Full title of trial	A phase 3 multi-centre double-masked randomised controlled trial of adjunctive intraocular and periocular steroid (triamcinolone acetonide) versus standard treatment in eyes undergoing vitreoretinal surgery for open globe trauma
Short title	**A**djunctive **S**teroid **C**ombination in **O**cular **T**rauma (**ASCOT**) Study
Version and date of protocol	Version 3.0 06/09/18
Sponsor:	Moorfields Eye Hospital
Sponsor protocol number	CHAD1031
Funder (s) :	NIHR – Health Technology Assessment (HTA)
EudraCT no	2014-002193-37
ACTIVE IMP(s):	Triamcinolone Acetonide
PLACEBO IMP(s):	Standard Care
Phase of trial	Phase 3
Sites(s)	Multi-site

Chief investigator:

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Senior Sponsor Representative:

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Signatures

The Chief Investigator and the R&D have discussed this protocol. The investigators agree to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

Chief investigator

David Charteris

Signature Date

Sponsor Representative

Maria Hassard

Signature Date

Contents

List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICTU	Imperial Clinical Trials Unit
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IOP	Intraocular Pressure
ISF	Investigator Site File
ISRCTN	International Standard Randomised

IVTA	Intravitreal Triamcinolone
MA	Marketing Authorisation
MEH	Moorfields Eye Hospital
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
PPV	Pars Plana Vitrectomy
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RAPD	Relative Afferent Pupillary Defect
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

Glossary of terms

Aphakia: Absence of lens inside eye

Applanation Tonometry: Method of measuring intraocular pressure

Endophthalmitis: Marked intraocular inflammatory response

Glaucoma: Visual loss associated with raised intraocular pressure

Hyaloid: Vitreous gel in the back chamber of the eye

Hypopyon: Settled collection of inflammatory cells in anterior chamber of the eye

Indirect ophthalmoscopy: Method of examining ocular fundus

Pseudohypopyon: Collection of material in anterior chamber mimicking inflammatory cells

Pseudophakia: Presence of artificial lens inside eye

Slit-lamp biomicroscopy: Examination of the eye using slit-lamp apparatus

Uveitis: Intraocular inflammation

Vitrectomy: Surgical procedure to remove the vitreous gel

1 Trial personnel

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2 Summary

Title:	A phase 3 multi-centre double-masked randomised controlled trial of adjunctive intraocular and periocular steroid (triamcinolone acetonide) versus standard treatment in eyes undergoing vitreoretinal surgery for open globe trauma
Short title:	**A**djunctive **S**teroid **C**ombination in **O**cular **T**rauma (**ASCOT)** Study
Trial medication:	Triamcinolone Acetonide (4mg/0.1ml IVTA and 40mg/1ml subtenons)
Phase of trial:	Phase III with internal pilot
Objectives:	The study aims to test the hypothesis that adjunctive triamcinolone acetonide, given at the time of surgery, can improve the outcome of vitreoretinal surgery for open-globe ocular trauma. The study will specifically analyse the influence of the study intervention on visual acuity, the incidence of retinal detachment and the development of scarring (proliferative vitreoretinopathy) in patients with open globe trauma. Side-effects and complications will be monitored and reported. Quality of life assessment will be undertaken on the study patients and a cost-effectiveness analysis carried out.
Type of trial:	Phase 3, double-masked, randomised, multi-site trial in patients undergoing pars plana vitrectomy following open globe trauma with an internal pilot
Trial design and methods:	A multi-centre phase III trial incorporating a two-stage internal pilot study to verify recruitment and retention rates. In total 300 patients will be recruited and randomly allocated to two treatment arms from 25-30 sites throughout the U.K. Both groups will receive standard surgical treatment and routine preoperative and postoperative treatment and care. The treatment arm will receive additional preoperative steroid combination (triamcinolone acetonide) consisting of 4mg/0.1ml into the vitreous cavity and 40mg/1ml subtenons. Participants and primary outcome assessors will be masked to treatment allocation. Postoperative examinations will not differ from the schedule followed for vitreoretinal cases and participants will be followed up for 6 months post-surgery. The primary outcome will be the proportion of participants with a clinically meaningful improvement in visual acuity in the study eye, defined as having a 10 letters or more difference between the ETDRS score measured at 6 months

	after initial surgery and at baseline. Removal of silicone oil, when used, (combined with cataract extraction + IOL implantation when applicable) will be planned for 3-5 months following study vitrectomy surgery unless contraindicated.
Trial duration per participant:	6 months
Estimated total trial duration:	42 months plus an additional 33 months extension
Planned trial sites:	Multi-site. 10 U.K. sites included in the internal pilot and 25-30 U.K sites for the main trial.
Total number of participants planned:	300
Main inclusion/exclusion criteria:	Inclusion: Adult subject with full thickness, open-globe ocular trauma undergoing pars plana vitrectomy Exclusion: Children, Pre-existing uncontrolled uveitis, Previous steroid induced glaucoma – (these patients are at risk of steroid related pressure rise and will be excluded), Pregnant or Breastfeeding females, Previous known adverse reaction to the IMP, Inability to attend regular follow up, Unable to give written informed consent, Current or planned systemic corticosteroid use of a dose above physiological levels (e.g. >10mg prednisolone)
Statistical methodology and analysis:	The primary analysis will be a complete case, ITT analysis. The effect of treatment will be assessed by comparing the proportion of participants between treatment arms who have a clinically meaningful minimum increase in visual acuity (VA) of 10 letters (ETDRS chart). The change in VA will be calculated by subtracting the total ETDRS score in the study eye at baseline from the 6-month follow-up score. The change in VA will be dichotomised into two groups: the baseline group which has a change in VA of less than 10, and the other group which has a VA change greater or equal to 10.A generalised linear model with change in VA groups as the outcome and study arm and baseline EDTRS as covariates will be fitted. The model will also incorporate a centre effect. The treatment effect estimate will be reported as an odds ratio and a difference in proportions of participants with an improvement in VA score of 10 or greater, with a two-sided 95% confidence interval and corresponding p-value. Results will be analysed at the 5% significance level.

3 Introduction

3.1 Background

Trauma is an important cause of visual impairment and blindness worldwide and a leading cause of blindness in young adult males [1].Globally it has been estimated that 1.6 million people are blind as a result of ocular trauma with 2.3 million suffering bilateral low vision [2]. Ocular trauma is the commonest cause of unilateral blindness in the world today with up to 19 million with unilateral blindness or low vision [2]. It is estimated that almost one million people in the United States live with trauma-related visual impairment [3]. Ocular trauma has extensive socio-economic costs - patients with open globe injuries lose a mean of 70 days of work [4]. In the United States work related eye injuries cost over $300 million per year (www.prevent blindness.org) this equates to an annual cost to the UK economy (for which no comparable data exists) of £37.5 million.

In the UK it is estimated that 5000 patients per year sustain eye injuries serious enough to require hospital admission and of these 250 will be permanently blinded in the injured eye [5]. Recent European studies document incidences of 2.4 and 3.2 per 100000 per year [6, 7] for open-globe injuries which suggests an annual incidence for the UK of between 1500 and 2000.

Ocular injuries which result in visual loss invariably affect the posterior segment of the eye and prevention of visual loss involves posterior segment (vitreoretinal) surgery. It is clear from recent published data that although vitreoretinal surgical techniques have improved, outcomes remain unsatisfactory and that development of the intraocular scarring response proliferative vitreoretinopathy (PVR) is the leading cause of this [8-11].

Proliferative Vitreoretinopathy (PVR)

Eyes sustaining penetrating or open globe trauma (OGT) are a group at high risk of severe visual impairment. Retinal detachment is common in these eyes and multiple surgical interventions are often necessary. PVR is the commonest cause of recurrent retinal detachment and visual loss in eyes with open globe trauma. It is documented to occur in 10-45% of all OGT[8-11], its incidence varying with the nature of the penetrating injury [8].

Proliferative vitreoretinopathy (PVR) is a process of fibrocellular scar tissue formation which complicates 5-12% of cases of primary retinal detachment, 16 – 41% of giant retinal tears and 10 -45 % of cases of posterior segment trauma [12]. PVR represents a difficult vitreoretinal surgical challenge and although final retinal attachment may now be achieved in many cases multiple surgeries are often needed and visual results are frequently very poor [12, 13]. Binocular vision outcomes are notably unsatisfactory in PVR [14]. PVR management is costly in patient time and healthcare resources [13].

3.2 Preclinical data

Clinical observation and laboratory investigations undertaken on eyes with PVR and surgical specimens have identified potential targets for pharmacological adjuncts to its surgical management [14]. The cellular components of PVR peri-retinal membranes (RPE, glial, inflammatory and fibroblastic cells) proliferate and may also be contractile and are thus targets for antiproliferative agents. There is a notable inflammatory component to the PVR process with marked blood-retinal barrier breakdown and a greater tendency to intraocular fibrin formation [15]. Macrophages and T lymphocytes have been identified in PVR membranes [14] and, although relatively small in number, they may play an important role in membrane development and contraction through growth factor production. Thus both cellular proliferation and the intraocular inflammatory response are realistic targets for adjunctive treatments in PVR.

Steroid treatment can potentially influence both the inflammatory and proliferative components of PVR. Experimental work has suggested that the corticosteroid triamcinolone acetonide can reduce the severity of PVR [16]. In addition it has been demonstrated that periocular corticosteroids can reduce the severity of experimental PVR [17]. Laboratory work has also demonstrated that triamcinolone appears to have no significant retinal toxicity [18] although *in vitro* it downregulates the proliferation of retinal cells.

3.3 Clinical data

Clinically, intravitreal triamcinolone has recently been extensively used to treat macular oedema, intraocular inflammation and subretinal neovascularisation without demonstrable retinal toxicity but with a notable incidence of raised intraocular pressure and cataract. Previous small scale, uncontrolled clinical studies of PVR have suggested that systemic prednisolone [19], infused dexamethasone [20] and intravitreal triamcinolone [21-23] may reduce the severity of PVR although none of these studies was of sufficient power to provide a definitive answer.

3.4 Rationale and risks/benefits

The proposed project is a phase 3, multicentre, randomised clinical trial to test the hypothesis that adjunctive steroid (triamcinolone acetonide) given locally at the time of surgery, can improve the outcome of vitreoretinal surgery for open-globe trauma (both visually and anatomically). Open-globe ocular trauma complicated by intraocular scarring (proliferative vitreoretinopathy, PVR) is a relatively rare, blinding, but potentially treatable, condition for which at present surgery is often unsatisfactory and visual results frequently poor. To date, no pharmacological adjuncts to surgery have been proven to be effective. Analysis of the costs and economic effectiveness of the trial intervention will also be carried out.

3.5 Assessment and management of risk

For the purposes of this study, triamcinolone acetonide is being used outside the terms of its license.

Risk/benefit analysis:

We have classified this trial as Type A = No higher than the risk of standard medical care (ADAMON project classification).

Triamcinolone acetonide has been used off label in clinical ophthalmic practice for many years. Ophthalmologists have experience of its periocular administration for over 50 years, with administration via the intraocular route adopted for over 30 years. It has been used to treat a variety of posterior segment ocular inflammatory pathology [24-27].

