A Feasibility Randomised Control Trial of Vitrectomy Plus Standard Care Intravitreal Ranibizumab or Aflibercept Injections versus Standard Care Intravitreal Ranibizumab or Aflibercept injections Alone In Patients With Centre Involving Diabetic Macular Edema

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Study Protocol

Keywords: Diabetic Macular Oedema, VIDEO Trial, definitive randomized trial, vitrectomy

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Abstract

Background: Most studies indicate that vitrectomy delivers sustained improvements in macular thickness. Evidence on whether acuity is improved is inconsistent. In the presence of traction vitrectomy is thought to be visually effective. In the absence of traction vitrectomy was usually performed as rescue therapy when repeated laser treatments had failed and visual improvement may not have been possible. Studies where vitrectomy was performed early in the disease showed visual benefit. All these data also predate the current gold standard anti VEGF therapy for DME and SD OCT imaging of the vitreo retinal interface.

We hypothesise that adding a vitrectomy and internal limiting membrane peel to standard care intravitreal Anti-VEGF injections in the management of CIDME will result in: improved or comparable visual outcomes, fewer anti-VEGF injections and reduced costs.

Methodology: VIDEO is a pragmatic stratified, single-masked, randomised, multi centre, controlled, feasibility trial with 12 months follow up. Stratification will be based in the presence or absence of OCT evident vitreomacular traction or epiretinal membrane. The primary outcome is Distance best corrected visual acuity. Secondary outcomes are Number of injections, Rate of completed follow, Rate of recruitment, Central macular thickness on OCT, Area under the curve of CMT, Area under curve of BCVA, Rate of loss of 15 or more letters from baseline, Rate of Rescue therapy, Rate of cataract surgery, Rate of complications. Recruitment target is 100 patients with 1:1 randomisation to the treatment arm (vitrectomy + standard care) or control arm (standard care) with 12 month follow up. Standard care is treat and extend intravitreal anti-VEGF injections.

Main inclusion criteria:

-Patient over 18 years of age

-Patient has capacity to give informed consent

-Patient has not previously been enrolled in this study in regards to their other eye

- Symptomatic visual loss attributable to diabetic macular oedema for less than one year

-Patient has a formal diagnosis of Diabetes Mellitus

-Patient has an HbA1c test (a blood test that looks at long term diabetic control) performed within the past 2 months.

Ophthalmic criteria:

-Symptomatic visual loss attributable to DMO for less than one year.

-Best corrected visual acuity of better than 35 ETDRS letters on formal testing

-Central macular thickness greater than 350 microns.

Discussion:

Outcomes should inform the effect size with which to inform the design of a definitive randomised control trial

ISRCTN Registry ISRCTN59902040 18.12.20 retrospectively registered
http://www.isrctn.com/ISRCTN59902040

Summary/synopsis

Title	The VIDEO Trial. A Feasibility RCT of Vitrectomy Plus Standard Care Intravitreal Ranibizumab or Aflibercept Injections versus Standard Care Intravitreal Ranibizumab or Aflibercept injections Alone In Patients With Centre Involving Diabetic Macular Edema
Protocol Short Title/Acronym	VIDEO Trial
Protocol Version number and Date	2.1 6th June 2020
Study Phase if not mentioned in title	
Is the study a Pilot?	Feasibility trial
IRAS Number	220073
REC Reference	
Study Duration	3 years
Methodology	Single-blind, stratified, randomised, multicentre, control trial.
Sponsor name	KCL
Chief Investigator	DAH Laidlaw
Funder Name	KCL, Fight For Sight
Medical condition or disease under investigation	Diabetic Macular Oedema
Purpose of clinical trial	To investigate the feasibility and expected effect size with which to inform the design of a definitive randomized trial
Primary objective	Distance Best Corrected Visual Acuity
Secondary objective (s)	Number of injections, Rate of recruitment, Rate of completed follow up, Central macular thickness on OCT, Area under the curve of CMT, Area under curve of BCVA, Rate of loss of 15 or more letters from baseline, Rate of Rescue therapy, Rate of cataract surgery, Rate of complications
Number of Subjects/Patients	100

