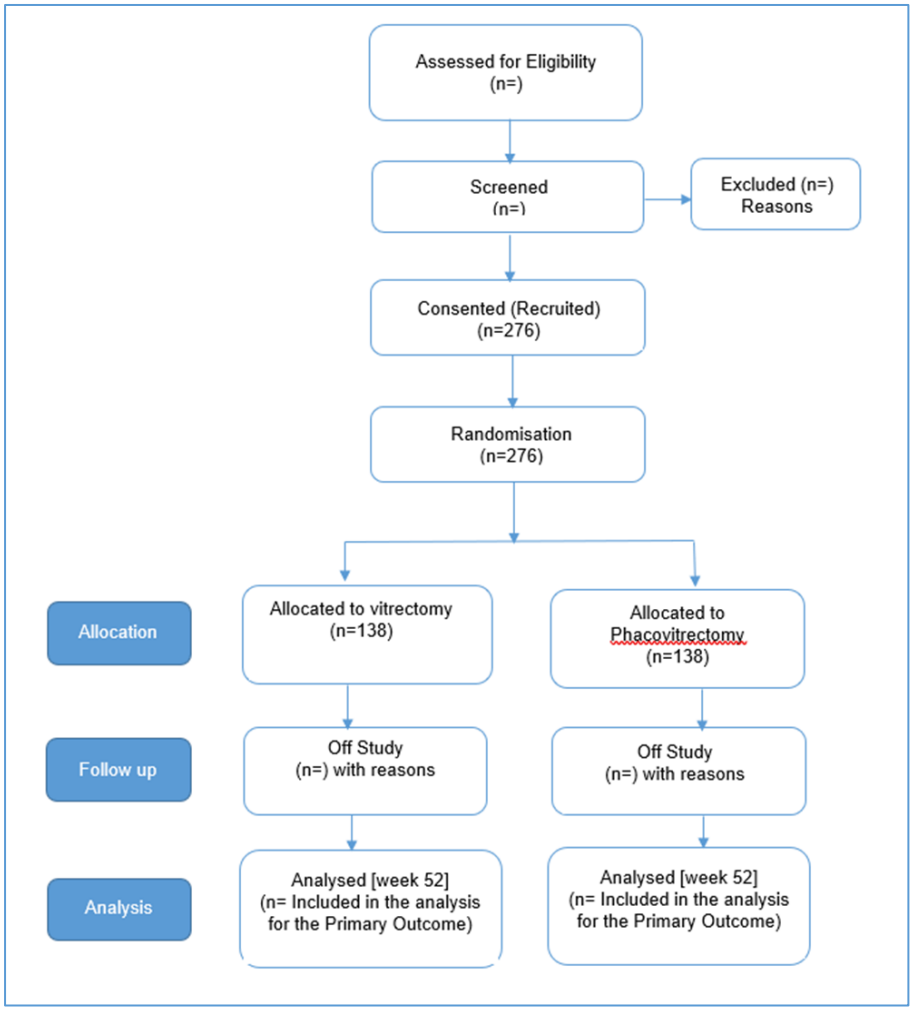

Figure 1. Flow Diagram for COMBAT

6.4. End of Study

For the purposes of submitting the end of trial notification to the Sponsor and the Research Ethics Committee (REC), the end of trial will be considered to be when database lock occurs. The trial will be stopped prematurely if:

- Mandated by the REC
- Mandated by the Sponsor (e.g. following recommendations from the DMEC and TSC)
- Funding for the trial ceases

The REC that originally gave a favourable opinion for the trial will be notified in writing when the trial has been concluded or if it is terminated early.

7. TRIAL SETTING AND PARTICIPANT ELIGIBILITY CRITERIA

7.1. Study Setting

Recruitment for COMBAT will take place in at least 30 hospital eye services (HES) across the four UK nations, with catchment areas that cover diverse populations. A list of study sites will be maintained in the TMF.

7.2. Eligibility Criteria

Eligibility for the trial will be confirmed by an ophthalmologist delegated to undertake this task on their site's delegation log. Patients will be eligible if they fulfil the following criteria:

Inclusion Criteria

- *Adults ≥50 years of age*
- *Non-highly myopic (< -6 diopters; ≤26.5 mm axial length) phakic RRD*
- *Naïve to previous vitreoretinal surgery*
- *Pars plana vitrectomy is planned to repair their RRD.*

Exclusion Criteria

- *Presence of a "formed/established cataract".*
  A "formed/established cataract" is defined as a cataract that, based on the Age-Related Eye Disease Study (AREDS) Research Group (16), is graded as nuclear sclerosis of ≥3 and/or if there is an anterior cortical cataract and/or a subcapsular posterior cataract involving the visual axis.
- *Pseudophakia or aphakia.*
- *High myopia (≥ -6 diopters; >26.5 mm axial length).*
- *Giant retinal tear (i.e. presence of one or more retinal tears of ≥3 clock hours in size).*
- *Retinal dialysis.*
- *Participation in an investigational drug study.*
- *Declined consent for participation.*

7.3. Co-enrolment Guidelines

Participants enrolled in investigational drug studies are not candidates for this study. Participants enrolled in other studies can take part in COMBAT provided that their participation will not jeopardise their participation in COMBAT. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

8. TRIAL TREATMENT

8.1. Trial Intervention and Comparator

Eligible patients will be offered participation in the COMBAT study. If they consent, they will be randomised (1:1) to the intervention or comparator group.

Intervention: Phacovitrectomy

Participants will undergo phacovitrectomy to remove the lens (phacoemulsification and intraocular lens implantation) and to repair the RRD (vitrectomy). Based on the BEAVRS database, most vitreoretinal surgeons in the UK are not currently undertaking combined phacovitrectomy for RRD. Phacovitrectomy, however, is common practice for other retinal disorders such as macular hole. Although a phacovitrectomy is done in the same manner whether the condition to be treated is macular hole or RRD, the calculations required for the surgeon to select which intraocular lens should be implanted are different if there is a RRD with a detached macula. For this reason, a Standard Operating Procedure (SOP) will be prepared for the phacovitrectomy group to guide surgeons on how to best determine the intraocular lens under these circumstances (17). Vitrectomy with any gauge size (e.g.23g, 25g, 27g) will be allowed for the surgery, as per standard care at the participating site. The choice of the tamponade agent will be at the discretion of the treating vitreoretinal surgeon, as per standard care.

Comparator: Vitrectomy (Standard Care)

Participants will receive vitrectomy to repair their RRD. The vitrectomy would be done as per standard care. Vitrectomy with any gauge size (e.g.23g, 25g, 27g) will be allowed for the surgery, as per standard care at the participating site. The choice of the tamponade agent will be at the discretion of the treating vitreoretinal surgeon, as per standard care. Then, if a cataract develops, phacoemulsification and intraocular lens implantation will be done as per standard clinical practice.

8.2. Rescue Treatment

In either randomised group, if the surgery fails to repair the RRD (i.e. if the retina remains detached or if it attaches but then re-detaches), further surgery is allowed as per standard clinical practice. The surgery will be done as per standard clinical practice. Similarly, if complications occur, these would be treated as per standard clinical practice.

8.3. Treatment Adherence

At all participating sites, investigators should ensure that participants receive the intervention allocated by the randomisation (phacovitrectomy or vitrectomy) and be followed-up until trial completion (i.e. 52 weeks (+/- 6 weeks) after surgery). Investigators and the research study team should do their best to retain all participants until trial completion.