Its use as an intraocular surgical adjunctive tool for visualisation of the posterior hyaloid during pars plana vitrectomy has been well established [28]. Additionally, intraocular triamcinolone has been found to reduce postoperative inflammation following vitrectomy surgery [29].

It has been investigated specifically to determine its effect on vitreoretinal scarring (PVR) with varying success [21-23].

It has an extremely well documented safety profile with the commonest significant side effect recorded as elevated intraocular pressure (IOP) [30]. Unpublished data from the pilot study [31] performed at the principal site, found a similar incidence of elevated IOP between both groups; 35% (n=7) in patients who received IVTA compared to 25% (n=5) in those patients who received standard care.

An audit of study sites revealed that over half (54%) of sites have used intraocular triamcinolone in vitrectomy surgery following open globe trauma, with 25% of sites using it routinely in this patient population.

The investigators feel that there is extensive clinical experience with the product and have no reason to suspect a different safety profile in the trial population.

4 Objectives

Primary: To determine whether adjunctive intraocular and periocular steroid (triamcinolone acetonide) improves visual acuity at 6 months compared to standard treatment in eyes undergoing vitreoretinal surgery for open globe trauma.

Secondary: To determine whether adjunctive intraocular and periocular steroid (triamcinolone acetonide) influences the development of scarring (proliferative vitreoretinopathy), retinal detachment, intraocular pressure abnormalities and other complications in eyes undergoing surgery for open globe trauma. In addition to assess the effects of treatment on quality of life measured using the EQ-5D, VFQ25 tools.

5 Trial design

5.1 Overall design

The study is a multicentre, prospective, individually randomised, patient and outcome assessor masked controlled trial that will test superiority of the intervention at 6 months. The trial design has been formulated in consultation with the accredited CTU unit at King's College London, a trial statistician, a methodologist at the Research Design Service and patients who have suffered severe ocular trauma. 25-30 vitreoretinal surgery centres throughout the UK have agreed to take part. 300 adult patients with open-globe trauma will be randomised 1:1 to receive adjunctive intraocular and periocular steroid (triamcinolone acetonide) versus standard care (surgery without adjunctive treatment). Operating surgeons will be masked until the end of surgery (when the adjunct is given) patients and primary outcome observers will be masked throughout.

A structured internal two stage pilot study with clear stop/go criteria is included and will ascertain recruitment and retention rates in 10 selected sites representing the differing types of study centre. Progression criteria from the internal pilot study will determine the decision to undertake the main trial and data from this pilot will contribute to the final analysis.

The primary outcome is the proportion of participants with a clinically meaningful improvement in corrected visual acuity in the study eye, defined as having a 10 letters or more difference between the ETDRS score (measured using validated ETDRS vision charts at a starting distance of 4 metres) measured at 6 months after initial surgery and at baseline. The sample size is based on detecting a 19% increase (55% to 74%) in the proportion of participants who have a meaningful minimum improvement in VA of at least 10 letter score, as measured by ETDRS vision charts. Secondary outcomes are **the ETDRS score at 6 months after surgery,** the development of scarring (proliferative vitreoretinopathy), retinal detachment, intraocular pressure

abnormalities and other complications in the study eye between initial surgery and 6 months after initial surgery. Quality of life assessments will also be undertaken using the EQ-5D, VFQ25 tools. Using this data, cost effectiveness and cost-consequence analyses to investigate the impact of injury and recovery will be carried out. Data collection will be undertaken at baseline (prior to initial study surgery), three months after initial surgery and six months after initial surgery.

Timetable : The project will run for 81 months with time allocated as follows: Months 0-5 project set-up, 6-73 patient recruitment (6-11 stage 1 internal pilot, 12 – 18 stage 2 internal pilot, 19-73 phase III), 74-79 final follow-up, 80-81 analysis, write up and results dissemination.

Initially 20 trial centres analysed the numbers of cases available for recruitment and this provided a total of 221 per year. A conservative assessment of recruited cases was taken as 110 per year (recruitment in the pilot study approached 100%) giving a total period to recruit the sample size of 300 cases over 33 months. Following trial set-up recruitment was closely monitored, (including an internal pilot phase) however recruitment figures were lower than anticipated. Up to November 2016 (recruitment month 24) 101 patients had been recruited, corresponding to 50% of the predicted 202 cases by this time point. Alternative strategies were therefore implemented, including the addition of more study sites and an extension of the recruitment period. An additional 33 months of recruitment were added to achieve to required sample size of 300 by month 73 (see section 14.2.2 for more details on revised projections).

6 Selection of Subjects

Patients with an open globe injury undergoing vitrectomy either as a primary or secondary procedure are the study population being investigated.

Open globe trauma (OGT) is classified as one of the following: a full thickness eyewall injury in the form of a rupture caused by a blunt object, laceration caused by a sharp object or an intraocular foreign body. Patients will be recruited at vitreoretinal outpatient or emergency clinics at 25-30 participating vitreoretinal surgical centres throughout the UK.

As the study intervention remains investigational, the worse injured eye in patients with bilateral eye injuries will be considered as the study eye for randomisation, and the better eye will receive standard treatment. We expect this to be a rare occurrence and are therefore not stratifying by binocularity.

6.1 Inclusion criteria

1. Adult subjects (Aged 18 years or over at the time of enrolment)
2. Full thickness, open-globe ocular trauma undergoing vitrectomy
3. Ability to give written informed consent
4. Willingness to accept randomization and attend follow-up for 6 months.

6.2 Exclusion criteria

1. Children (Age less than 18 years old at time of enrollment)
2. Pre-existing uncontrolled uveitis - Patients with pre-existing uveitis are likely to be rare in the study population however they have a pre-disposition to a more aggressive form of proliferative vitreoretinopathy and will therefore be excluded. (This does not include patients whose uveitis is secondary to their injury or retinal detachment)
3. Definitive diagnosis of previous steroid induced glaucoma – these patients are at risk of steroid related pressure rise and will be excluded (this does not include patients in whom a query of previous steroid-induced raised IOP has been postulated)
4. Pregnant or Breastfeeding females (Females of childbearing potential must be willing to use an effective method of contraception (hormonal or barrier method of birth control; true abstinence) from the time consent is signed until 6 weeks after their completion of the trial. Females of childbearing potential must have a negative urinary pregnancy test within 7 days prior to being registered for trial treatment (Subjects are considered not of child bearing potential if they are permanently sterile (i.e. they have undergone a hysterectomy, bilateral tubal occlusion, or bilateral salpingectomy) or they are postmenopausal)
5. Allergy or previous known adverse reaction to triamcinolone acetonide
6. Inability to attend regular follow up
7. Unable to give written informed consent
8. Current or planned systemic corticosteroid use of a dose above physiological levels (e.g. >10mg prednisolone)

7 Recruitment

The study is a multicentre trial involving 25-30 U.K sites. Ethically approved trial specific adverts will be distributed to all sites for display. Recruitment will be monitored closely at regular intervals and if required, additional sites may be employed.

Patient Identification Centres will be identified as the study progresses and confirmed prior to study commencement.

Refer to section 14.2.2

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

Informed consent will be taken by a suitably qualified and experienced individual who has been delegated this duty by the CI/PI on the delegation log. All site PIs will be GCP trained.

Rarely, eligible patients may present for emergency surgery out of hours or on occasions where the site PI or delegated individual is not on site. On this occasion informed consent may be taken by individuals who are GCP aware and familiar with key aspects of the study.

Informed consent will be obtained before any trial-specific procedures are completed i.e. those that are outside routine clinical care. Clinical findings documented during an ocular assessment that has been performed as part of routine clinical care may be used to populate the baseline CRF provided they are performed ≤ 14 days of the study intervention.

It is the responsibility of the Investigator, or a person delegated by the Investigator to obtain written informed consent from each subject prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

“Adequate time” must be given for consideration by the patient before taking part. The date when the patient information sheet (PIS) has been given to the patient will be recorded.

On occasions where emergency surgery is planned within 24 hours of patient identification, the investigator or designee will ensure that the patient is happy that they have been given ‘adequate time’ to consider their decision.

The Investigator or designee will explain the patients are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No clinical trial procedures will be conducted prior to taking consent from the participant. Consent will not denote enrolment into trial.

A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and subjects will be re-consented as appropriate.

8.2 Randomisation procedures

Randomisation is conducted via a telephone service to the ESMS Global service, intraoperatively. All randomised patients must first be registered on the study eCRF system. This is normally done by the study team prior to the patient going to theatre, but in some cases the randomisation service may also assign a study PIN if no member of the research team is available. This step can cause a few minutes delay to the process and so should be avoided where possible.

Appropriate study site staff must be delegated by the site PI to access the eCRF system and submit patient details to acquire a study PIN, enter patient baseline and outcome data. This delegation must be documented in the site 'delegation of authority' form. The trial manager will submit a request for each user to access the system to the KCTU (ctu@kcl.ac.uk) and an individual login will be sent to the person. Requests will not be accepted if they are submitted to the KCTU directly by the recruiting site.

300 adult participants with ocular trauma will be randomised 1:1 at the level of the individual using the randomised permuted blocks of varying sizes with stratification by trial site.

Randomisation and subsequent treatment allocation are performed **intraoperatively** once the operating surgeon has confirmed that the retina is attached. Therefore, **prior to commencing the study vitrectomy**, we advise that the site PI or delegated individual follow the following process:

Where a study team member is available

Preoperative preparation for randomisation:

1) Patient is consented for study participation

2) Pre-operative eligibility criteria are satisfied (including negative urinary pregnancy test where relevant) and baseline assessments performed **including ETDRS vision**
3) Register the patient on InferMed MACRO eCRF to receive PIN
4) Identify staff member in theatre who will be responsible for making telephone call to obtain treatment allocation and confirm he/she is familiar with ESMS telephone number and has patient identifiers, MACRO PIN, stratification information and other details that must be communicated to the ESMS service
5) Theatre staff member locates 2 vials of the study IMP (triamcinolone acetonide 40mg/ml) to ensure availability for use depending on treatment allocation and to provide details to ESMS at randomisation

Intraoperative randomisation:

1) Operating surgeon confirms attached retina (i.e. final confirmation of eligibility)
2) Surgeon completes surgical procedure and confirms is ready to randomise
3) Theatre staff member telephones ESMS global on 0207 188 0300 and communicates the following information:
    i. MACRO PIN
    ii. PATIENT INITIALS
    iii. PATIENT DOB
    iv. STUDY EYE
    v. BASELINE PRIMARY OUTCOME SCORE i.e. ETDRS VISION
    vi. IMP BATCH NUMBER AND EXPIRY DATE OF BOTH VIALS
4) Treatment allocation revealed and communicated to operating surgeon **such that patient is unaware and remains masked (i.e. if under local anaesthetic)**
5) Surgeon administers IMP according to protocol depending on treatment allocation
6) The randomisation service will automatically generate confirmation emails to key site staff, masked or unmasked to treatment allocation, depending on the role of the study site staff. This will include site pharmacists.