Trial Design	A pragmatic stratified, single-masked, randomised feasibility study with 12 months follow up. Stratification will be on the basis of presence or absence of OCT evident vitreo-macular traction/epiretinal membrane
Endpoints	12 months follow up
Main Inclusion Criteria	-Patient over 18 years of age -Patient has capacity to give informed consent -Patient has not previously been enrolled in this study in regards to their other eye - Symptomatic visual loss attributable to diabetic macular oedema for less than one year -Patient has a formal diagnosis of Diabetes Mellitus -Patient has an HbA1c test (a blood test that looks at long term diabetic control) performed within the past 2 months. <u>Ophthalmic criteria</u> -Symptomatic visual loss attributable to DMO for less than one year. -Best corrected visual acuity of better than 35 ETDRS letters on formal testing -Central macular thickness greater than 350 Microns
Statistical Methodology and Analysis	Undertaken by statistician

Introduction

Diabetic macular edema (DME) is a prevalent cause of sight loss in working age patients. The current standard NICE approved treatment involves intravitreal injections of anti-VEGF drugs, initially on a monthly basis. Whilst potentially restoring lost vision this therapy involves frequent protracted hospital visits and a considerable economic and capacity burden on health care funders and providers. The effect of anti-VEGF therapy is also transient; depending on the drug and treatment regime patients need 3-13 injections in the first year (mean 7-9) and approximately 5 in the second year. Around 25% of patients do not respond to anti-VEGF therapy.

Ranibizumab (Lucentis) is approved by NICE for the management of patients with centre involving diabetic macular edema (CIDME). The following are extracts from the Lucentis Summary of Medical Product Characteristics and NICE Guidance

Ranibizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and

the manufacturer provides Ranibizumab with the discount agreed in the patient access scheme revised in the context of this appraisal 2.

The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks.

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DMO and RVO, initially three or more consecutive monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography (OCT) or fluorescein angiography).

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly 1.

An alternative Anti-VEGF preparation is Aflibercept. NICE guidelines for Aflibercept follow those for Lucentis in that:

Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema only if:

the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and

the company provides aflibercept with the discount agreed in the patient access scheme.

Aflibercept is given as a single 2 mg intravitreal injection every month for 5 consecutive months, often followed by 1 injection every 2 months with no requirement for monitoring between visits. After the first 12 months, the treatment interval may be extended based on visual and anatomic outcomes.

However many centres administer Aflibercept as a single 2mg intravitreal injection every months for 5 months and then follow a treat and extend pathway, extending the treatment interval based on the same

visual and anatomical parameters used to gauge the treatment interval for Lucentis.

NICE advise that the schedule for monitoring should be determined by the treating physician.

Aflibercept should be discontinued if the patient is not benefiting from continued treatment.

Most studies indicate that vitrectomy delivers sustained improvements in macular thickness. Evidence on whether acuity is improved is inconsistent. In the presence of traction vitrectomy is thought to be visually effective. In the absence of traction vitrectomy was usually performed as rescue therapy when repeated laser treatments had failed and visual improvement may not have been possible. Studies where vitrectomy was performed early in the disease showed visual benefit. All these data also predate the current gold standard anti-VEGF therapy for DME.

We hypothesise that adding a vitrectomy and internal limiting membrane peel to standard care intravitreal Ranibizumab or Aflibercept injections in the management of CIDME will result in: improved or comparable visual outcomes, fewer anti-VEGF injections and reduced costs.

Study Design & Flowchart

5.1 Trial objectives and purpose

To investigate the effectiveness of vitrectomy with ILM peeling plus standard care intravitreal Ranibizumab or Aflibercept injections compared to standard care intravitreal injections alone in the management of centre-involving diabetic macular edema.

To investigate the feasibility and expected effect size with which to inform the design of a definitive randomized trial of this question

5.2 Study description

The study aims to recruit 100 participants in a pragmatic, stratified, single-masked, multicentre, randomised feasibility study with 12 months follow up.

Patients will be recruited from NHS Ophthalmology units in the United Kingdom.

Stratification will be on the basis of presence or absence of OCT evident vitreomacular traction (VMT) or epiretinal membrane (ERM).

Included will be patients with persistent centre involving diabetic macular edema (defined as a central subfield thickness of 350 microns or greater) 12 weeks after initiation of Ranibizumab or Aflibercept therapy for centre involving diabetic macular edema.