8.4. Post-Trial Care

After participants have completed the trial, arrangements for their future care will be as per standard practice within the NHS.

9. ASSIGNMENT OF TREATMENT

9.1. Sequence Generation

When a potentially eligible person with a RRD is identified, they will be informed about the COMBAT study. If they are willing to take part, informed consent will be obtained, and eligibility confirmed. If eligible, the baseline visit (see Data Collection section, below) will be undertaken (as soon as possible and before the surgery) and participants will be randomised (1:1) to receive phacovitrectomy or vitrectomy. An automated system with the allocation concealed to the ophthalmologist recruiting the participant will be used to generate the random allocation sequence. A minimisation algorithm will be used to ensure balanced allocation of participants across treatment groups for potentially important factors including centre, surgeon's experience (consultant/vitreoretinal fellow), presenting BCVA (BCVA ≥ 69 ETDRS letters [Snellen equivalent ≥ 20/40; logMAR ≥ 0.3], 24–68 ETDRS letters [Snellen equivalent ≤20/50-20/320; logMAR 0.4–1.2], <24 ETDRS letters [Snellen equivalent <20/320]); macular status (macula on & fovea on, macula off & fovea on, fovea off <7 days, fovea off 7-14 days, fovea off 15-30 days, fovea off >30 days); and presence/absence of PVR-C.

9.2. Allocation Concealment Mechanism

An automated system will be used to generate the random allocation sequence, which will conceal the allocation from the ophthalmologist.

9.3. Allocation Implementation

Sites will be provided with trial specific randomisation guidelines. Randomisation will be completed by an appropriately trained and delegated member of the research team. Each participant will be allocated their own unique trial identifier during the randomisation process, which will be used throughout the study for participant identification on all data collection forms and questionnaires. The patient's allocation will be provided only to unmasked staff (e.g. the surgeon, theatre team).

9.4. Masking

Optometrists obtaining the primary outcome measure will be masked to treatment allocation. Masked assessors will not have access to clinical information about the participant and only to blank worksheets, which they will be given to record pertinent data. The trial statistician, who has no role in decision-making with regard to the conduct of the trial, will be unmasked. This will facilitate linkage with the DMEC. The remainder of the trial team at the NICTU will be unmasked for the purposes of managing data collection, reviewing cases to assess protocol deviations, and safety reporting. Staff delivering treatments and participants receiving the treatments will not be masked to treatment allocation.

10. OUTCOME MEASURES

10.1. Primary Outcome Measure

Change in Best-Corrected Visual Acuity (BCVA) in the affected study eye from baseline to 52 weeks (+/- 6 weeks) after surgery (equivalence margin +/- 7 ETDRS letters).

10.2. Secondary Outcome Measures

All at 52 weeks (+/- 6 weeks) after surgery for all outcomes except *:

- *Primary anatomical success (proportion of eyes with an attached retina after one vitrectomy).*
- *Final anatomical success (proportion of eyes with an attached retina after two or more vitrectomies).*
- *Intraoperative complications (total number and by severity score). (18, 19).*
- *Postoperative complications (total number and by severity score). (18,19).*
- *Number and type of surgeries performed.*
- *Refractive error* (difference between aimed (sought) and obtained post-operative refraction 12 weeks after surgery in the phaco-vitrectomy arm and 6-8 weeks post-cataract surgery, if this takes place, as per standard of care, in the vitrectomy only arm).*
- *Proportion of participants with BCVA <69 letters*
- *Proportion of participants with BCVA <34 letters.*
- *Time to achieve 'best vision'.*
- *Change in BCVA from baseline over time.*
- *Health related quality of life measured using EuroQol-5 level (EQ-5D-5L) (20).*
- *Vision-specific quality of life measured using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) (21).*
- *Participant's experience, and acceptability of treatments.*
- *Use of health and social care services and non-health care costs.*
- *Safety*

10.3. Safety Outcomes

Participants will be assessed/asked at each visit, specifically about safety outcomes.
The following are specific intraoperative and postoperative complications of cataract surgery and will be recorded and reported on the study worksheets:

- Zonulodyalisis
- Iridodyalisis
- Posterior capsule rupture
- Posterior dislocated lens fragments
- Anterior and posterior synechiae (in clock hours)
- Optic capture and whether or not this resulted in subsequent problems
- Posterior capsule opacification
- Opacification of the intraocular lens

It will be recorded whether or not these previously listed complications are associated with patient's symptoms (e.g. photophobia) upon questioning the participant, and/or whether or not they lead to inability/difficulty to visualise the fundus by the investigator as a result. Other possible complications of cataract surgery (not listed above) will be captured in the CORDs complication list below (e.g. non-infectious uveitis, endophthalmitis).

In addition, safety outcomes related to the vitrectomy, will be recorded and reported following the CORDS classification below (18,19). Minor complications (scored 1 or 2) will not need to be reported.

Complication	Median
General intraoperative	
Subconjunctival hemorrhage	1
Chemosis	1
Subretinal hemorrhage not involving macula, ≤1 quadrant	3
Subretinal hemorrhage not involving macula, >1 quadrant	4
Suprachoroidal hemorrhage not involving macula and no kissing[a]	5
Subretinal hemorrhage involving macula, ≤3 disc areas	7
Subretinal hemorrhage involving macula, >3 disc areas	8
Suprachoroidal hemorrhage involving macula or kissing	9
General postoperative	
Subconjunctival hemorrhage	1
Chemosis	1
Refractive changes: <2-dimensional	2
Early raised IOP, self-resolving	2
Early hypotony, self-resolving	2
Serous choroidal detachment: peripheral	3
Persistent localized subretinal fluid: peripheral, nonprogressive	3
Visual field loss not related to retinal detachment but attributable to surgical procedure: not affecting driving license	4
Refractive changes: ≥2-dimensional	4
Persistently raised IOP manageable with drops	4
IOL displacement	4
Macular edema	4
Suprachoroidal hemorrhage: not involving macula and no kissing	5
Persistent localized subretinal fluid: submacular	5
Loss of visual acuity attributable to surgical procedure: moderate (3-5 lines ETDRS chart)	6
Persistent hypotony (IOP <5 mm Hg) without macular folds	6
IOL dislocation	6
Macular hole formation	6
Visual field loss not related to retinal detachment but attributable to surgical procedure: affecting driving license	7
Corneal decompensation/severe corneal edema	7
Persistently raised IOP requiring surgery	7
Serous choroidal detachment: large, kissing	7
Retinal redetachment owing to new or worsening PVR	7
Loss of visual acuity attributable to surgical procedure: severe (≥6 lines on ETDRS chart)	8
Persistent hypotony with macular folds	8
Suprachoroidal hemorrhage: involving macula or kissing	9
Endophthalmitis	9
Sympathetic ophthalmia	9
Phthisis	10

PPV intraoperative	
Unintended enlargement of sclerotomy	2
Leaking ports at the end of surgery requiring suturing	2
Small bubble formation when inserting PFCL	2
Cataract development intraoperatively (owing to lens touch): without capsular breach	4
Iatrogenic retinal tears	4
Suprachoroidal infusion	5
Subretinal infusion[a]	5
Cataract development intraoperatively (owing to lens touch): with capsular breach	5
Vitreoretinal incarceration in sclerotomy	5
Intraoperative displacement of PFCL under the retina	6