The surgeon completes a treatment allocation form for ALL randomised participants (contained with the study pack) to confirm treatment allocation as either INJECTION GIVEN or INJECTION NOT GIVEN, along with the volume injected and returns this to the site pharmacy. For 'INJECTION GIVEN' participants, additional IMP information will be completed e.g. BN/EXP date/Dose administered. Pharmacy will retain this information until the end of the trial, when the trial manager will collect and reconcile this information to confirm all patients allocated to the injection received the injection and will communicate this information to the trial statistician.

Where a study team member is unavailable (usually out of hours only)

In the rare event that a participant is eligible for the study out of hours (overnight or at weekends) but their condition requires urgent treatment and a member of the research team is unavailable, the following process should be followed:

Physician attending patient to access the 'out of hours' ASCOT study pack

Physician to familiarise him or herself with consent process, GCP guidance and other relevant information

If patient is eligible and willing to participate, physician to obtain consent on ASCOT consent form and file the original in the ASCOT file for the study team to retrieve and the copy in the patient medical notes.

The physician must then telephone the ESMS emergency service pre-operatively and advise them that they will require an **ASCOT out-of-hours randomisation service**. The service will then request detailed information, available from the ASCOT out of hours study pack and the clinical records, including:

1) Name of recruiting site

2) Site identification number of recruiting site

3) Name of attending physician

4) Patient initials

5) Patient date of birth

The ESMS service will then allocate a MACRO PIN to the patient.

The treating physician must then ensure all the information required in the process above is available and the process should be followed as usual.

8.3 Masking and Unmasking

Masking:

Participants and primary outcome assessors will be masked to treatment allocation and will confirm their masking status in writing prior to measuring vision. These outcome assessors may consist of technicians, nursing staff or healthcare assistants who are familiar with measuring visual acuity using the ETDRS chart. A trial-specific SOP for measuring visual acuity will be prepared. The operating surgeon is masked up until the end of the study operation at the point of randomisation.

Within the first few days after IMP administration there is a possibility that the intraocular triamcinolone may migrate into the anterior chamber. This may appear as a pseudohypopyon and the clinical picture could mimic endophthalmitis.

It is expected that participants will be followed up in their treatment site. Operating surgeons will be encouraged to anticipate this occurrence and communicate this to the reviewing team in the immediate postoperative period.

However, it is possible (although unlikely) that a participant attends a unit other than their study site within the early postoperative period. In this circumstance a treating clinician should be made aware of the patient's treatment allocation if he/she suspects a diagnosis of endophthalmitis such that a) a patient is not subjected to unnecessary invasive interventions where the findings are that of an innocuous pseudohypopyon or b) urgent treatment is withheld under the false premise that the observed hypopon is a pseudohypopyon.

Emergency Unmasking:

The study code should only be broken for valid medical or safety reasons highlighted in the circumstance above where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the study site research team should remain masked.

The procedure(s) to be used for un-masking during and out of office hours by study physicians and other treating physicians will be as follows:

The code breaks for the trial are held by ESMS Global, Medical Toxicology and Information Services Ltd.

In the event that a treating physician needs to know whether the patient received active triamcinolone, in order to make the next treatment decision (i.e. only where such knowledge is necessary to treat the patient and where failure to deliver such treatment would cause harm to the patient) and regardless of whether that request is

coming from the site PI or a physician not involved in the trial, a formal request for unmasking must be made to ESMS. Local pharmacies should not provide the code break information, even where local staff may be aware of the treatment allocation.

If the person requiring the unmasking is not the CI/PI then, where possible (e.g. in office hours), that health care professional will be referred back to the study team where the patient can be appropriately assessed and the study team will request emergency code break if absolutely needed. The Chief Investigator will be consulted in advance of any emergency code break if possible but if not available, the most senior physician available at the recruiting study site should make the decision.

If the person requiring the unmasking is not the CI or site PI and it is not possible to contact the study team (e.g. over-night or at weekends), the ESMS service will also be used. All patients will be given an emergency card to present to their GP or hospital doctor in the event of a medical emergency and this card will advise them of the patients study number, details of the trial, inform them of the possibility that they have been given the study IMP and the emergency number to call if code break is needed. The treating physician will call the ESMS service, who will discuss the emergency and provide code break if needed. Where ESMS feel code break is not needed but the physician believes it is required, despite discussion, ESMS will attempt to contact the CI on his personal number provided to ESMS but if he is not contactable, or if the caller is adamant that the situation is so urgent the delay while trying to contract the CI would be detrimental to the patient, ESMS will break the code as requested. ESMS will then fax the KCTU with details of the call and this information will be passed to the Trial Manager and CI to follow up.

The Trial Manager will retain a log of emergency code breaks and will ensure the statistician is provided with this information at analysis. It will also be documented as appropriate at the end of the study in any final study report and/or statistical report.

The CI/Investigating team will notify the R&D office (acting on behalf of the Sponsor) in writing as soon as possible following the code break detailing the reasons for code break.

Unmasking for the submission of SUSAR reports:

All SAE reports will be assessed by the CI or appropriate GMC registered delegate.

In the event that the CI identifies a serious event which is unexpected in the context of the Summary of Product Characteristics of Triamcinolone and which the site physician and CI agree is possibly, probably or definitely IMP related, it is necessary to break the code for that patient before reporting Triamcinolone related events to the MHRA.

The decision to code break must be considered carefully.

The following procedure will be used to unmask for the submission of a SUSAR report to the regulatory agencies.

- The Chief Investigator or appropriate delegate will contact the ESMS service and request emergency code break.
- If the patient was on active treatment, the CI will liaise with the Sponsor office to prepare the CIOMS report
- If the patient was not on active treatment, the CI will advise the Sponsor that a potential SUSAR was detected but excluded and does not require reporting
- Where a SUSAR is reported, all site physicians and the DMC members must be notified. The DMC Chair will advise if a DMC meeting is required and will make recommendations to the TSC Chair where appropriate
- Where the patient was not on active treatment, the study site physicians need not be informed that the event was classified as a potential SUSAR if they are not already aware and the patient will continue with follow up assessments. The statistician will be made aware of the emergency code break
- Where the patient was on active treatment, the study site physicians at all sites must be informed that the event was reported as a SUSAR. Where possible, the patient will continue with follow up assessments since the treatment is only given once in this study and need not be made aware of the code break unless clinically necessary. Information about the code break should be restricted to staff not collecting primary outcome data where possible. The trial manager will work with the site to document whether this has been successful. The statistician will be made aware of the emergency code break

8.4 Screening Period

Patients who are invited to attend the hospital specifically for the purposes of screening will be asked to sign a written consent form by a member of the study team or delegated individual.

A full medical and ophthalmic history will be obtained to confirm eligibility. B scan ultrasonography may have been performed previously as part of routine clinical care to guide patient management and confirm the need for proceeding to vitrectomy

surgery. There is no restriction on timelines within which this investigation needs to have been performed in order to help determine eligibility for study enrolment.

a. Baseline assessment will occur within 14 days of the study intervention

b. During treatment and follow up phase, visits should occur within a stipulated time window (as highlighted in section 8.5) of the scheduled date.

c. Randomisation is the last procedure to be completed intraoperatively after final confirmation of eligibility.

Screening does not necessarily constitute enrolment.

Screen failures i.e. patients who do not meet eligibility criteria at time of screening may be eligible for rescreening subject to acceptable parameters (e.g. a patient who has sustained open globe trauma but there is uncertainty as to whether they will proceed to vitrectomy surgery).

8.5 Table of study assessments

The table below may be used as a guide and represents routine standard care. Patients may require fewer visits (for example if silicone oil tamponade is not used, or more frequent visits as their clinical need requires (e.g. re-operations etc.) The restrictions on time windows allowed for scheduled visits relate only to data entry points and are highlighted as shaded columns on the table (i.e. baseline, months 3 and 6)

	Screening	Baseline -14 to day 0	* Study PPV Day 0	Day 1	Day 10	Week 4- 6	Month 3 (+/- 4 weeks)	Month 3-5 ROSO Surgery (If used) (+/- 2 weeks)	ROSO Post-op Review	Month 6 (+/- 4 weeks)
Informed Consent	X									
Medical and Ophthalmic Histories	X	X	X							
Urinary Pregnancy test	X									
ETDRS VA		X					X			X
Biomicroscopic Ocular Examination		X					X	X	X	X
IOP		X					X	X	X	X
Health Questionnaires		X					X			X

(VFQ-25, EQ-5D-5L CSRI)										
eCRF		X	X				X			X
Adverse Event CRF										
Early Study Withdrawal										
Protocol Deviation										

Complete as required per participant

Key: * = IMP administration in treatment group, ETDRS VA = ETDRS visual acuity, IOP = Intraocular pressure, VFQ -25 = visual functioning questionnaire, , EQ -5D = euroquol health questionnaire, CSRI = contact service resource information CRF= case report form, PPV = pars plana vitrectomy, ROSO = removal of silicone oil

Shaded Columns =	**Data Collection Points (i.e eCRF COMPLETION REQUIRED)**
Black X =	Performed as part of routine NHS care
Red X =	Performed in addition to routine care as part of study

Screening/baseline may occur concurrently

8.6 Baseline Assessments

Baseline assessments will be performed within 14 days prior to the study vitrectomy. Data collected as part of routine clinical care may be used to populate the baseline CRF prior to informed consent but the patient will not be registered on the eCRF and no data will be entered onto the eCRF system until the patient has signed a consent form. The eCRF system will generate a unique study ID for all patients consented and screened to the study.

The following baseline assessments will be recorded: demographics (including sex, date of birth, ethnicity), laterality (left or right eye being the study eye), date of ocular injury, date of primary repair, best corrected ETDRS visual acuity in both eyes, injury classification, location of wound, Intraocular Foreign Body (IOFB) status, presence of RAPD, anterior segment status, intraocular pressure, lens status, vitreous cavity haemorrhage, retinal attachment status, the presence and grade of PVR. The method of data collection will be through a combination of medical history, applanation tonometry, slit-lamp biomicroscopy or indirect ophthalmoscopy, and intraoperative findings. Quality of life data will be collected using the ED-5Q and VFQ25 tools and a client service receipt inventory (CSRI) questionnaire.

8.7 Treatment procedures

The following medications are only administered to participants allocated to the treatment arm of the study:

1. 4mg/0.1ml triamcinolone acetonide administered into the vitreous cavity by the operating surgeon at end of procedure
2. 40mg/1ml of triamcinolone acetonide administered into the subtenons space at the end of the procedure (where subtenons anaesthesia is used for postoperative analgesia, surgeons will be requested to administer the local anaesthetic mid-procedure i.e. not concurrently with the IMP)

8.8 Subsequent assessments

See table in section 8.5

Participants' follow up will mirror the schedule of standard NHS care and the table in section 8.5 is a guide offering an expected schedule of visits. Data entry time points will be at: i) baseline, ii) study vitrectomy, iii) month 3 and iv) month 6 (refer to shaded columns in schedule of visits table section 8.5).