The study Group: Vitrectomy, ILM peeling, Ranibizumab or Aflibercept PRP laser with ongoing NICE mandated standard of care intravitreal injections of Ranibizumab or Aflibercept

The Control Group: Ongoing NICE mandated standard of care intravitreal injections of Ranibizumab or Aflibercept.

Eligible patients will only be enrolled after receiving 3 loading doses of Ranibizumab or Aflibercept, with subsequent randomisation to the treatment or control group.

The treatment group will undergo vitrectomy within 4 weeks of enrolment.

Both groups will receive NHS standard, treat and extend Ranibizumab or Aflibercept injections.

Aflibercept injections will be given monthly for 5 months and thereafter on a treat and extend basis if the centre is practising this regimen as standard treatment.

Follow up will be for 52 weeks.

The Feasibility study data will be used to plan subsequent definitive trials.

The trial is summarised in the following diagram

Outcome Measures

The following will be reported at 12 months:

6.1 Primary Outcome Measure

- Distance Best Corrected Visual acuity (primary outcome)

6.2 Secondary Outcome Measures

- Number of injections
- Rate of recruitment
- Rate of completed follow up
- OCT ETDRS Central Sub Field Macular thickness
- Area under the curve of CMT
- Area under the curve of BCVA
- Rate of loss of 15 or more letters from baseline
- Rate of rescue therapy
- Rate of cataract surgery
- Rate of complications

6.3 Explanatory Variables

The following data will be used in a provisional exploratory analysis to identify factors (if any) predicting a beneficial outcome from vitrectomy and internal limiting membrane peeling as an adjunct to the standard

care of patients undergoing Ranibizumab or Aflibercept intravitreal therapy for CIDME:

- Demographic data
- Duration of diabetes
- Duration of symptomatic acuity loss
- Baseline near and distance acuity
- Baseline Central Sub Field Thickness

Subject Selection

Subjects will be recruited from Diabetic Macular Oedema Clinics from a minimum of 2 sites. Data from these sites will guide further inclusion of additional sites.

After meeting eligibility criteria and giving fully informed written consent: we aim to recruit 100 patients for 12 month follow up with 1:1 randomisation.

7.1 Subject inclusion criteria

7.1.1 General inclusion criteria

- The patient over 18 years of age
- Patient has capacity to give informed consent
- Patient has not previously been enrolled in this study in regards to their other eye
- Symptomatic visual loss attributable to diabetic macular edema for less than one year

7.1.2 General Health

- Patient has a formal diagnosis of Diabetes Mellitus
- Patient has an HbA1c test (a blood test that looks at long term diabetic control) performed within the past 2 months.

7.1.3 Ophthalmic criteria

- Symptomatic Visual loss attributable to DME for less than one year.
- Best corrected visual acuity of better than 35 letters on formal testing
- Central macular swelling greater than 349 Microns

The principle investigator or sub-investigator completes Form A (Inclusion Criteria) to ensure eligibility. This check list will act as a screening log and will be completed for all patients screened for the study and all patients recruited.

Form A – Inclusion Criteria – see appendix 2

7.2 Subject exclusion criteria

With justification if necessary – for example consider contra-indications to trial treatments, incompatible concurrent treatments, recent involvement in other research.

- History of chronic renal failure requiring dialysis or transplantation
- Patient suffered a major thromboembolic event within the past 6 months as (defined as TIA, Stroke, or MI)
- Patient has undergone major surgery within the past 6 months or has major surgery planned over the next 12 months defined as requiring GA or reduced mobilisation
- Known adverse reaction to anti-VEGF medications
- Blood pressure greater than 180 systolic or 100 diastolic
- Use of Pioglitazone (diabetic medication)
- Any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study)
- Very poor glycaemic control and has started intensive therapy within the previous 3 months.
- The patient will use an investigational drug during the study
- Previous macular laser within 750 microns of the foveal centre
- Previous Vitrectomy surgery in the study eye
- Other than intravitreal Ranibizumab or Aflibercept therapy or cataract surgery: any other laser, surgical or injection therapy in the last 24 weeks
- Cataract surgery within 3 months
- Concomitant ophthalmic disease liable to affect central macular thickness or visual acuity
- Centre involving vitreous haemorrhage
- Proliferative Diabetic Retinopathy
- Presence of visually significant cataract prior to enrolment. (see below for advice regarding posterior capsular opacification (PCO))*

The patient has any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study)

*Presence of clinically significant PCO should ideally be identified prior to enrolment. Successful treatment with YAG capsulotomy without worsening of CMO meets the inclusion criteria. Presence of clinically significant PCO at enrolment, or worsening of CMO as a consequence of YAG capsulotomy is grounds for exclusion.