PPV postoperative	
Anterior displacement of tamponade agent: PFCL	3
Leaky sclerotomy requiring suturing	3
Anterior displacement of tamponade agent: silicone oil	4
Emulsification of tamponade agents	4
Macular folds: not involving fixation	4
Noninfectious uveitis	4
Incomplete removal of tamponade agent	5
Retinal slippage	6
Subfoveal PFCL	7
Subretinal displacement of silicone oil and heavy silicone oils	7
Unexplained visual acuity loss associated with insertion/removal of silicone oil	7
Maculopathy related to light toxicity	7
Maculopathy related to dye toxicity	7
Macular folds: involving fixation	7
Retinal redetachment owing to new tear formation	7

10.4. Definition of Study Eye

The unit of randomisation will be the participant, not the eye. In participants presenting with RRD in both eyes, if both eyes are eligible, the “study eye” will be the eye with the best BCVA. If both eyes have the same BCVA, the study eye will be, arbitrarily, the right eye. If both eyes are eligible, the fellow eye would be treated, if possible, in the same way as the study eye. For instance, if both eyes of a patient are eligible and the randomisation allocates vitrectomy for the study eye, the fellow eye would receive vitrectomy too, if possible. This would apply also if the fellow eye does not have a RRD at presentation but develops it during the trial period (i.e. the participant will be offered the same type of surgery in the fellow eye to that received in the Study Eye, provided that this is pertinent and the participant is agreeable).

11. SCREENING, CONSENT and RECRUITMENT

11.1. Recruitment Strategy

COMBAT will include at least 30 sites across the UK. Large and small units across the four nations have been invited to take part in COMBAT to ensure full recruitment and applicability of the results to general practice across the UK. Considering that urgent vitreoretinal cases and specifically RRD are

currently done by vitreoretinal fellows in the UK, vitreoretinal fellows will be allowed to take part in the trial.

Potentially eligible participants will be identified by members of the direct care team from urgent optometry referrals, from Eye Casualty and from Retina and Vitreoretinal clinics at participating sites. A member of the COMBAT team will then meet with potential participants who express interest in taking part in COMBAT in order to give verbal and written details about the trial, including the Participant Information Leaflet (PIL). An audio version of the PIL will be made available where required. If a participant is eligible and provides informed consent, they will be enrolled in the trial. As part of the consent process, patients will be asked if they agree to be invited, at a later date, to take part in a series of 3 (maximum) interviews. Participants will also be asked if, following completion of their participation in the COMBAT trial, data collected as part of their standard care, can be used for future follow-up research.

11.2. Screening Procedure

Participants will be screened against the eligibility criteria specified in this protocol. All screening data will be recorded via electronic data capture (EDC) which must be completed by the Principal Investigator (PI) or designee to document all participants screened for the study and all participants recruited. Participants screened and not recruited to the study will be documented via EDC, including reasons for not being enrolled. A minimal dataset will be recorded for these non-recruited patients which will include Age, Sex at Birth, Sexual Orientation, Ethnicity, Preferred language, Socio-economic Status (e.g. Employment Status, Education level) and partial post code (with the exception of those in Scotland) to determine if there are differences with those willing to participate and recruited. Consent will not be requested to collect this full minimal dataset as data is fully anonymised and is partially collected as part of standard care. Where these data are not routinely collected, participants will be provided with a brief questionnaire and consent will be implied by its completion and return.
The PI or designee will be required to submit screening data to the NICTU at set time points.

11.3. Informed Consent Procedure

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible participants may only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific interventions.

A COMBAT PIL will be co-produced by the COMBAT PPI Group and research team. This will contain brief and clear information, in plain English, about the purpose of COMBAT and what will happen if the person wishes to take part in the trial. The NICTU will provide COMBAT PILs approved by the REC, to all sites. The PI or designee will be responsible for ensuring that all participants are given a copy of the PIL and allowed adequate time to review it and the opportunity to ask any study related questions. All participants should have the capacity to self-consent. This should be judged by the PI or the designated member of the study team who will have the responsibility for taking consent. An audio version of the PIL and PILs in languages other than English will be available so that, even if potential participants prefer an audio version or do not understand English, they will be able to read about COMBAT and to join the study, if they wish. This will be highlighted to all sites to support diversity of recruitment.

Informed Consent Forms (ICF) approved by the REC will be provided to all sites by the NICTU. The PI or designee is responsible for ensuring that the ICF is signed and personally dated by the participant before any trial interventions are administered. If consent is not given, a patient cannot be recruited into the trial.

Two copies of the ICF must be signed and personally dated by the participant and the individual taking consent. The signed ICF will either be uploaded to the electronic case records (if the site uses electronic patient records) or filed in the patient's medical notes (if the site uses paper medical records). One signed ICF will be retained by the participant and the other will be kept by the site in the Investigator Site File (ISF).

Following recruitment of a patient, the PI or designee will issue a letter to the participant's General Practitioner (GP) to inform them that their patient is participating in the study, if this is approved by the participant.

11.4. Withdrawal of Consent

Participants may withdraw their consent from the trial at any time without prejudice. If consent is withdrawn, this will be documented in the participant's medical notes and in the CRF. In the event of a request to withdraw from the study, anonymised data recorded up to the point of withdrawal will be included in the study analysis.

COMBAT participants taking part in interviews will be informed that withdrawal of their interview data will not be possible once the interviews have been transcribed.

12. SCHEDULE OF ASSESSMENTS

12.1. Participant Schedule

The frequency of assessments and follow up specifically for the trial are detailed in the schedule of assessments in Table 2. The time points are based on the date of surgery which, ideally, should be the same day as the date of randomisation. The schedule defines the timing of assessments necessary for data collection. Participants will be followed until the final follow up assessment at week 52.

Procedures	Baseline/Screening	Day of Surgery	Week 1 (+ 1 week)	Week 6 (+/- 1 week)	Week 12 (+/- 2 weeks)	Week 52 (+/- 6 weeks)
Informed Consent	X					
Confirmation of eligibility	X					
BCVA[+]	X			X	X	X
Fundus examination	X*		X	X	X	X
Biometry & Focimetry	X					
Aimed refraction[~]	X					
EQ5D-5L, NEI VFQ-25 Questionnaires	X			X	X	X
ModRUM					X	X
Patient Cost Questionnaire					X	
Acceptability Survey						X
Semi-structured interviews				X	X	X
Randomisation	X					
Surgical details		X[@]				
Achieved refraction[~]				X	X	X
Adverse events (including intraoperative and postoperative complications)	X	X	X	X	X	X
Completion of Worksheets	X	X	X	X	X	X

Table 2. Schedule of Assessments

+ At week 1, visual acuity will be measured as per standard clinical practice by a non-masked member of the team. At all other visits (baseline, week 6, week 12 and week 52) full refracted BCVA will be obtained by an optometrist who is masked to the patient's allocation.

* Recording the following characteristics of the RRD: macula on/macula off; extension (number of quadrants affected: 1, 2, 3 or 4); total number of retinal tears present; number of breaks of $\geq$1 clock hours in size; presence/absence of PVR-C; presence/absence of inferior (from 4:00-8:00 clock hours) retinal tears in detached retina; @ = Characteristics of the RRD (as outlined above) to be confirmed (or ruled out) intraoperatively.