8.9 Laboratory procedures

None

8.10 Definition of end of trial

The trial will end on the date of the last 6 month follow up visit by the last participant.

8.11 Discontinuation/withdrawal of participants and 'stopping rules'

Participants will be withdrawn from the study if:

- The administration of an intraocular or periocular corticosteroid is deemed necessary by their consultant (the use of intraocular triamcinolone as a surgical adjunct to visualise the hyaloid is permitted in both groups, as it is subsequently cleared intraoperatively. The likelihood of therapeutic doses remaining at the end of the procedure is considered to be extremely low)
- They are commenced on systemic corticosteroids at a dose higher than physiological levels (e.g. >10mg oral prednisolone)
- They express a wish to do so

A withdrawal CRF including reasons for withdrawal and any follow-up information collected will be completed on subject withdrawal. Withdrawn subjects will not be replaced as attrition has been accounted for in the sample size calculation. Participants who wish to withdraw will be asked if they are willing to undertake visually acuity assessment at 6 months and supply other study data collected at this routine visit.
The trial might be prematurely stopped in the event where new evidence arises to suggest a significantly poorer outcome associated with trial treatment.
The DMEC will be responsible for monitoring the safety of participants throughout the trial and will make recommendations to the TSC, who will convene shortly after each meeting of the DMEC.

9 Name and description of all drugs used in the trial

9.1 Treatment of subjects

Investigational product/treatment

Triamcinolone Acetonide 4mg/0.1ml intravitreal cavity and 40mg/1ml subtenons (Kenalog, E.R. Squibb and sons)

No other preparations of triamcinolone may be used in the study.

No placebo is used. Standard care will be used as a comparator.

9.2 Concomitant medication

Participants who are on systemic steroid therapy of greater than physiological doses (e.g. >10mg oral prednisolone) will not be eligible for the study.

Participants will be advised to continue their routine concomitant medications throughout the study as there is an extremely low likelihood of the IMP reaching systemic concentrations high enough to cause interactions.

10 Investigational Medicinal Product

10.1 Name and description of investigational medicinal product(s)

Triamcinolone acetonide (Kenalog). The study will use the per-operative combination of (a) intra-vitreous cavity triamcinolone acetonide 4mg (0.1ml) and (b) sub-Tenons capsule (i.e. peri-ocular) triamcinolone acetonide 40mg (1.0ml) as adjunctive medication. Triamcinolone acetonide is commercially available as Kenalog (E.R. Squibb and sons) and widely used in posterior segment ocular disease to treat macular oedema and intraocular inflammation.

10.2 Name and description of each Non-IMP (NIMP)

The following non-investigational medicinal products (NIMPs) may be used by the subjects in both groups to their operated eye as part of their normal routine care:

Pre-operatively: pupil dilating drops may be instilled. Local policy on preoperative dilating agents will be followed but examples may include and are not restricted to, G cyclopentolate and G phenylephrine

Peri-operatively: Subconjunctival antibiotics will be administered at the surgeon's discretion in line with local pharmacy formulary e.g. Cefuroxime (Zinacef) 125mg or gentamicin in β-lactam sensitive individuals. Sub-conjunctival steroid injections may be administered at the surgeon's discretion e.g. 4mg dexamethasone or 4mg betamethasone

Post operatively; Routine postoperative topical antibiotics and cycloplegic drops may be used at the discretion of the operating surgeon e.g. G. Chloramphenicol 0.5% qds 2 weeks, g. Cyclopentolate 1.0% tds 1 week. Routine postoperative topical steroids

may be used at the surgeon's discretion e.g. G dexamethasone 0.1% or G prednisolone acetate 1% with a duration and frequency depending on the level of postoperative inflammation

The above NIMPs may be used as part of routine clinical care and are detailed in this protocol as a guide only. Local policy for pre-, per- and postoperative medications will be followed and remain at the discretion of the operating surgeon. These will be documented routinely in the medical notes/operative notes according to local site policy, but will not be recorded in the eCRF.

All NIMP suspected Adverse Drug Reactions (ADR) or side effects will be reported through the yellow card system, as per normal NHS practice, and not through the trial pharmacovigilence processes. This is the responsibility of the treating physician and not the study sponsor or CI.

10.3 Summary of findings from non-clinical studies

Refer to explanatory text of section 3.2

10.4 Summary of findings from clinical studies

Refer to explanatory text of chapter 3.3

10.5 Summary of known and potential risks and benefits

Refer to explanatory text of chapter 3.5 and 3.6

10.6 Description and justification of route of administration and dosage

Route: intravitreal cavity and subtenons (after port closure) to deliver drug as close to target tissue (retina) as possible and avoid systemic side effects i.e. local administration

10.7 Dosages, dosage modifications and method of administration

Triamcinolone Acetonide **4mg/0.1ml** – intravitreal cavity after ports closure

Triamcinolone Acetonide **40mg/1ml** – subtenons injection after ports closure

No dose modifications or deviations from administration.

10.8 Preparation and labelling of Investigational Medicinal Product

No trial-specific preparation or labelling will be required for the purposes of the study. Local pharmacy policy for sourcing and stocking of triamcinolone will be followed. It is anticipated that site theatres will routinely stock the IMP and an 'off the shelf' approach will be adopted.

10.9 Drug accountability

As IMPs are to be sourced from hospital stock, then each site should follow their own procedures for the shipment, receipt, distribution (if applicable), return and destruction of the IMPs. The trial manager will check that local procedures are in place (request for their SOPs and check).

Sites should record the Batch Number (BN) and Expiry (Exp) date as a minimum for all IMPs that are used. Used IMP vials will be disposed of as per local standard care but only after recording the expiry date and batch number in the medical notes and eCRF. The dose of IMP given by the surgeon will also be confirmed and recorded in the eCRF.

10.10 Source of IMPs including placebo

The IMP will be sourced from routine hospital stock and their handling and management will be subject to standard procedures of the site pharmacist. Sourcing of IMP is also discussed in the IMP management plan

No placebo drug is used for this study; standard care is used as the comparator.

10.11 Dose modifications

No dose modifications are anticipated as the IMP is administered on a single occasion at the time of the primary study vitrectomy

10.12 Assessment of compliance

N/A as IMP is administered by surgeon at the time of the primary study vitrectomy

Surgeons will be required to return a document to site pharmacy containing Batch Number, Expiry Date and Dose Given.

10.13 Post-trial IMP arrangements

Repeat administrations after the trial has ended are at the treating clinician's discretion. The IMP is commercially available in the UK but the use is unlicensed in

the eye, hence local procedures for administration will be followed and lie outside the remit of the investigating team.

11 Recording and reporting of adverse events and reactions

11.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to an investigational medicinal product which **is related** to any dose administered to that subject. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*

Term	Definition
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results 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
Important Medical Event	These events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered ‘serious’.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) in the case of a product with a marketing authorization, in

	the summary of product characteristics for that product, (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
SUSAR	Suspected Unexpected Serious Adverse Reaction

11.2 Recording adverse events

Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. Adverse events will be reportable to the Sponsor for each participant for their duration in the trial as per the protocol.

Regarding Ocular Events

All ocular adverse events (AEs) reported by patients and observed by the study team will be recorded in the medical records and CRF following randomisation until the patient has completed their final study visit at 6 months with the exception of some events which are inevitable consequences of the surgical intervention and extremely unlikely to be IMP –related (refer to later in text for examples). These events will only be recorded in the medical records.

Patients who have consented but are subsequently not randomised will not be followed up as part of the study and hence adverse events will not be reported for these patients.

The following expected ocular events will be considered AEs and will be actively monitored for by the investigators:

AEs will include the following expected ocular events: elevated intraocular pressure (IOP), hypotony (IOP <6mmHg), pseudohypopyon, retinal detachment, further ocular surgery, endophthalmitis, scleritis, uveitis, rubeosis. AEs will be recorded whether or not considered to be drug related or expected or unexpected.

More specifically, the following definition for raised IOP will be used for the purposes of this study:

More specifically, the recording of severity of Raised IOP will be as follows:

Mild: > 25mmHg but <35mmHg

Moderate: ≥ 35mmHg

Severe: Any interventional invasive procedure (e.g. surgery/laser) required to control the elevated IOP acutely or long-term, during the study period

Examples of ocular events that will **not** be considered adverse events as they are expected findings in this disease population and as such will only be recorded in the medical notes. Reporting these findings as AEs are not deemed to add additional safety data to the study:

Subconjunctival haemorrhage, conjunctival chemosis, periorbital oedema, routine postoperative pain, cataract, corneal epithelial defect secondary to intraoperative epithelial debridement. If any of the above events occur to a severity or duration that is unexpected by the PI, they may then be reported as AE's, making clear the reason (e.g. 'prolonged post-operative pain' or 'severe subconjunctival haemhorrage').

Regarding Non-ocular AEs:

As the IMP is administered locally and the systemic absorption negligible, the likelihood of a non-ocular event being related to IMP administration is extremely low [32]. As this trial is an effectiveness trial detailed AE reporting on non-ocular events is not required to answer the research question. Therefore, if a non-ocular adverse event occurs it will be recorded in the medical notes **and only logged on the eCRF if it may be considered an adverse reaction (i.e. possibly, probably or definitely IMP related)**. All serious **adverse reactions** are immediately reportable to the sponsor (within 24hrs of the investigator becoming aware of it).

11.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

- Severity
- Causality
- Expectedness
- Seriousness

11.3.1 Severity

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

11.3.2 Causality

The assessment of relationship of adverse events to the administration of IMP is a clinical decision made by the investigators based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

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 the trial medication). 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 the trial medication). 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

11.3.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) **or clearly defined in this protocol**
Unexpected	An adverse event which is not consistent with the information about the IMP listed in the Investigator Brochure (or SmPC if Licensed IMP) nor clearly defined in this protocol

The reference document to be used to assess expectedness against the IMP is the SPC. The protocol will be used as the reference document to assess disease related and/or procedural expected events and is assessed by the investigator.

11.3.4 Seriousness

Seriousness as defined for an SAE in section 11.1.

11.4 Procedures for recording and reporting Serious Adverse Events

All ocular events that meet the definition of serious will be recorded in the hospital notes, the AE eCRF, and the SAE log.

All non-ocular events that meet the definition of serious will be recorded in the hospital notes but will only be recorded in the eCRF and SAE log if they are possibly, probably or definitely IMP-related (i.e. a serious adverse reaction) (Refer to later in section 11.4 for further clarification and justification).

The Chief or Principal Investigator (or delegated individual) will report SAE's to the sponsor within 24hours of becoming aware of its occurrence. This can be done verbally or via email to pharmacovigilance@moorfields.nhs.uk in the first instance. However an SAE form will need to be completed for all SAEs and sent by email by to the sponsor using the following: pharmacovigilance@moorfields.nhs.uk. The sponsor will send copies to the trial manager and chief investigator for review.

All SUSARs will be processed by the sponsor who will notify the REC and MHRA, of all SUSARs within 7 calendar days if fatal or life threatening or 15 calendar days otherwise. The sponsor will prepare a report on the SUSAR with the CI and submit

the completed report on the SUSAR system. The sponsor together with the CI and trial manager will inform the site PIs, DMC and RMC with a copy of the report.