7.3 Form A: Inclusion/Exclusion criteria

Form A summarises the Inclusion and Exclusion criteria

	Question	Required answer
	General Inclusion	
1.	Is the patient over 18 years of age?	Yes
2.	Does the patient have capacity to give informed consent?	Yes
3.	Has the patient previously been enrolled in this study in regards to their other eye?	No
	General Health	
4.	Does the patient have a formal diagnosis of Diabetes Mellitus?	Yes
6.	Has the HbA1c test been performed within the past 2 months.	Yes
7.	Is there a history of chronic renal failure requiring either dialysis or renal transplantation?	No
8.	Has the patient suffered a major thromboembolic event within the past 6 months as (defined as TIA, Stroke, or MI)	No
9.	Has the patient undergone major surgery within the past 6 months or is major surgery planned over the next 12 months defined as requiring GA or reduced mobilisation	No
10.	Is there a documented allergy or a significant adverse event to anti-VEFG therapy in the past?	No
11.	Is the current blood pressure over 180 systolic and/or 100 diastolic?	No
12	Is the patient on pioglitazone	No
13	The patient has any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study)	No
14	The patient has very poor glycaemic control and has started intensive therapy within the previous 3 months.	No
15	The patient will use an investigational drug during the study	

	Past Ocular History	
16	Has the eye received macular laser photocoagulation within 750 microns of the foveal centre at any point in the past?	No
17	Has the eye undergone vitrectomy at any point in the past?	No
18	Other than intravitreal Ranibizumab or Aflibercept therapy or cataract surgery has the eye undergone any other laser, surgical or injection therapy in the last 24 weeks	No
19	Was any cataract surgery performed at least three months prior to recruitment?	No
20	Besides diabetic maculopathy with or without associated vitreo-retinal interface abnormalities, does the eye suffer from any other underlying ophthalmic diseases liable to impair visual acuity, including but not limited to: visually significant cataract, AMD, uveitis, vein occlusion, glaucoma, optic neuropathy, amblyopia?	No
21	Has the patient had symptomatic visual loss attributable to diabetic macular edema for less than one year?	Yes
	Present Ocular Status	
22	Does the eye have either (i) active (untreated or partially-treated) proliferative diabetic retinopathy or (ii) very severe non-proliferative diabetic retinopathy?	No
23	Is the current BCVA better than 35 ETDRS letters?	Yes
24	Is the central sub field thickness greater than 349 microns?	Yes
25	Is there any fresh, central axis-involving vitreous haemorrhage?	No
26	Presence of clinically significant cataract or media opacity	No
	Stratification criteria	Yes
27	Presence or absence of localized distortion of the inner retinal surface on the OCT scan due to epiretinal membrane or vitreomacular traction with associated retinal thickening that is contiguous with the central sub field thickening.	**Yes**: stratify to traction group **No**: stratify to the no traction group

Study Treatments

Participants meeting the inclusion and exclusion criteria will be randomised to the vitrectomy group or the standard care group, in a 1:1 ratio. It is unfeasible to perform a sham operation therefore participants will not be double masked. Subsequent investigators performing the technical measures used as outcome variables will be unaware of the randomisation group, so the trial will be singled masked in this regard.

Following randomisation, the Vitrectomy group will undergo Vitrectomy within 4 weeks where logistically possible within the department. As a Pilot study, limitations are recognised and is considered acceptable if Vitrectomy is performed within 10 weeks at the latest. Following loading doses (3 for Ranibizumab and 5 for Aflibercept) both groups will continue Ranibizumab or Aflibercept on a treat and extend basis with appropriate follow up. Therefore, the intended difference in treatment between the 2 groups will be Vitrectomy within 4 weeks of randomisation.