~ All participants will have biometry prior to surgery and the "aimed refraction" determined. In the phacovitrectomy arm, the "achieved refraction" determined at week 12 will be used to estimate the "refractive error" (secondary outcome). In the vitrectomy only arm, the "achieved refraction" used to estimate the "refractive error" (secondary outcome) will be that obtained at 6-8 weeks post-cataract surgery, if this takes place. Surgeons will be allowed to repeat the biometry prior to cataract surgery in the vitrectomy only arm, if this is part of their standard of care, and determine again their "aimed refraction"; this latter "aimed refraction" will be used to calculate the "refractive error" (secondary outcome).

BCVA = best-corrected visual acuity; RRD = rhegmatogenous retinal detachment; PVR = proliferative vitreoretinopathy; EQ-5D-5L = EuroQol - Five Dimension - Five Level; ModRUM = Modular Resource Use Measure, NEI-VFQ-25 = National Eye Institute Visual Function Questionnaire.

Participating sites are advised to ensure that follow-up appointments are scheduled in a timely manner and that visits take place within the study windows (this is plus one week for visit at week 1, and +/- one week at week 6, +/- two weeks for visit at week 12 and +/- six weeks for visit at week 52).

12.2. Demographics

Demographics including Date of Birth, Sex at birth, Sexual Orientation, Ethnicity, Preferred Language, Family Context, Socio-economic Status (e.g. Employment Status, Education level) and post code will be recorded for recruited participants. The proportion of participants in the demographic groups will be monitored throughout the study to try to ensure a diverse population is recruited into the COMBAT study.

12.3. Previous Medical and Ophthalmic History

Researchers should check the medical and ophthalmic records of the participant to ensure that the study eye had not had previous surgery for a RRD (i.e. that it is an eye with a RRD naïve to previous vitreoretinal surgery) and that it is not a highly myopic eye (these would be reasons for exclusion).

12.4. Clinical Outcomes

Best-Corrected Visual Acuity (BCVA)

The primary outcome is change in BCVA from baseline to 52 weeks (+/- 6 weeks) after surgery in the study eye. There is no consensus on the core outcomes to be measured in trials for RRD but BCVA is routinely measured in the standard care of patients with RRD and in ophthalmology trials. It is considered, together with retinal reattachment, as a main outcome of surgical success in clinical practice. BCVA closely relates to patient-reported quality of life. Full-refracted distance BCVA will be measured in both eyes using the ETDRS Visual Acuity charts at 4 meters by masked optometrists/ophthalmologists at baseline and at week 6, 12 and 52 after surgery, following the COMBAT SOP.

Note: If the surgery takes place more than three days after the baseline assessment, or if the patient reports a change in their vision since the baseline assessment, the BCVA should be repeated before the surgery.

Retinal Reattachment

Patients will be evaluated using slit-lamp biomicroscopy with wide angle non-contact or contact lenses and/or indirect ophthalmoscopy, as per standard practice at participating sites, and the status of the retina (fully attached/detached) will be recorded in the appropriate CRF.

Intraoperative and Postoperative Complications

Intra- and post-operative complications will be prospectively recorded using CORDS (The Classification for the Reporting of Complications in Retinal Detachment Surgical Trials) (19), a robustly developed classification of complications of vitreoretinal surgery (18). Complications will be scored as per this classification and analysed. Intraoperative and postoperative complications of cataract surgery will be also recorded.

Furthermore, presence/absence of posterior capsule opacification (PCO) and performance of YAG laser posterior capsulotomy will be prospectively recorded during the trial in the appropriate CRF (Note: surgeons who routinely do posterior capsulectomy at the time of the phacovitrectomy will be allowed to do so in COMBAT, recording this procedure in the pertinent surgical CRF).

Number and Type of Surgeries Performed

The number and type (e.g. surgery for retinal re-detachment – i.e. if surgical failure occurs; cataract surgery; other) of surgeries performed throughout the trial will be recorded in the appropriate CRFs.

Refractive Error

For all participants, focimetry and biometry will be obtained at baseline by ophthalmologists, vitreoretinal fellows, optometrists, nurses or technicians, as done prior to cataract surgery at each participating site. The COMBAT SOP for the biometry and determination of the intraocular lens to be used in participants undergoing phacovitrectomy will be followed to determine the power of the intraocular lens to be implanted. Based on this, the aimed (sought) refraction planned to be achieved postoperatively will be recorded in the appropriate CRF. The aimed refraction will be compared with the achieved refraction, as obtained at the month 3 postoperative visit, to determine the refractive error in the phacovitrectomy arm. The refractive error will be also determined, as per standard practice (i.e. with the refraction obtained at 6-8 weeks post-cataract surgery), for those eyes of participants in the vitrectomy only group who subsequently receive cataract surgery.

Proportion of Participants with Different Levels of BCVA and Time to Achieve Best Vision

The proportion of participants with BCVA <69 and with <34 letters at 52 weeks (+/- 6 weeks) after surgery in the study eye will be recorded in the CRF and analysed. Similarly, the time to achieve ‘best vision’ in the study eye will be also determined and analysed. This will be defined as the best BCVA recorded at the earliest time point during the trial (e.g. if a patient achieved a BCVA of 79 letters at week 6, and no higher at any other time point [i.e. remained 79 at 12 and 52 weeks], their “time to achieve best vision” will be 6 weeks).

12.5. Patient Reported Outcomes and Health Economics Study Instruments

EuroQol-5 Dimension-5 Level (EQ-5D-5L)

The EQ-5D-5L (20) is a generic preference-based measure of health, which provides a description of health using five dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each with five levels of severity. Responses can be converted to an overall utility score and used to calculate quality adjusted life years (QALYs). Respondents are also asked to place their health on a visual analogue scale where 0 represents the worst imaginable health state and 100 the best imaginable health state.

National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

The National Eye Institute Visual Function Questionnaire (NEI VFQ-25) will be used to provide vision specific patient-reported quality of life (QoL) (21). The NEI VFQ-25 is a validated questionnaire that has been used widely to evaluate visual outcomes in patients with eye diseases including RRD. In addition to eliciting information about general health and vision, it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision.

The above tools will provide a comprehensive evaluation of health-related and vision-related quality of life at baseline, and at 6, 12 and 53 weeks post-surgery. This will allow examination of a potential “response shift” that may occur over time. Response shift occurs when an individual reports their QoL

at two (or more) points in time but does not use the same frame of reference on each occasion, thereby distorting the comparison of QoL over time. Questionnaires will be self-completed by participants with large font questionnaires used when required.

In addition to the standard 25 questions contained in the NEI VFQ-25 questionnaire, we will include a question aimed at assessing the perceived change in QoL by the participants from preoperative levels. This question will be added at each time point this questionnaire is administered, except at the baseline visit. We will be asking participants how much they perceive their QoL to have changed since before they had their surgery [with potential answers being “much better”, “slightly better”, “about the same”, “slightly worse”, “much worse”]. Answers to this question would allow anchoring QoL data with visual outcomes data.

ModRUM (Modular Resource Use Measure)

The ModRUM (22) will be used to measure a participant’s use of healthcare relating to their eyes. The ModRUM is a validated, concise, generic, measure designed to collect self-report data on the healthcare services people use in UK-based studies Questionnaires will be self-completed by participants with large font questionnaires used when required.