Example of exception for reporting SAEs:

Further ocular surgery (including cataract surgery) is an expected routine occurrence in this disease population independent of IMP administration, and has been listed as an expected adverse event. Although it involves hospitalisation (an admission to hospital) the investigators do not consider that this requires expedited reporting on a serious event form as this does not add additional safety data to the study. However, these events will be logged and recorded on the AE log within the eCRF, specifying that the patient was hospitalised that that the event was not reported on an SAE form in an expedited manner.
However, if any of the above events require unexpected urgent surgery and the investigator deems the event to be possibly, probably or definitely related to the IMP, they should report them in an expedited manner on an SAE form.

Clarification for recording and reporting non-ocular AEs

a) coryzal illness not satisfying criteria for serious – record in medical notes do not log on eCRF as AE
b) a coryzal illness requiring admission to hospital – record in notes but neither log on eCRF nor report as an SAE
c) a fall resulting in fractured wrist requiring hospital admission and urgent surgery to repair – record in medical notes but neither log on eCRF nor report as an SAE
d) a rash of unknown cause **not** satisfying criteria for seriousness **but which is possibly, probably or definitely IMP related if, in the view of the treating physician, there is no more likely cause** – record in notes AND **log on eCRF as AE**
e) a rash of unknown cause resulting in hospital admission or subsequent life-threatening course which is possibly, probably or definitely IMP related if, in the view of the treating physician, there is no more likely cause– record in notes AND complete sponsors SAE form AND **immediately report to sponsor** AND **complete eCRF AE log, stating the patient was hospitalised and an SAE report was sent**

PLEASE REFER TO FLOW CHART IN APPENDIX 2 FOR OUTLINE OF AE/SAE RECORDING AND REPORTING

11.4.1 Notification of deaths

All deaths will be considered an SAE and reported to the sponsor irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. The timeline for reporting this information will be within 24hours of becoming aware of its occurrence.

11.5 Development Safety Update Reports

The sponsor will provide the main REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and the Sponsor's office. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

11.6 Annual progress reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The chief investigator together with the trial manager will prepare the APR.

11.7 Pregnancy (If applicable)

All female study participants of child bearing potential will have had a negative urine pregnancy test within 7 days of study treatment and will have to confirm the use of appropriate contraception for the duration of the study.

In the unlikely event that a participant become pregnant whilst actively being followed up as part of the trial, the sponsor will be notified in writing as soon as possible according to their SOP. The patient's General Practitioner will be informed, (if not already aware) for routine follow up of their pregnancy

All NIMPs used as part of routine clinical care, will be continued, unless prohibited by local site policy.

For a child born to a pregnant trial subject the General Practitioner will be contacted to provide information on any congenital birth abnormalities to the trial sponsor.

11.8 Overdose

Patients are masked to their treatment allocation and have no involvement in IMP administration. As the IMP is administered intraoperatively at a dose that is commonly used, the likelihood of an overdose is extremely low.

11.9 Reporting Urgent Safety Measures

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

11.10 The type and duration of the follow-up of subjects after adverse events.

After adverse events subjects will be followed up until it is considered that the effects of the adverse event have ceased or have become part of routine ophthalmic care.

As the IMP is given on one occasion at the beginning of the study any new adverse events occurring after a participant has completed the study (6 months post potential IMP exposure) will not be monitored for, recorded or reported as it is highly unlikely to be related to the IMP due its duration of action.

11.11 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial.

The sponsor of a clinical trial shall notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor’s SOP on the ‘MEH S09 Study Oversight’ will be followed.

12 Data management and quality assurance

12.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.

The electronic Case Report Forms (eCRFs) will not bear the subject's name or other personal identifiable data. The subject's initials, date of birth and participant identification number, will be used for identification. Source data worksheets will be completed for each participant but will not be removed from the recruiting study sites. Signed consent forms will be filed in the Investigator Site File.

12.2 Data collection tools and source document identification

Study data will initially be recorded on a Source Data Worksheet and then transcribed to the eCRF system (InferMed MACRO), hosted at the King's Clinical Trials Unit at King's College London.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the eCRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

12.3 Data handling and analysis

- InferMed MACRO eCRF version 4 will be used to record the study data. Staff will be allocated data entry or monitor roles to access the system. All requests for user access must be submitted to the KCTU by the trial manager, allowing a 7 day period for requests to be processed. Study site staff will enter data, ideally within 7 days of data collection. The trial manager will raise data discrepancies within the system and sites will respond to each before the discrepancy is closed. At the end of the trial, once all queries are resolved and all data fields are completed with data or missing data codes (where applicable), the trial manager will lock the database for analysis
- Requests for data exports or amendments to the eCRF system must be authorised by the trial statistician and requests formally submitted to the KCTU (ctu@kcl.ac.uk)
- Data exports from the randomisation system will be subgroup unmasked
- Victoria Cornelius (ICTU) and Catey Bunce (KCL) will be responsible for overseeing all the statistical aspects of the trial (subgroup masked and masked respectively) and trial statistician Suzie Cro (ICTU) will be

responsible for undertaking interim analysis for DMC reports and the final study analysis subgroup masked.

- Data entry will be undertaken at study sites by designated research personnel

13 Record keeping and archiving

All study documents are to be retained for a period of 5 years following conclusion of the study.

Following the submission of the end of study report the Sponsor will arrange for archiving of the Trial Master File in accordance with the Sponsor's process. The Sponsor will notify the Clinical Trials Pharmacist when the Pharmacy file may be archived, in line with the Sponsor's SOP. The Sponsor will also notify the local PIs that the Investigator Site Files (ISFs) may be archived

The Investigator Site Files will be retained and archived at site in accordance with the Trusts' procedures.

Following the end of the retention period the Sponsor will notify the Principal Investigators in writing that the required retention period has completed and that documents can be destroyed. A copy of the instruction to the Trust Archivist to destroy the ISF will be requested.

14 Statistical Considerations

Victoria Cornelius (ICTU) and Catey Bunce (KCL) will be responsible for all statistical aspects of the trial from design through to analysis and interpretation. Suzie Cro (ICTU) will be responsible for undertaking interim and final analyses.

Outcomes

Internal Pilot progression criteria

Stage 1: Funded study months 6 – 12:

It is planned that five study sites will be set up by month 4 and ten study sites by month 5. It is anticipated that they should be recruiting participants to the internal pilot at the start of month 6.

Progression criteria for stage 1 at funded study month 12 (recruitment month 6)

The trial to proceed to stage 2 of the internal pilot if:

- Ten study sites are set up by month 10.

  AND

- At least 30 participants have been recruited to the trial during the first six months of recruitment period.

Stage 2: Funded study months 12 – 18

It is planned that twenty study sites will be set up by study month 12 and able to recruit participants at the start of month 13.

Progression criteria for stage 2 at funded study month 18 (recruitment month 12)

The trial to proceed to full trial if:

- Less than 7 out of 30, or less than 8 out of 40 stage 1 pilot participants have withdrawn from the trial by their six month follow up appointment

  AND

- An additional 48 participants have been recruited to the trial during recruitment months 6-12.

If the progression criteria for either stage 1 or 2 are not met due to an inadequate number of study sites being open, the reasons for these delays will be examined and discussed with the funders. Reasons for failure to meet recruitment and retentions

rate will be examined in detail and the feasibility of the trial will be assessed in the light of information obtained from the internal pilot. If appropriate, the recruitment targets will be redrawn and further study sites will be added to the trial in order to meet sample size requirements within the funding period.

14.1.1 Primary outcome

The proportion of patients with an improvement from baseline to 6 months of at least 10 on the corrected visual acuity in the study eye (total ETDRS letter score measured at a starting distance of 4 metres)

14.1.2 Secondary outcomes

(a) Total EDTRS score in the study eye at the 6 months follow up appointment

(b) The proportion of patients in whom retinal detachment with PVR occurs at any timepoint within 6 months of the study vitrectomy

(c) The proportion of patients in whom stable complete retinal reattachment (without internal tamponade present) is achieved at 6 months post study vitrectomy

(d) The proportion of patients in whom stable macular retinal reattachment (without internal tamponade present) is achieved at 6 months post study vitrectomy

(e) The proportion of patients in whom a tractional retinal detachment occurs at any timepoint within 6 months of the study vitrectomy

(f) The number of operations to achieve stable retinal reattachment (either complete or macula) at 6 months after the study vitrectomy

(g) The proportion of patients who suffer hypotony (<6mm Hg) at any timepoint within 6 months of the study vitrectomy

(h) The proportion of patients who suffer raised intraocular pressure (>25mm Hg)

at any timepoint within 6 months of the study vitrectomy

(i) The proportion of patients who develop macula pucker by 3 and 6 months and/or require macular pucker surgery at any timepoint within 6 months of the study vitrectomy

(j) Quality of Life –

- Client Service Receipt Inventory (CSRI). Primary and secondary health and social care service use will be recorded using a brief CSRI created for the study. The CSRI will be recorded at baseline (1 page), 3 and 6 months (2 pages). At baseline, participants will be asked to recall service use in the last 4 weeks and at 3 and 6 months participants will be asked to recall their service use for the previous 3 months.
- EQ-5D-5 [33] . The EQ-5D is a generic, preference based, health-related quality of life (HRQoL) measure. It consists of two parts, a five item questionnaire and a visual analogue scale (EQ-VAS). The EQ-5D-5L questionnaire is scored between -0.59 and 1, with 1 meaning full HRQoL. Currently, no scoring algorithm exists to

convert EQ-5D-5L responses into an index score therefore we will use an interim scoring algorithm that maps responses onto the EQ-5D-3L [34]. The EQ-VAS is a thermometer scored between 0-100, with respondents asked to mark their current HRQoL level.

- VFQ-25 [35]. The VFQ25 measures vision related QoL. Items are converted into a score between 0-100, where 100 represents full capability, and then the subscales are averaged to produce the composite score.

14.2 Sample size and recruitment

14.2.1 Sample size calculation

Published data [36] indicate that the distribution of best corrected visual acuity (VA) ETDRS letter score at six months will be skewed in this population and this is in line with results from the pilot randomised controlled trial for this study (n=40). Our pilot trial also showed that the majority of participants had VA baseline values that were zero (35/40) and indicated that the shape of the distribution of VA at six month differs between the active and control arm. Both of these factors impact the choice of suitable methods for analysis and thus an appropriate approach to calculate the sample size.

The mean difference observed in VA between arms in the pilot study was 3.1 (32.9 – 29.8) with a pooled standard deviation of 28.9. This summary statistic which showed a small average difference between arms did not fully reflect the true benefit that participants received. In the pilot data 80% (n=16) versus 55% (n=11) saw a meaningful improvement in VA of 10 letters or more in the active versus control group respectively. Whist the sample size is relatively small, this demonstrate that analysing the outcome as a continuous variable may potentially miss detecting an important difference in the proportion of participants who did have a clinically important improvement in VA of 10 or more.