8.1 Anti-VEGF treatment

8.1.1 Initial Anti-VEGF treatment – loading doses

All consenting patients meeting NICE criteria for Anti-VEGF treatment for DME will receive either:

i. 3 intravitreal injections of 0.5mg Ranibizumab (Lucentis) as loading doses, 1 month apart, as per NICE guidelines or
ii. 5 intravitreal injections of 2mg Aflibercept (Eylea) every month for 5 consecutive months

Patients who still meet the inclusion criteria after 3 injections of anti-VEGF treatment will be invited to enter the trial.

Those who do not meet the eligibility criteria, or do not give consent will be followed up routinely in DME clinics.

8.1.2 Treat and Extend Anti-VEGF

Treat and Extend allows the incremental extension of inter-treatment visits based on patient disease activity. Stable disease permits an increase in the intervals between visits, while active disease marks a return to more frequent visits.

VIDEO eligibility criteria require limited response to Ranibizumab or Aflibercept after 3 injections. Therefore all participants in this trial will require further treatment. The 4th injection will be scheduled for 4 weeks after the 3rd injection.

From this visit patients treated with Ranibizumab will receive injections and follow up inline with the treat and extend pathway.

Aflibercept patients will receive an additional 2 monthly injections following enrolment before continuing inline with treat and extend pathway.

NICE guidelines recommend ‘Treat and extend’ Aflibercept after 12 months, but also ‘the schedule for monitoring should be determined by the treating physician.’

‘Treat and Extend Aflibercept’ after 5 injections is a regimen widely used in centres across the UK. In these centres it is recognised as Standard care.

We are accepting Sites already using Aflibercept in this regimen and not encouraging deviation from NICE guidance specifically for acceptance onto this trial.

The treat and Extend regiment is classified as: once maximum visual acuity is achieved and/or there are no signs of disease activity, (defined as Acuity +/- 5 letters and OCT not improved by >50 microns over 3 consecutive visits) the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur.

The treatment interval may be extended by up to one month at a time for DME to a maximum of 12 weeks. Inter treatment interval should not be increased from 8 to 12 weeks at the 40 or 42 weeks visit.

If disease activity recurs, (Acuity deterioration of six or more letters from best recorded post randomization acuity attributable to an increase in OCT CMT) the treatment interval should be reduced to a 4 week follow up or, if previously extended beyond 4 weeks, the inter treatment interval should be reduced by 4 weeks.

If Post randomization from week 24 onwards there is an acuity deterioration of six or more letters attributable to worsening of OCT CMT compared to trial baseline over two or more consecutive visits then the clinician may opt to continue 4 weekly injections or opt for a rescue therapy.

Form G outlines the protocol for follow up visits.

8.1.3 Rescue therapy

From 24 trial weeks onwards subjects fulfilling failure criteria may be considered for rescue treatment. Failure is defined as a deterioration of six or more ETDRS letters of acuity measured on two consecutive visits compared to trial baseline and attributable to increased OCT CMT. The choice of rescue therapies includes alternative anti-VEGF agents and intravitreal steroid therapy as permitted by NICE guidance. Macular laser is not a permitted rescue therapy within the trial follow up period.

8.1.4 Cataract surgery and Posterior Capsular Opacification

Patients with visually significant cataract may undergo cataract surgery at any time up to month 9.

A more formal and thorough assessment of the presence of clinically significant cataract should take place at month 8. This permits sufficient time for planned cataract surgery and recovery.

Post-operative treatment: To avoid topical steroid confounding results, we advise a 2 week course of Maxidex, 1 drop 4 times a day, in conjunction with topical NSAID 4 times a day for 60 days. This ensures patients undergoing cataract surgery by month 9 (the cut off date for cataract surgery) should have been off all treatment for at least 30 days.

Posterior Capsular Opacification (PCO) should be identified and treated prior to enrolment as part of standard treatment. Deterioration of CMO as a consequence of YAG capsulotomy is grounds for exclusion, as is presence of clinically significant PCO or cataract at week 0.

8.1.5 Injection technique

Ranibizumab or Aflibercept must be administered by a qualified professional experienced in intravitreal injections. The drug should be inspected for particulate matter and discoloration prior to injection. The injection should be undertaken in the standard manner for the investigating unit.