Patient Cost Questionnaire

A questionnaire will measure the out-of-pocket costs to the participant when they attend hospital appointments relating to their eyes and the impact on their ability to work or undertake usual activities. Questionnaires will be self-completed by participants with large font questionnaires used when required.

Participant Experience and Acceptability

A mixed methods evaluation of participant experience and treatment acceptability will be undertaken. This will include serial semi-structured interviews, which will be conducted with a selection of participants from participating sites across all UK nations, at week 6, 12 and 52 post-surgery. Serial interviews will allow us to explore different facets of participant experience and variation over time, to cross-check information received at different interview sittings, and to understand how perceptions change and are recalled (or are re-constructed) for individual participants over time. Participants will be purposefully selected from both randomised groups on the basis of key demographic variables (including Date of Birth, Sex at birth, Sexual Orientation, Ethnicity, Preferred Language, Family Context, Socio-economic Status (e.g. Employment Status, Education level) and post code. Sample size will be determined by data saturation, but for adequate diversity in key characteristics across sites, we estimate interviewing approximately 20 participants, at 3 (maximum) time points each. The interview schedule will be informed by input from the COMBAT PPI group and will be designed to explore/identify:

i. Participant experiences of treatment over time, and factors influencing these experiences.
ii. Treatment characteristics, consequences and outcomes that are important to participants, and how these vary over time.
iii. Participant perceptions about the impact of treatment on their quality of life, including influences on physical, social, and emotional functioning, relationships, employment, civic and recreational activities.
iv. Acceptability of treatments (informed by Sekhon’s framework (23)) including participants’ perceptions of effectiveness, burden, affective attitude to the treatment, coherence/understanding of the treatment, and self-efficacy.
v. Treatment preferences.

The Theoretical Framework of Acceptability (TFA) Questionnaire

The interview data will also inform the adaptation of the generic Theoretical Framework of Acceptability (TFA) questionnaire, to generate a study specific acceptability questionnaire as recommended by the TFA authors (23). This (cross-sectional) questionnaire will be administered to all participants at week 52 post-surgery to compare patient-reported experience of treatments on the basis of key domains of acceptability.

12.6. Process Evaluation with the Purpose of Informing Implementation

A process evaluation focused on the provider perspective of phacovitrectomy will be carried out as part of the COMBAT trial, in accordance with the MRC framework guidelines (24), to assess how the

treatment pathways were delivered, barriers and facilitators to implementation, and the influence of local service and wider contexts in implementing phacovitrectomy. This is a necessary step, strongly recommended by the MRC, to facilitate subsequent scaled implementation, and avoid the risk that, even if the trial has positive findings, it leads to moderate or poor uptake and fails to impact adequately on clinical practice, both in the UK and beyond.

Firstly, semi-structured, theory-driven interviews will be carried out with multidisciplinary groups of healthcare providers, including surgeons, nurses and service managers. These will start 6-12 months after a site starts recruitment to the COMBAT trial, allowing them to develop a level of familiarisation with the service. At the start of recruitment to the trial, these staff will be asked to record important items they needed to put in place at their site to allow implementation of trial procedures (e.g. training of staff to carry out biometry on people with macula-off RRD). Data collection will be guided by the updated Consolidated Framework for Implementation Research (CFIR) (25), which allows systematic study of barriers and drivers to intervention implementation. The topic guide will address how the phacovitrectomy pathway is locally implemented, the implementation process and the people involved in it, including communication with patients, service alterations, and impacts on surgical or other workloads within the sites. Secondly, a structured analysis of the required skills and resources and wider strategies used to introduce phacovitrectomy and support implementation over time will be carried out by a study researcher using the ERIC framework (Expert Recommendations for Implementing Change) (26). We expect that this will be done via a structured interview with the lead surgeons and other staff and service managers at each site. Together with the analysis of barriers and facilitators, and patient data about treatment experience and acceptability; this will assist the development of an implementation blueprint for phacovitrectomy by the end of the study, which would be ready for us if the COMBAT results favour phacovitrectomy and is likely to include for example strategies related to training staff to carry out biometry on people with macula-off RRD and to influence the attitude of surgeons towards phacovitrectomy for non-highly myopic, phakic, RRD.

13. DATA COLLECTION AND MANAGEMENT

13.1. Data Collection

Data collection forms (“trial worksheets”), will be provided to sites by the NICTU to collect all the clinical data required for the trial. The trial worksheets will be considered the data source for the trial and can be uploaded (if the site uses electronic patient records) or filed (if the site uses paper medical records) in the participant medical record. All clinical data will be transferred to the NICTU via a bespoke web based electronic case report form (eCRF).

Participant identification on the eCRF will be through their unique participant study number, allocated at the time of randomisation. Questionnaires will be given to participants by site research staff at visits for self-completion and returned to the NICTU for entry into the eCRF.

13.2. Data Quality

To ensure accurate, complete, and reliable data are collected, the CI and NICTU will provide training to site staff. Source data verification (SDV) will be completed by the NICTU to check the accuracy of entries on the eCRF against the source documents (i.e. worksheets) and adherence to the protocol. The extent of SDV to be completed is detailed in the Monitoring Plan.

Quality control will be implemented by the NICTU in the form of SOPs which encompass aspects of the clinical data management process and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements. Data validation will be implemented, and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

A DMEC will carry out reviews of the study data at staged intervals during the study.

13.3. Data Management

Trial data will be entered onto the eCRF by site staff, except for SAE & questionnaire data which will be entered by NICTU staff and interview data which will be collected by QUB designated research

staff. All data will be processed electronically as per NICTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within an agreed time period. All queries will be responded to and any amended information will then be entered in the study database.

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size

COMBAT is powered to demonstrate treatment equivalence for the primary outcome. Based on two one-sided t-tests at the 2.5% significance level, a 15.2-letter standard deviation (27) and an equivalence margin of +/- 7 ETDRS letters (with a difference of 7 or fewer letters being considered not clinically meaningful) (28,29), 248 participants would be required to be 90% sure the 95% confidence interval will exclude a difference in means of more than 7 ETDRS letters. Allowing for 10% dropout, we will require a minimum of 276 participants. This sample size will be sufficient to detect a difference of 16% in the rate of retinal reattachment surgery between groups, which is clinically relevant.

14.2. Data Analysis

Statistical Methods

As this is an equivalence trial for the primary outcome, the primary statistical analysis will be per protocol, but an intention-to-treat analysis will be also undertaken (30). The difference between randomised groups for change in BCVA (using 95% confidence interval [CI]) from baseline to week 52 post surgery) will be compared to the permitted maximum difference (PMD) of +/-7 ETDRS letters using an analysis of covariance model adjusting for baseline BCVA and minimisation factors. If the 95% CI of the treatment difference lies wholly within both upper and lower margins of the PMD, phacovitrectomy could be deemed equivalent to vitrectomy alone. A 7 ETDRS letter equivalence margin is not considered clinically important and could relate to test re-test variability (28,29).

A secondary analysis from baseline to week 52 post-surgery will be compared to the permitted maximum difference (PMD) of +/-7 ETDRS letters using two one sided 2-sample t-tests.

The primary analysis will use data from the study eye only. Analyses of categorical secondary outcomes will use general linear models (GLM) with adjustment for minimisation covariates. Relative risk, risk difference and odds ratio will be reported where possible. Analyses of continuous secondary outcomes will use ANCOVA adjusting for corresponding baseline and minimisation factors, as appropriate. For time to best vision, we will use two-sample t-test or non-parametric alternative based on distribution of the data. For change in BCVA over time, we will compare the Area Under the Curve between groups. Statistical significance for secondary outcomes will be based on two-sided tests with $p<0.05$ as the criterion for statistical significance.