We will report and analyse the primary outcome as a binary variable (change in VA <10, change in VA $\geqslant$10) instead of a continuous one since this would allow us to detect and report a more clinically meaningful result. As: 1) we anticipate an unusual and non-identical distributions for the EDTRS letter score at follow-up in the two treatment arms resulting in a use of a complex model for analysis which would make it harder to communicate results; 2) the binary outcome represents a more clinically meaningful and tangible result for patients and clinicians that can be easily communicated (e.g. the results would show XX% of patients had a clinically meaningful improvement in VA in the treatment arm compared with the control arm); 3) Given the finding of the pilot study if a duel primary outcome is used the results

may show a significantly larger proportion of participants in the treatment arm with a meaningful improvement in VA not coupled with a small and non-statistically significant improvement in letter score. This duel result may lead to a potentially confusing message for clinical practice.

With 140 per group and using the cut-off for significance of 5% we will have 90% power to detect a 19% increase (55% to 74%) in participants who have a meaningful minimum improvement in VA of at least 10. Equivalently, with 140 per group and using a 5% significance level we have 85% power to detect a 17% increase (55% to 72%) in participants who have a meaningful minimum improvement in VA of at least 10.

Previous trials run by Moorfields and involving tertiary teaching hospitals experienced no more than 5% dropout rate at six month follow up (from the current unpublished pilot and [37-39]). As this is a multi-centre trial including non-specialist centres we anticipate the dropout rate will be higher. Therefore allowing for a 7% dropout rate we will aim to recruit 300 participants to the trial.

A change of 10 letters is widely accepted to be a clinically meaningful in research studies of eye disease [13, 15, 19-22, 37-40].

14.2.2 Planned recruitment rate

The following table displays the estimated recruitment numbers for the trial by site:

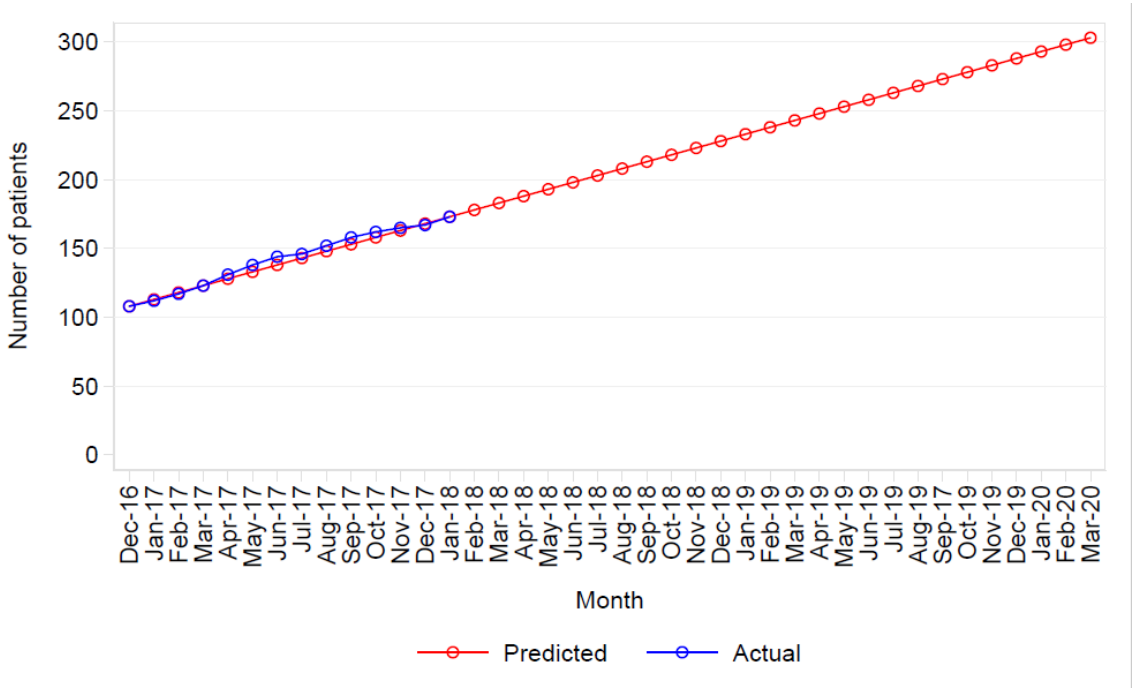
	Site	Category	Estimated Annual Cases	Anticipated recruitment proportion throughout trial	Average anticipated annual recruitment no.	**Internal pilot min no. recruited (6 months)**
1.	Birmingham*	A	25	0.5	12.5	4
2.	Kings College London*	A	25	0.5	12.5	5
3.	Moorfields *	A	25	0.7	17.5	6
4.	Maidstone *	B	12	0.6	7.2	3
5.	Sunderland *	B	14	0.5	7	3
6.	Cambridge *	C	12	0.5	6	3
7.	Liverpool*	C	8	0.5	4	N/A
8.	Sheffield	C	10	0.5	5	N/A
9.	St Thomas' London	C	12	0.5	6	N/A
10.	South Tees	C	12	0.6	6	N/A
11.	Hull *	D	4	0.6	2.4	1

12.	Whipps Cross London	D	6	0.5	3	N/A
13.	Bristol	E	6	0.5	3	N/A
14.	Edinburgh*	E	4	0.5	2	1
15.	Glasgow *	E	6	0.5	3	1
16.	Western Eye London	E	10	0.5	5	N/A
17.	Portsmouth	B	4	0.5	2	N/A
18.	Oxford	C	4	0..5	2	N/A
19.	Plymouth	E	4	0.5	2	N/A
20.	Derby	D	4	0.5	2	N/A
21.	Nottingham	C	20	0.5	10	N/A
22.	Southend	D	10	0.5	5	N/A
23.	**Manchester**	A	**10**	**0.5**	**5**	**N/A**
24.	**Wolverhampton**	C	**14**	**0.5**	**7**	**N/A**
25.	**Newcastle**	A	**6**	**0.5**	**3**	**N/A**
26.	**Leicester**	C	**20**	**0.5**	**10**	**N/A**
27.	**Canterbury**	D	**4**	**0.5**	**2**	**N/A**
28.	**Stoke Mandeville**	D	**2**	**0.5**	**1**	**N/A**
	Total:		**293**		**153.1**	**30**

Key

A= Large teaching hospital, B= Medium non-teaching hospital, C= Medium teaching hospital, D = smaller non-teaching hospital, E= smaller teaching (N.B ‘teaching' refers to previous experience with RCTs, on site trial and R&D facility), * = Stage 1 internal pilot sites (N.B. all sites included in the phase 2).

Originally the trial was designed with 33 months recruitment to achieve the recruitment target of 300. However, up to November 2016 (recruitment month 24) only 101 patients had been recruited, corresponding to 50% of the predicted 202 cases by this time point. Over the period November 2016 to June 2017 recruitment averaged 5.9 per month. The observed recruited numbers were used to project a realistic recruitment rate of 5 per month, requiring an additional 33 months of recruitment (up to March 2020) to achieve the required sample size (see below figure).



14.3 Statistical analysis plan

14.3.1 Summary of baseline data and flow of patients

The following variables collected at baseline will be summarised by group and assessed for imbalance. No statistical tests will be performed to compare differences but evaluation will be by clinical opinion on the number/size of the differences between the treatment groups.

Demographics (including sex, date of birth , ethnicity), laterality, location of wound, FB status, date and classification of injury, date of primary repair, presence of RAPD, whether one or both eyes has been injured, anterior and posterior ocular findings including retinal attachment status and presence and grade of PVR.

A CONSORT flow diagram will be produced to show number of eligible patients, number recruited and randomised, number withdrawing with reasons for withdrawal [41].

14.3.2 Primary outcome analysis

The primary analysis will follow the intention to treat principle as specified in ICH E9 [42], where all participants are analysed in the arm to which they were allocated to

regardless of subsequent procedures. The proportion of participants with an improvement of visual acuity score of 10 or more in the study eye, as measured by the ETDRS vision chart will be compared between treatment arms. The change in VA will be calculated by subtracting the total ETDRS score (at 4 and 1 metres) at baseline from the 6-month follow-up score. The change in VA will then be dichotomised into the baseline group, which has a change in VA of less than 10 and the group with a meaningful improvement as having a VA change greater or equal to 10.

We will fit a generalised linear model (GLM) with change in VA groups (as defined above) as the outcome and study arm and baseline value of the ETDRS as covariates. It is anticipated that 25-30 centres will recruit, and that some sites could recruit a small number of participants. Therefore centre will be included in the model as a random intercept following guidance given by Kahan (2014) [43]. If the model fails to converge centre will instead be fitted as a fixed effect. If including centre as a fixed effect results in unstable model estimates e.g. if there are a number of sites with very few randomisations (<5) and events we will exclude centre from the model since in that case it increases the standard error of the estimate rather than reducing it [44]. The model will use a logit link and a binomial distribution, therefore the treatment effect estimate will be reported as an odds ratio for improvement in VA score of 10 or greater, with a two-sided 95% confidence interval and corresponding p-value. We will also report the difference in proportions of participants with an improvement in VA score of 10 or greater, with a two-sided 95% confidence interval and corresponding p-value. If model assumptions are not deemed to be valid or the model appears to be miss-specified, we will undertake a sensitivity analysis with an alternative model. Results will be assessed at the 5 % significance level.

ETDRS will also be analysed as a continuous outcome. The mean treatment group difference at 6 months will be estimated using a GLM with identity link and Gaussian family, including adjustment for baseline ETDRS and centre as specified above. If model assumptions are not met a suitable non-parametric alternative or transformation will be explored. This is an important principle secondary outcome and originally a co-primary outcome.

14.3.3 Secondary outcome analysis

Analysis for secondary outcomes such as quality of life scores will be undertaken in a similar manner to the primary analysis described above. For binary outcomes we will fit a GLM with a logit link and binomial family. For continuous outcomes we will fit a GLM with identity link and Gaussian family. For count outcomes we will fit a GLM with a log-link and Poisson family, which will include an over dispersion parameter if required. Similar to the primary outcome analysis, the models will include treatment

arm and adjustment for baseline values where appropriate. Centre will be included as a random intercept unless convergence issues are experienced then centre will be incorporated as a fixed effect (or excluded where there are a number of sites with very few randomisations (<5) and events). Analysis will be on an ITT basis as well as complete case only. Outcomes will be reported as odds ratios and differences in proportions for binary outcomes, relative risks for count outcomes and differences in means between study arms for continuous outcomes. The 95% confidence interval and corresponding p-value will be given. All tests will be two sided, at the 6 month primary time point and assessed at the 5% significance level.

Safety outcomes will be reported as patient proportions and rates between arms with 95% confidence intervals using exact methods where appropriate. Where the number of adverse events is sufficient and of particular clinical interest then time to event analyses will be undertaken to estimate the hazard of the adverse event over time by treatment arm. A detailed statistical analysis plan will be developed for approval by the Trial Steering Group prior to the first closed DMC meeting. Regular interim reports will be prepared as requested by the Data Monitoring Ethics Committee.