The periocular skin, eyelid and ocular surface should be disinfected with povidone iodine 5%, following topical anaesthesia.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 ml should be delivered and then the needle should be held in position for at least 5 seconds to minimize reflux. A different scleral site should be used for subsequent injections.

8.1.6 Medication supply and storage

It is anticipated that all sites will already have a regular supply of Ranibizumab (Lucentis) or Aflibercept (Eylea), given that it is a commonly administered intravitreal injection. The MHRA have determined that VIDEO is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) and as such routine NHS Ranibizumab and Aflibercept stock may be used, without specific trial labelling. Medications must be stored in accordance with the manufacturer's instructions and also in accordance with local policy. The safety and supply of Ranibizumab and Aflibercept will be overseen by the site's non-trial pharmacy, but if any issues of concern arise, the Chief Investigator or Trial Manager should be informed.

8.2 Pars Plana Vitrectomy with ILM peel +/- PRP laser

Surgery will be performed by Consultant Vitreo-retinal surgeon

Choice of anaesthesia is dependent on surgeon, patient choice and local standard practices.

Pars Plana Vitrectomy (PPV) typically uses 3-port 25 or 23 gauge sutureless ports. Posterior vitreous detachment (PVD) will be induced if posterior vitreous detachment is not already present.

After core vitrectomy, ERM (if present) and ILM may be removed using end-gripping forceps augmented by dual blue dye or other vital stains, with repeat staining to confirm ILM removal. Surgery should aim to remove a radius of 1 .5-2 disc diameters of ILM.

For patients with severe non-proliferative diabetic retinopathy Pan Retinal Photocoagulation (PRP) laser is advised: with a treatment area equivalent to 1200-1500 burns of 500 micron diameter between the arcade and Ora serrata.

Patients with Mild or Moderate Non proliferative diabetic retinopathy do not require PRP laser as standard.

Intracameral antibiotic is routinely administered in line with department guidelines, and wound sites are checked and sutured where necessary.

For post-operative medication we advise a 2 week course of chloramphenicol eye drops 4 x a day, and a 4 week course of either Predforte 1% (prednisolone acetate) eye drops or Maxidex 0.1% (dexamethasone) eye drops 4 times a day.

For routine cases we would advise an additional post-operative follow up at 2 weeks. Thereafter patients will be seen regularly for Anti-VEGF treatment.

8.2.1 Participant treatment at study end

At the end of the study (52 weeks after enrolment) all patients will be followed up in standard DME clinics for further treatment or discharge, as necessary.

8.2.2 Table of treatment (Form D)

Form D summaries the Treatment pathway

Trial Weeks	Trial Visit Number	Standard Care Group	Vitrectomy Group
-12 to 0		Records based Identification of potentially eligible treatment naive patients, assessment, issue of PIS, provisional recruitment, injections of intravitreal Ranibizumab or Aflibercept # 1-3 at 4 weekly intervals	
0	Baseline	Ranibizumab or Aflibercept Injection and either Fulfills eligibility and willing to participate with CMT>349 microns Confirmation of eligibility, formal recruitment and randomization. Consent taken or Return to standard care	
		Anti-VEGF injection #4	Anti-VEGF injection #4
1-4	2	-	Vitrectomy (consent for surgery taken as for standard care)
4	3	Anti-VEGF injection #5	Anti-VEGF injection #5
8-12	4	Treat and Extend Anti-VEGF injection #6 and follow up	Treat and Extend Anti-VEGF injection #6 and follow up
12-24	5	Treat and Extend Anti-VEGF injection # 7 and follow up	Treat and Extend Anti-VEGF injection #7 and follow up
16-36	6	Treat and Extend Anti-VEGF injection #8 and follow up	Treat and Extend Anti-VEGF injection #8 and follow up
20-48	7	Treat and Extend Anti-VEGF injection #9 and follow up	Treat and Extend Anti-VEGF injection #9 and follow up
24-52	8	Treat and Extend Protocol Anti-VEGF #10 injection and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF #10 injection and follow up or Rescue therapy
28-52	9	Treat and Extend Protocol Anti-VEGF injection #11 and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF injection #11 and follow up or Rescue therapy
32-52	10	Treat and Extend Protocol Anti-VEGF injection #12 and follow up	Treat and Extend Protocol Anti-VEGF injection #12 and follow up