The primary outcome will be analysed according to pre-specified subgroups (e.g. surgeon experience [consultant/vitreoretinal fellow]; macula/fovea on/off, presence of PVR-C; number of quadrants of detached retina, presence of inferior breaks in detached retina) by including the corresponding interaction term in the GLM and using 99% confidence intervals.

A sensitivity analyses will be conducted for the primary outcome; looking at change in vision, if surgery takes place more than 3 days after the baseline assessment.

Baseline characteristics, follow-up measurements (including occurrence of cataract surgery) and safety data will be reported using descriptive summary measures depending on scale of measure/distribution.

Rates of PCO and of YAG posterior capsulotomy will be analysed as per categorical outcomes by using GLM with adjustment for minimisation covariates. Relative risk, risk difference and odds ratio will be reported, where possible. We will undertake a sensitivity analysis on the basis of the performance (or not) of an intraoperative capsulectomy, if numbers allow, to explore the potential effect on outcomes of this manoeuvre. Participants will be consented for COMBAT researchers to review their medical records and establish contact with their optometrist to gather information about whether participants in the vitrectomy only arm receive cataract surgery and, if they do, whether YAG-

capsulotomy is undertaken after the trial ended. These data will be used to provide long-term outcomes with regard to cataract surgery, refractive error, and rates of YAG-posterior capsulotomy.

Missing Data

Every effort will be made to minimise missing baseline and outcome data and data queries will be generated for site staff as required to request missing information.

Standard approaches will be used to detect patterns in missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. We plan for the principal analysis to be based upon available case data with no imputation of missing values. Sensitivity analyses will be undertaken to assess the impact of missing data by imputing extreme values (lowest and highest), as stated above.

A detailed Statistical Analysis Plan (SAP) will be prepared and made publicly available before undertaking the final analysis.

Analysis of Quality of Life Data

Quality of life will be assessed at baseline and at different time points throughout the trial. We will investigate the impact and nature of response shift (changes in quality-of-life assessment due to changes in an individual's frame of reference rather than 'true change'). The nature of response shift (reconceptualization, reprioritization, and recalibration) will be examined using Oort's procedure (31,32). Response shift will be determined by examining changes in the model parameters over time: the value of error variances and intercepts for recalibration; factor loadings for reprioritization; and pattern of factor loadings for reconceptualization. A sample size of 200 is likely to achieve 80-90% power in the assessment of response shift using SEM (32). Thus, the sample size of COMBAT (276 participants) should be adequate to address this. Oort's Procedure involves four major steps: 1) Establish an appropriate measurement model of observed scores at two times of measurement; 2) Construct a model verifying the hypothesis of no response shift and compare its fit with the model from step 1 using the likelihood ratio test (LRT) to determine the global presence of response shift. 3) If there is evidence of response shift, conduct an iterative process (by relaxing one constraint at a time) starting from the model in step 2. Relaxing the constraints on error variances (non-uniform recalibration) will be performed first, followed by intercepts (uniform recalibration) and factor loadings (reprioritization), thus following a hierarchy in testing the different forms of response shift proposed in previous research. This will continue until relaxing a proposed constraint leads to a non-significant LRT. 4) Estimate a final model, in which differences in factor means are indicative of ''true change'' after accounting for response shift. SEM models will be fitted using a robust maximum-likelihood estimator with a Satorra-Bentler correction. A root-mean-square error of approximation (RMSEA) close to 0.05 and comparative fit index (CFI) of 0.95 will be used as indicators of good fit. The LRT will be considered significant if the p-value is <0.05.

Health Economics Evaluation

A within-trial cost-utility analysis will estimate the 52-week cost-effectiveness of phacovitrectomy compared with vitrectomy and subsequent cataract surgery. Current guidelines for conducting (33,34) and reporting (35) economic evaluations will be followed. A NHS and Personal Social Services perspective will be used for the base-case analysis. A secondary analysis will be undertaken from a broader perspective to include non-healthcare costs (e.g. productivity losses and out of pocket costs). Responses to the EQ-5D-5L (20) at baseline, 6,12 and 52 weeks (+/- 6 weeks) after surgery will be converted into utility scores calculated using the method recommended by NICE (33); at the time of writing this protocol, this is currently a model developed by Hernández Alava et al. (36). QALYs will be calculated using the area under the curve method. A secondary analysis will calculate utility scores and QALYs using responses to the EQ-5D-5L (primary measure) and the Visual Function Questionnaire-Utility Index (VFQ-UI)(37) (secondary measure). The latter uses responses from six items on the NEI-VFQ-25 (21). Health and social service resource use data will be measured from baseline to 52 weeks (+/- 6 weeks) after surgery using both the trial worksheets and the ModRUM (22) and will include, for example, surgery costs, ophthalmology, optometrist and other outpatient visits, and GP and nurse consultations. A study specific Patient Cost Questionnaire will collect non-healthcare costs to the participant. Unit costs from publicly available sources will be used (e.g. NHS

Reference Costs), for health and social care and will be inflated to current prices where necessary and presented in £ sterling. Missing data will be summarised, and patterns analysed. For the base-case analysis using a bivariate regression of costs and QALYs, results will be expressed as an incremental cost per QALY gained. Univariate sensitivity analyses will assess the uncertainty around key parameters (e.g. methods for imputing missing data, surgery time) and probabilistic sensitivity analysis will assess the uncertainty around the incremental cost-effectiveness ratio (cost per QALY) and facilitate the presentation of cost-effectiveness acceptability curves. Since this is an equivalence trial for the primary outcome, there may be similar health benefits between randomised groups, but costs may differ, and a long-term cost-comparison may be the most appropriate analysis. A Markov decision type model will be used to estimate any long-term cost-effectiveness by extrapolating costs and outcomes beyond the trial period if appropriate. The model will be populated by data from COMBAT supplemented with data from the literature and expert opinion. An annual 3.5% discount rate will be applied to any future costs and QALYs.

A detailed health economic analyses plan (HEAP) will be prepared and made publicly available before undertaking the final analysis.

Participant Experience and Treatment Acceptability

Qualitative data from interviews will be transcribed, and thematic analysis carried out (38) to identify, analyse and report patterns/themes within data, including temporal patterns. These qualitative data (from interviews conducted prior to 12 months) will also be used to provide study-specific items relevant to the seven components of acceptability defined by the TFA questionnaire. Scores on this questionnaire will be calculated and compared between trial arms.

Subsequently, we will use Pillar Integration Process (PIP) (39) to integrate findings from the qualitative and quantitative data. PIP is a systematic, analytical method created to integrate quantitative and qualitative data in a transparent manner, where the data has undergone an initial separate analysis. PIP will help to describe and account for patterns in quantitative assessments of patient experience, identify nuances and sub-group differences.

Nested Process Evaluation to Assess Implementation and Scalability Aspects Post-Trial

Qualitative data from interviews with providers will be transcribed verbatim, and subjected to theory-driven framework analysis, based on the CFIR framework domains. The analysis will seek to identify barriers and facilitators to implementation of phacovitrectomy as captured by the CFIR domains. The data will be examined for novel themes, which may not fit within the existing CFIR domains; these will be coded separately and included in the final synthesis. Similarities and differences across institutions/services and provider professional groups, amongst other factors, will be used to group findings. A novel CFIR-based coding framework for qualitative data, with associated coding graphs to visually illustrate strength of each domain as present in the findings and themes within each domain will be used. Our team developed and reported this methodology recently (40).