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14.3.4 Sensitivity and other planned analyses

We anticipate a low percentage of missing primary outcome data and that missing data will be missing at random (MAR). The primary analysis method employs maximum likelihood estimation and is thus efficient for handing missing outcome data under a missing at random (MAR) assumption. Although a low percentage of missing data is predicted, a sensitivity analysis of the primary outcome will be undertaken in order to assess the impact of missing visual acuity scores at 6 months follow-up. Due to the anticipated small number of missing data and the difficulty in establishing that missing data will be missing at random (MAR), we will initially undertake a worse-case/best-case analysis for examining the impact of missing data. The sensitivity analysis will consider patients in the surgery only group with missing outcomes having a meaningful change in VA and patients in the treatment group with missing data not having a meaningful change in VA. Our missing data analysis is complete if the results show that they are consistent with the primary analysis. If not, a range of more plausible assumptions will be explored following principles laid out in Carpenter & Kenwood[45]. We will examine patterns of missingness and the reasons which caused the data to be missing. This will be achieved by examining the observed data and reasons for withdrawal in discussion with the clinical investigators. We will use this information to derive a series of missing data models. If data are thought to be missing at random (MAR) conditional on additional variables not included in the primary analysis model then the treatment effect will be estimated conditioning on the identified variable for example: conditioned on VA or severity of trauma at baseline.

Missing not at random scenarios (MNAR) will be explored using a range of plausible assumptions and viewing these graphically using a mean score approach via the rctmiss procedure in stata [http://www.mrc-bsu.cam.ac.uk/software/stata-software].

14.3.5 Health Economics Analysis

We will analyse the incremental cost effectiveness of the trial intervention (intraocular and periocular steroid) in eyes undergoing vitreoretinal surgery for ocular trauma compared to surgery alone in terms of changes in visual acuity. To enable this analysis we will, from a public sector, multi-agency perspective [46-48]:

(a)Fully cost the vitreoretinal surgery and follow up.

(b)Record study participant primary and secondary care health service use and social care use over the six month follow up period (using a research nurse interviewer administered client service receipt inventory (CSRI), costed using National unit costs [49, 50], and making use of routine hospital data on surgical and post-operative care as part of the CRF).

(c) Conduct a primary cost effectiveness analysis (using the trial primary outcome measure of visual acuity as our measure of effectiveness).

(d) Conduct a secondary cost-consequence analysis (to take account of impact on wider effects such as employment and visual acuity), including calculation of QALYs using EQ-5D as our measure of utility to generate a cost per QALY for comparison with the NICE ceiling of £20,000 - £30,000 [51].

(e) Through bootstrapping we will generate cost effectiveness acceptability curves to communicate to policy makers the probability that the intervention is cost-effective [52].

14.4 Randomisation methods

See section 8.2

14.5 Interim analysis

Internal Pilot analysis

At the end of stage 1 of the internal pilot the recruitment rates will be tabulated by month and site.

At the end of stage 2 of the internal pilot the recruitment rates will be tabulated by month and site along with the number of participants from stage 1 who have withdrawn.

Reports for DMC will be drawn up at interval requested by the DMC. The contents of the report will be agreed prior to the first study DMC meeting.

There are no other planned interim analyses.

14.6 Other statistical considerations

Deviations from the statistical analysis plan will be reported and justified in the final manuscript.

15 Name of Committees involved in trial

The overall management structure of this study will consist of Trial Management Group (TMG), Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC). The TMG will be responsible for the day-to-day running and management of the trial. The trial manager and CI will also send regular progress reports to all site PIs. TMG will meet twice in trial set-up and then quarterly subsequently. A Lay Advisory Group (LAG) will be established and will liaise with the TMG and TSC.

The TSC will ensure the overall integrity of the study by monitoring its progress, investigating any serious adverse events, and taking account of regular reports from the DMEC and TMG. The TSC will consist of an independent Chair, and other members including an independent retinal specialist, a trauma specialist and a PPI representative. The TSC is expected to meet annually (or more often, if determined by the Chair).

The DMEC will to monitor the trial data to ensure that the trial is being implemented in accordance with the highest standards of patient safety and ethical conduct.

Throughout the trial, the DMEC will monitor data on recruitment, adverse events, emerging external evidence, sample characteristics and primary outcomes and make recommendations on whether an interim analysis is required. The DMEC will consist of an independent Chair (a senior clinician with expertise in ocular trauma trials) and three other members: a trial statistician not involved in the study; a treatment provider; and a PPI representative. The DMEC membership will be approved by the

NIHR. DMEC meetings will be attended by the Chief Investigator (or delegated co-investigator), 1 Principal Investigator, CTU Manager, Trial Statistician and Trial Manager. The DMEC will meet on the same time schedule as the TSC.

In addition an initial set-up meeting and subsequent annual meetings will be arranged for lead investigators at each study site. It is anticipated that these will be held at the Britain and Eire Vitreoretinal surgeons (BEAVRS) annual meeting.

16 Direct Access to Source Data/Documents

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Ethics and regulatory requirements

The sponsor will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before the site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee must apply for NHS permission from their Trust Research & Development (R&D) and be granted written permission.

Prior to the enrolment of patients the Trial Manager will ensure that all site staff are appropriately trained on the Protocol and study related procedures. This will be in the form of a site initiation meeting.

It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section 11.9 for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply the Sponsor with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

Two previous pilot studies using the trial intervention have been approved and have not produced any issues of concern in relation to ethics approval. Intraocular triamcinolone is in routine clinical use for other ophthalmic indications (see background above) and has a safety profile which is well documented. The risk of systemic side effects of the trial intervention is remote and there are no additional invasive investigations. The main ethical issue is of gaining consent to participate in the trial within a short time-frame before urgent surgery. In practice this is an unusual occurrence as definitive vitrectomy surgery is most commonly undertaken as a planned elective procedure following initial primary repair. The CI's team have extensive experience of obtaining consent within a short period before surgery for other studies (acute retinal detachment repair) – no problems or concerns have been encountered from these studies and this will be made clear in the ethics application.

18 Monitoring requirement for the trial

A trial specific monitoring plan will be established for the study as part of the oversight planning. The trial will be monitored with the agreed plan.

19 Finance

The trial is funded by the National Institute of Health Research (NIHR) via the Health Technology Assessment (HTA) funding stream.

20 Insurance

MEH participates in the Clinical Negligence Scheme for Trusts (CNST), run by the NHS Litigation Authority, which pools the risk of clinical negligence claims. NHS indemnity (for negligent harm) will cover MEH employees, both substantive and honorary, who are working in the course of their NHS employment and in respect of conducting research projects which must have received NHS Permission. MEH will not accept liability for any activity that has not been properly registered and Trust approved.

21 Publication policy

Publications and or study report findings will be submitted onto the European clinical trials database in line with current EU guidance.

http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

22 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

23 References

1. Esmaeli, B., et al., *Visual outcome and ocular survival after penetrating trauma. A clinicopathologic study.* Ophthalmology, 1995. **102**(3): p. 393-400.
2. Negrel, A.D. and B. Thylefors, *The global impact of eye injuries.* Ophthalmic Epidemiol, 1998. **5**(3): p. 143-69.
3. Blindness, N.S.t.P., *Vision Problems in the US: Data Analysis*. 1980, New York National Society to Prevent Blindness. p. 25-26.
4. Schein, O.D., et al., *The spectrum and burden of ocular injury.* Ophthalmology, 1988. **95**(3): p. 300-5.
5. Desai, P., et al., *Incidence of cases of ocular trauma admitted to hospital and incidence of blinding outcome.* Br J Ophthalmol, 1996. **80**(7): p. 592-6.
6. Pinna, A., et al., *Epidemiology, visual outcome, and hospitalization costs of open globe injury in northern Sardinia, Italy.* Ophthalmic Epidemiol, 2007. **14**(5): p. 299-305.
7. Cillino, S., et al., *A five-year retrospective study of the epidemiological characteristics and visual outcomes of patients hospitalized for ocular trauma in a Mediterranean area.* BMC Ophthalmol, 2008. **8**: p. 6.
8. Cardillo, J.A., et al., *Post-traumatic proliferative vitreoretinopathy. The epidemiologic profile, onset, risk factors, and visual outcome.* Ophthalmology, 1997. **104**(7): p. 1166-73.
9. Spiegel, D., et al., *Severe ocular trauma managed with primary pars plana vitrectomy and silicone oil.* Retina, 1997. **17**(4): p. 275-85.
10. Framme, C. and J. Roider, *[Epidemiology of open globe injuries]*. Klin Monbl Augenheilkd, 1999. **215**(5): p. 287-93.
11. Mittra, R.A. and W.F. Mieler, *Controversies in the management of open-globe injuries involving the posterior segment.* Surv Ophthalmol, 1999. **44**(3): p. 215-25.
12. Charteris, D.G., et al., *Proliferative vitreoretinopathy-developments in adjunctive treatment and retinal pathology.* Eye (Lond), 2002. **16**(4): p. 369-74.
13. Patel, N.N., et al., *Resources involved in managing retinal detachment complicated by proliferative vitreoretinopathy.* Retina, 2004. **24**(6): p. 883-7.
14. Charteris, D.G., *Proliferative vitreoretinopathy: pathobiology, surgical management, and adjunctive treatment.* Br J Ophthalmol, 1995. **79**(10): p. 953-60.
15. Johnson, R.N. and G. Blankenship, *A prospective, randomized, clinical trial of heparin therapy for postoperative intraocular fibrin.* Ophthalmology, 1988. **95**(3): p. 312-7.
16. Tano, Y., D. Chandler, and R. Machemer, *Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide.* Am J Ophthalmol, 1980. **90**(6): p. 810-6.
17. Rubsamen, P.E. and S.W. Cousins, *Therapeutic effect of periocular corticosteroids in experimental proliferative vitreoretinopathy.* Retina, 1997. **17**(1): p. 44-50.

18. Albini, T.A., et al., *Long-term retinal toxicity of intravitreal commercially available preserved triamcinolone acetonide (Kenalog) in rabbit eyes.* Invest Ophthalmol Vis Sci, 2007. **48**(1): p. 390-5.
19. Koerner, F., et al., *Postoperative retinal fibrosis--a controlled clinical study of systemic steroid therapy.* Graefes Arch Clin Exp Ophthalmol, 1982. **219**(6): p. 268-71.
20. Williams, R.G., et al., *Does the presence of heparin and dexamethasone in the vitrectomy infusate reduce reproliferation in proliferative vitreoretinopathy?* Graefes Arch Clin Exp Ophthalmol, 1996. **234**(8): p. 496-503.
21. Munir, W.M., et al., *Intravitreal triamcinolone for treatment of complicated proliferative diabetic retinopathy and proliferative vitreoretinopathy.* Can J Ophthalmol, 2005. **40**(5): p. 598-604.
22. Cheema, R.A., et al., *Triamcinolone acetonide as an adjuvant in the surgical treatment of retinal detachment with proliferative vitreoretinopathy.* Ophthalmic Surg Lasers Imaging, 2007. **38**(5): p. 365-70.
23. Ahmadieh, H., et al., *Triamcinolone acetonide in silicone-filled eyes as adjunctive treatment for proliferative vitreoretinopathy: a randomized clinical trial.* Ophthalmology, 2008. **115**(11): p. 1938-43.
24. Diabetic Retinopathy Clinical Research, N., et al., *Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema.* Arch Ophthalmol, 2009. **127**(3): p. 245-51.
25. Scott, I.U., et al., *A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular Edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6.* Arch Ophthalmol, 2009. **127**(9): p. 1115-28.
26. Conway, M.D., et al., *Intravitreal triamcinolone acetonide for refractory chronic pseudophakic cystoid macular edema.* J Cataract Refract Surg, 2003. **29**(1): p. 27-33.
27. Challa, J.K., et al., *Exudative macular degeneration and intravitreal triamcinolone: 18 month follow up.* Aust N Z J Ophthalmol, 1998. **26**(4): p. 277-81.
28. Peyman, G.A., et al., *Triamcinolone acetonide as an aid to visualization of the vitreous and the posterior hyaloid during pars plana vitrectomy.* Retina, 2000. **20**(5): p. 554-5.
29. Sakamoto, T., et al., *Triamcinolone-assisted pars plana vitrectomy improves the surgical procedures and decreases the postoperative blood-ocular barrier breakdown.* Graefes Arch Clin Exp Ophthalmol, 2002. **240**(6): p. 423-9.
30. Vasconcelos-Santos, D.V., et al., *Secondary ocular hypertension after intravitreal injection of 4 mg of triamcinolone acetonide: incidence and risk factors.* Retina, 2008. **28**(4): p. 573-80.
31. Banerjee, P.J., et al., *A pilot study of intraocular use of intensive anti-inflammatory; triamcinolone acetonide to prevent proliferative vitreoretinopathy in eyes undergoing vitreoretinal surgery for open globe trauma; the Adjuncts in Ocular Trauma (AOT) Trial: study protocol for a randomised controlled trial.* Trials, 2013. **14**: p. 42.
32. Veritti, D., et al., *Drug safety evaluation of intravitreal triamcinolone acetonide.* Expert Opin Drug Saf, 2012. **11**(2): p. 331-40.
33. Group., E. *UserGuide_EQ-5D-5L*. Available from: http://www.euroqol.org/about-eq-5d/publications/user-guide.html.
34. van Hout, B., et al., *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15**(5): p. 708-15.
35. Mangione, C.M., et al., *Development of the 25-item National Eye Institute Visual Function Questionnaire.* Arch Ophthalmol, 2001. **119**(7): p. 1050-8.
36. Andreoli, M.T. and C.M. Andreoli, *Surgical rehabilitation of the open globe injury patient.* Am J Ophthalmol, 2012. **153**(5): p. 856-60.
37. Charteris, D.G., et al., *A randomized controlled trial of combined 5-fluorouracil and low-molecular-weight heparin in management of established proliferative vitreoretinopathy.* Ophthalmology, 2004. **111**(12): p. 2240-5.

38. Wickham, L., et al., *Randomized controlled trial of combined 5-Fluorouracil and low-molecular-weight heparin in the management of unselected rhegmatogenous retinal detachments undergoing primary vitrectomy*. Ophthalmology, 2007. **114**(4): p. 698-704.
39. Asaria, R.H., et al., *Adjuvant 5-fluorouracil and heparin prevents proliferative vitreoretinopathy : Results from a randomized, double-blind, controlled clinical trial.* Ophthalmology, 2001. **108**(7): p. 1179-83.
40. Wiedemann, P., et al., *Adjunctive daunorubicin in the treatment of proliferative vitreoretinopathy: results of a multicenter clinical trial. Daunomycin Study Group.* Am J Ophthalmol, 1998. **126**(4): p. 550-9.
41. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**.
42. *ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group.* Stat Med, 1999. **18**(15): p. 1905-42.
43. Kahan, B.C. and T.P. Morris, *Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects?* Statistics in Medicine, 2013. **32**(7): p. 1136-1149.
44. European Medicines Agency, *Guideline on adjustment for baseline covariates in clinical trials*. 2015: Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf.
45. Carpenter, J. and M.G. Kenward, *Missing data in randomised controlled trials - a practical guide*. 2007, Birmingham.
46. Edwards, R.T., et al., *Economic evaluation alongside pragmatic randomised trials: developing a standard operating procedure for clinical trials units.* Trials, 2008. **9**: p. 64-64.
47. Glick, H., et al., *Economic evaluation in clinical trials*. 2005, Oxford: Oxford University Press.
48. Drummond, M., et al., *Methods for the economic evaluation of health care programmes*. 3rd edition. ed. 2005, Oxford: Oxford University Press.
49. Curtis, L., *Unit costs of health and social care. Canterbury: Personal Social Services Research Uni at the University of Kent. http://www.pssru.ac.uk/project-pages/unit-costs/2014/. Accessed 9 July 2016.* 2014.
50. Department of Health, *NHS reference costs 2013-14*. 2015: https://www.gov.uk/government/publications/nhs-reference-costs2013-to-2014. Accessed 9 July 2016.
51. National Institute for Health and Care Excellence (NICE), *Gude to the methods of technology appraisal 2013.* https://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technologyappraisal-2013-pdf. Accessed 9 July 2016.
52. Fenwick, E., B.J. O'Brien, and A. Briggs, *Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions.* Health Econ, 2004. **13**(5): p. 405-15.

APPENDIX 1 – VISUAL ACUITY ASSESSMENT PROCEDURE

1) Identify Visual Acuity Assessment Sheet in ASCOT Worksheet Booklet

2) Determine whether patient is APHAKIC (NO LENS INSIDE EYE) or presently has Silicone Oil *in situ* **without unmasking yourself to their treatment allocation**

3) Record your name, designation and masking status and sign at top of sheet

4) Record Patient Study ID and Assessment Date

5) Identify study eye and select corresponding worksheet and LOGMAR chart (i.e CHART 1 for RIGHT eye or CHART 2 for LEFT eye)

6) ASK patient to wear **distance** spectacle correction **ONLY** if spectacles have been updated since study surgery

7) Occlude fellow eye (non-study eye) and ask patient to read letters from correct chart at 4 metres and on worksheet number of letters read on each line

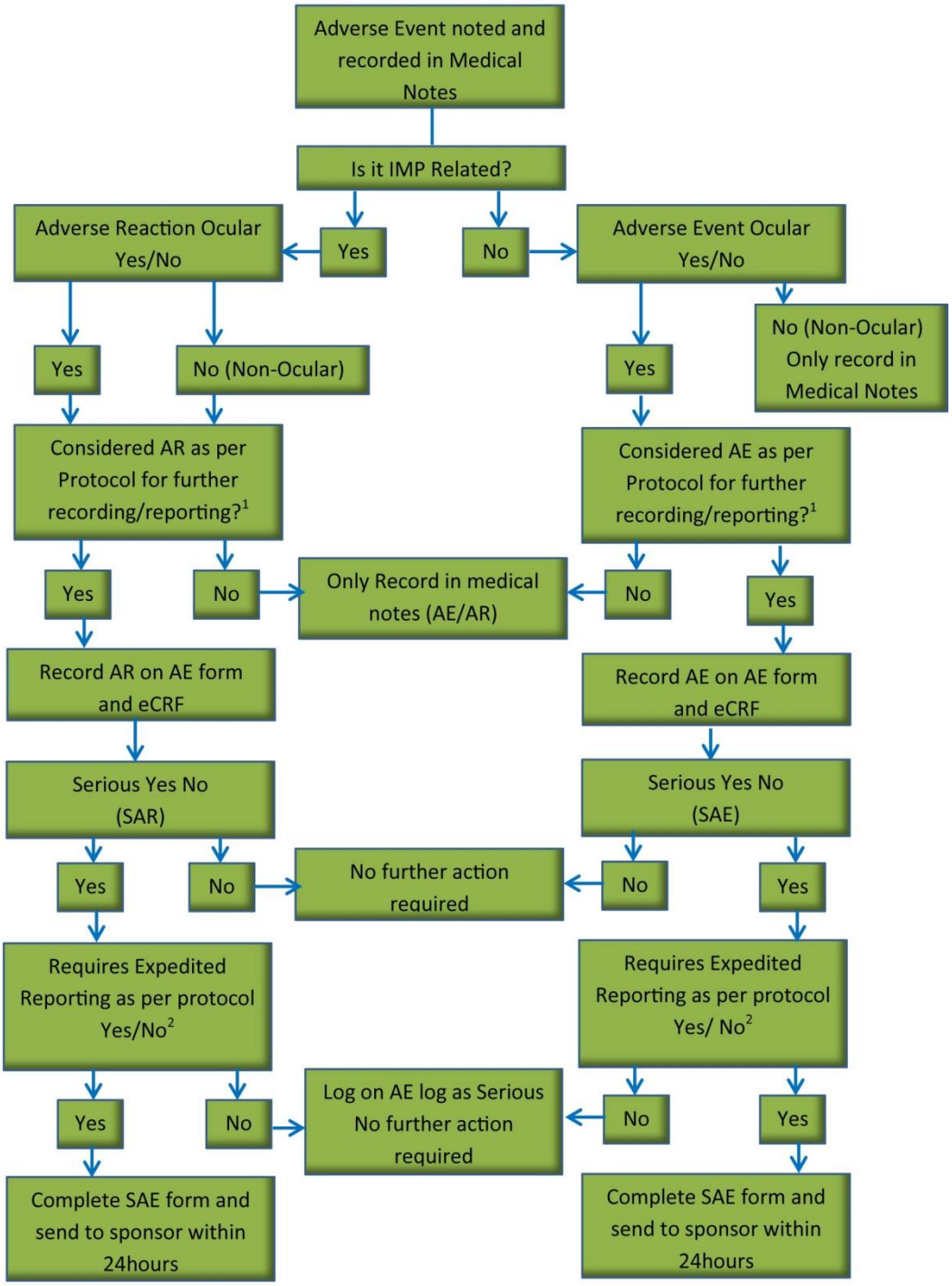
8) Add pinhole to aid patient when no more letters are read

9) If patient is aphakic or has silicone oil *in situ*: use + 2, +4, +6, +8, +10, +12 dioptre spheres **with pinhole** to see if vision can be improved and more letters achieved

10) If fewer than 20 letters are read at 4 metres, then move patient to 1 metre and repeat Steps 7 to 9 until no more letters can be read

11) If 0 (ZERO) letters are read at 1 metre with pinhole and best spherical correction then assess ability to count fingers (CF), see hand movements (HM) or perceive light (PL)

APPENDIX 2 - SAFETY RECORDING AND REPORTING



Footnote:
1- See Protocol section 11.2
2- See Protocol section 11.4

Appendix 3: Amendment history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1.0	1.1	180315	EL Robertson, V Cornelius, D Charteris,	3 month recruitment window changed from +/- 3 weeks to +/- 6 weeks
2.0	2.0	230316	EL Robertson, V Cornelius, D Charteris,	Move one of the primary outcomes to a secondary outcome
3.0	3.0	150218	C Bunce, S Cro, D Charteris, V Cornelius, EL Robertson,	Update the protocol following the recruitment extension