Structured interviews with surgeons and managerial personnel will inform the identification of implementation activities at the sites. These be mapped directly onto the ERIC implementation strategies framework (25). The reported activities will be coded onto one or more of the 73 ERIC-listed strategies. Any activities that do not match the ERIC framework will be added and included in the final synthesis of implementation strategies tailored to the service.

In the final step of the process evaluation, the emerged CFIR-coded barriers/drivers will be matched against the ERIC-coded implementation activities using the CFIR-ERIC matching tool, which is a software available through the CFIR framework website (https://cfirguide.org/choosing-strategies/). This matching will offer an initial determination of what kind of barriers are suitably addressed by what kind of implementation activities to inform the implementation blueprint that will emerge as a deliverable of these analyses.

Studies Within a Trial (SWATs)

The Cochrane methodology reviews of recruitment and retention for randomised trials found little evidence for strategies targeting underserved groups and what limited evidence is available is methodologically poor (41,42). Greater inclusion of underserved populations is also a NIHR Equality, Diversity and Inclusion (EDI) strategic priority and meeting this need will require evidence of the effects of strategies that might be used.

We will therefore include one observational ("SWAT A") and one intervention SWAT ("SWAT B) in COMBAT to target recruitment and retention of underserved groups. These will be registered on the SWAT repository. SWAT A will record the proportion in each of the demographic groups who are recruited and retained at each site. We will inform sites that we are monitoring recruitment to underserved groups and offer rewards to the best performing site teams over the recruitment period. We will also collect information over the course of the trial on how often the translated PIL are used and whether people for whom these are used are recruited and retained. SWAT B will evaluate whether an EDI-informed PIL increases the recruitment of underserved groups compared to the standard PIL. The exact content of the modified PIL is contingent on qualitative, diverse PPI work to be done during (around) the first year of the COMBAT study, but we envisage that the modified PIL will use terminology that addresses the importance and value of participants from diverse backgrounds being involved in research, without targeting any specific underserved group. Once the modified PIL is finalised it will be submitted to the ethics committee as an amendment for approval. COMBAT sites that are willing to take part in this SWAT will be asked to use the modified or the standard PIL, in random order. Participants will be randomised (1:1 using mixed block sizes) to either the SWAT intervention or comparator group by the COMBAT study statistician, who will generate the randomisation sequence. The appropriate PILs will be then placed in sealed opaque sequentially numbered envelopes in the order of this randomisation sequence by staff at the Northern Ireland Clinical Trials Unit (NICTU). The NICTU will then give the appropriate envelopes to each sites taking part in this SWAT. When offering the trial to potential participants, the COMBAT team at each site will give the next envelope containing the PIL as sequentially numbered by the NICTU and will record the number of the envelope given to each potential participant in the screening log.
Detailed procedures for the SWATs will be recorded outside of the study protocol and, together with a SWAT analysis plan, will be made publicly available prior to analysis in the COMBAT website.

15. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

15.1. Terms and Definitions

Adverse event (AE) reporting will follow the Health Research Authority (HRA) guidelines on safety reporting in clinical trials that are not of investigational medicinal products (non-CTIMP).

An AE is defined as any untoward medical occurrence in a participant in a research study, including occurrences which are not necessarily related to the administration of any of the research procedures. If serious, as per the definition below, it would be considered a serious adverse event (SAE).

An adverse reaction (AR) is defined as an AE that is deemed to be possibly, probably or definitely related (see table 3, section 15.3, below) to the study procedures (e.g. obtaining BCVA). If serious, as per the definition below, it would be considered a serious adverse reaction (SAR).

A **serious** adverse event (or reaction) (**SAE/SAR**) is defined as an untoward medical occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity; or
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator

Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. However, hospitalisations for a pre-existing condition, including elective procedures for conditions that have not worsened during the trial do not constitute a SAE.

15.2. Adverse Eventing Recording and Reporting

The AE reporting period for the trial begins upon consent and ends at week 52 (the last follow up visit). All reportable unexpected AEs/ARs and SAEs/SARs should be followed until they are resolved. If the event has not been resolved by the time of the participant's 52-week visit, it will be recorded as ongoing.

The PI or designee should record all directly observed AEs/ARs and those spontaneously reported by the participant in trial worksheets (which constitute the data source for the trial), which will then be filed or uploaded in the medical records of the participant, in accordance with GCP.

It is expected that many participants will experience events that are in keeping with pre-existing medical conditions rather than being related to the trial. Events associated with any pre-existing medical conditions that the participant may have when entering the trial will not need to be reported. The exception to this will be death: even if death occurs as a result of the participant's pre-existing condition, death should be reported as a SAE.

Refractive error will be studied in detail as an outcome of the trial. Thus, this will not be reported as an AE. All other, general or specific complications of pars plana vitrectomy, will be reported.

Potential visual field loss will be investigated and confirmed by obtaining a visual field in patients complaining of loss of peripheral vision at any point during the trial. If confirmed, visual field loss will be recorded in the corresponding worksheet.

Treatments used for complications occurring in CORDS will be recorded. If as a result of the occurrence of a complication a participant needs to be admitted to the hospital for treatment, this will be reported as a SAE/SAR.

Development/progression of a cataract in the vitrectomy group will be recorded and reported. Cataracts will be graded following the AREDS classification (16). Development of cataract will be determined when there is progression from no cataract (i.e. Nuclear Sclerosis [NS] and Posterior Subcapsular [PSC] and Cortical Sclerosis [CS] $\leq$ 1) to any cataract (i.e. NS and/or PSC and/or CS >1). Progression of cataract will be considered when there is progression from any cataract to higher stages (i.e. from 1 to any higher grade: 2 or 3) (16).

SAEs will be reported on the SAE form. SAEs should be reported to the NICTU within 24 hours of the investigator becoming aware of the event, by email to clinicaltrials@nictu.hscni.net. The site should not wait until all information about the event is available before notifying the NICTU. The NICTU will acknowledge receipt of the SAE form by email. Information not available at the time of the initial report must be sought and submitted to the NICTU as it becomes available. The NICTU will notify the CI of all SAEs reported.

A SAE occurring to a research participant will be reported to the main REC if the event was:

a) Related (i.e. SAR): that is, it resulted from administration of any of the research procedures, and
b) Unexpected: that is, the type of event is not listed in the protocol (or in the SmPC of any drugs used) as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to REC within 15 days of the NICTU becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website. The CI will include a report on the safety of participants in the annual progress report to REC.

15.3. Assessment of Causality

For unexpected AE/ARs the PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to any of the research procedures (Table 3).

Table 3. Categories of Causality for Adverse Events

Category	Definition
Definitely*	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably*	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
Possibly*	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of a research procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of a research procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not Related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

15.4. Assessment of Severity

For unexpected AE/ARs the PI or designee should make an assessment of severity according to the following categories (Table 4).

Table 4. Categories of Severity for Adverse Events

Category (Severity)	Definition
Mild (Grade 1)	The adverse event is easily tolerated by the trial participant, causing minimal discomfort and not interfering with everyday activities.
Moderate (Grade 2)	The adverse event is sufficiently discomforting to interfere with normal everyday activities.
Severe (Grade 3)	The adverse event prevents normal everyday activities.
Life Threatening (Grade 4)	The adverse event has life threatening consequences; urgent intervention indicated.
Death (Grade 5)	The adverse event results in death.

15.5. Assessment of Seriousness

The PI or designee should make an assessment of seriousness, i.e. does the event fulfil any of the following criteria:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

15.6. Assessment of Expectedness

The PI or designee should make an assessment of expectedness for AE/ARs (Table 5). The evaluation should be performed using the expected AE/AR listed above (see section 10.3: Safety Outcomes).

Table 5. Categories of Expectedness for Adverse Events

Expectedness	Definition
Expected	The AE/AR is listed in the protocol (section 10.3) as expected.
Unexpected	The AE/AR is not listed in the protocol (section 10.3)

Unexpected AE/AR and SAE/SAR should be reported in the appropriate AE/SAE forms.

15.7. Recording and Reporting of Urgent Safety Measures

If the PI, designee, or a member of study staff become aware of information that necessitates an immediate change in study procedure to protect trial participants from any immediate hazard, they should report the urgent safety measure immediately to the NICTU by phone and follow this up in an email to clinicaltrials@nictu.hscni.net.

The NICTU will report the urgent safety measure immediately to the CI and the Sponsor using the dedicated email addresses researchgovernance@qub.ac.uk & k.taylor@qub.ac.uk and will liaise with the Sponsor and site to implement immediate procedures to eliminate any hazard. The NICTU will report any urgent safety measure immediately by phone to the REC and will follow this up with an email within three days of becoming aware of the urgent safety measure.

The PI or designee should respond to queries from the NICTU immediately to ensure adherence to these reporting requirements.

16. DATA MONITORING

16.1. Data Access

The agreement with each PI will include permission for trial related monitoring, audits and ethics committee review, by providing direct access to source data and trial related documentation. Each participant's confidentiality will be maintained, and their identity will not be made publicly available, to the extent permitted by the applicable laws and regulations.

16.2. Monitoring Arrangements

The NICTU will be responsible for trial monitoring. The frequency and type of monitoring (on site, remote or both) will be detailed in the monitoring plan and agreed by the Sponsor.

Before the trial starts at a participating site, training will take place to ensure that site staff are fully aware of the trial protocol and procedures. Checks will take place to ensure all relevant essential documents and trial supplies are in place. Monitoring during the trial will check the accuracy of data entered into the CRF against source documents, adherence to the protocol, procedures and GCP, and the progress of participant recruitment and follow up.

The PI or designee should ensure that the monitor can access all trial related documents (including source documents (i.e. data collection worksheets) that are required to facilitate the Source Data Verification (SDV) monitoring process. The extent of SDV will be documented in the monitoring plan.

17. REGULATIONS, ETHICS AND GOVERNANCE

17.1. Regulatory and Ethical Approvals

The trial will comply with the principles of GCP and the requirements and standards set out in the UK policy framework for health and social care research. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a REC. The trial will be registered at https://www.isrctn.com before randomisation of the first participant.

17.2. Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval by the REC. Changes to the protocol may require ethics committee approval before implementation. The NICTU in collaboration with the Sponsor will submit all protocol modifications to the REC for review in accordance with the governing regulations.

17.3. Good Clinical Practice

The trial will be carried out in accordance with the principles of the ICH-GCP guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

17.4. Protocol Compliance

The investigators will conduct the study in compliance with the protocol given approval by the REC. A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented.

A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants in the trial; or
(b) the scientific value of the trial.

The PI or designee is responsible for avoiding serious breaches to occur and, in the rare event of their occurrence, to ensure that serious breaches are reported directly to the NICTU using the dedicated email address (clinicaltrials@nictu.hscni.net) within one working day of becoming aware of the breach. The NICTU will notify the Sponsor and CI immediately to ensure adherence to reporting requirements to REC where a serious breach has occurred.

Protocol compliance will be monitored by the NICTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs, participant consent) is being completed appropriately.

17.5. Participant Confidentiality

In order to maintain confidentiality, all CRFs, questionnaires, study reports and communication regarding the study will identify participants by their assigned unique trial identifier and initials only. Participant confidentiality will be maintained at every stage and participant details will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.6. Indemnity

Queen's University Belfast (QUB) will provide indemnity for any negligent harm caused to participants. QUB will provide indemnity for negligent and non-negligent harm caused to participants by the design of the research protocol by staff at QUB.

17.7. Record Retention

The PI will be provided with an ISF by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The PI is responsible for the archiving of essential documents at their site in accordance with the requirements of the applicable regulatory requirements, Sponsor and local policies. The PI has a responsibility to allow the Sponsor to access archived data, which can be audited by the Sponsor on request. Following confirmation from the Sponsor, the NICTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility. This must be documented in writing to the NICTU and Sponsor.

The TMF will be held by the NICTU in the BHSCT and the essential documents that make up the file will be listed in a SOP. On completion of the study, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the Sponsor.
The study data may be used in future research studies, and participants will be asked for their consent to allow this. All necessary ethical approval will be secured and in place where applicable for any future research studies.

17.8. Competing Interests

The CI of COMBAT, Professor Noemi Lois, has no conflicts of interest to declare. The members of the TMG have no financial or non-financial competing interests and the members of the DMEC and TSC will be asked to confirm that they have no conflict of interest. In the event that a DMEC or TSC member reports a conflict of interest, advice will be sought from the Sponsor. The research costs are funded by the NIHR HTA Programme.

18. DISSEMINATION/PUBLICATIONS

18.1. Publication Policy

The study will be used to inform participants and public, clinicians and policy makers of the best options available to treat people who present with phakic, non-highly myopic RRD.

The results of COMBAT will be disseminated widely through presentations at national and international ophthalmology meetings and in invited lectures. The results will be presented at participant group meetings. The COMBAT PPI Group will contribute to the dissemination efforts to ensure the results are available to participants, their families, and the public.

The research team includes lead clinicians and researchers with contacts across the world. They will use these international contacts to ensure trial results are disseminated widely and incorporated into future guidelines on the management of RRD.

COMBAT will be reported in accordance with the CONSORT guideline (43). If necessary, the CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances (CONSERVE) statement (44) will be applied if extenuating circumstances require major modifications to the trial. The protocol, SAP and HEAP will be made publicly available to ensure transparency in the methods used in the study.

In accordance with the open access policies proposed by the NIHR, we plan to publish the clinical findings of the trial as well as a separate paper describing the health economic findings in high quality, high impact, peer reviewed open access journals. Other papers are planned (e.g. to present data on patient experience and acceptability of the treatments, and the results of the SWAT, among others).

We will actively promote the findings of the study to journal editors and opinion leaders in ophthalmology to ensure findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. The most significant results will be communicated to the wider public through media releases. An ongoing update of the study will be provided on the NICTU website.

18.2. Authorship Policy

Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org).

18.3. Data Sharing Statement

Following publication of the primary and secondary outcomes and after data has been fully exploited by the COMBAT research team, there may be scope to conduct additional analyses on the data collected. In such instances, formal requests for data will need to be made in writing to the CI via the NICTU. If there are requests for data sharing, these will be reviewed on a case-by-case basis by the CI and NICTU with approval by the Sponsor required before data are shared.

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