		or Rescue therapy	or Rescue therapy
36-52	11	Treat and Extend Protocol Anti-VEGF injection # 13 and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF injection #13 and follow up or Rescue therapy
40-52	12	Treat and Extend Protocol Anti-VEGF injection # 14 and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF injection # 14 and follow up or Rescue therapy
44-52	13	Treat and Extend Protocol Anti-VEGF injection # 15 and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF injection # 15 and follow up or Rescue therapy
48	14	Treat and Extend Protocol Anti-VEGF injection # 16 and follow up or Rescue therapy	Treat and Extend Protocol Anti-VEGF injection # 16 and follow up or Rescue therapy

Final 52 weeks	8-15	Final assessment Injection at 52 weeks only if required in keeping with Treat and Extend Protocol Return to standard NHS care with appropriately timed appointment

A 52 week visit is performed regardless of the timing of the last injection visit. On completion of the 52 week visit the patient is returned to standard NHS care with a patient specific follow up date arranged.

8.2.3 Treatment and Follow up protocol (Form G)

Form G summaries the Treatment and follow up protocol

Criterion	Criterion	Treatment/Follow Up
A	Baseline and post randomization week 4	Mandated Ranibizumab or Aflibercept injection (injections 4 and 5)
B	Post randomization week 8 onwards Acuity improvement between visits of six or more letters not attributable to cataract surgery	Continue Ranibizumab or Aflibercept at same treatment interval
C	Acuity deterioration of six or more letters from best recorded post randomization acuity attributable to an increase in OCT CMT	Continue Ranibizumab or Aflibercept at 4 weeks interval or if previously extended beyond 4 weeks reduce inter treatment interval by 4 weeks
D	Post randomization week 24 onwards Acuity deterioration of six or more letters attributable to worsening of OCT CMT compared to trial baseline over two or more consecutive visits	Investigator discretion to opt for rescue therapy OR Continue Ranibizumab or Aflibercept at 4 weeks interval
E	Post randomization week 8 onwards Acuity +/- 5 letters and OCT not improved by >50 microns over 3 consecutive visits.	Increase inter treatment interval by 4 weeks up to a maximum of 12 weeks. (Do not increase inter treatment interval from 8 to 12 weeks at the 40 or 42 weeks visit)
F	COVID19 treatment interruption: Missed visit + Acuity deterioration of six or more letters from best recorded post randomization acuity attributable to an increase in OCT CMT	Continue treatment Review at last successful treatment interval. e.g. controlled on 8/52 visits prior to missed appt, review at 8/52 and continue treat and extend as above.
G	COVID19 treatment interruption: Seen within 6/12 Missed visit and condition stable (Acuity +/- 5 letters and OCT not improved by >50 microns since last visit)	Opportunistic extension Continue treatment and keep new extended interval. (If subsequent signs of deterioration reduce interval by 4 weeks as per

		criterion C)
H	COVID19 treatment interruption: Seen >6/12 ago Missed visit and condition stable (Acuity +/- 5 letters and OCT not improved by >50 microns since last visit)	Monitor patient without treatment. Review at ½ the interval since last treatment. e.g if last seen 6/12 ago review at 3/12
Cataract Surgery/Laser Capsulotomy Indications		
Lens opacity or posterior capsular opacification deemed to be clinically significant based on clinical examination including slit lamp bio microscopy.		

Rescue Therapy: (criterion D) From 24 trial weeks onwards subjects fulfilling failure criteria may be considered for rescue treatment. Failure is defined as a deterioration of six or more ETDRS letters of acuity measured on two consecutive visits compared to trial baseline and attributable to increased OCT CMT. The choice of rescue therapies includes alternative anti-VEGF agents and intravitreal steroid therapy as permitted by NICE guidance. Macular laser is not a permitted rescue therapy within the trial follow up period.

Cataract surgery: Patients with visually significant cataract can undergo cataract surgery at any time.

Concomitant And Excluded Therapies

Concomitant medications are any prescription drugs used by a patient during the study, until conclusion of study participation (week 52) or early termination. The paper source documents and electronic case report forms will record administration of these medications. Use of concomitant treatment with a clinical device should also be recorded.

Patients will be assessed for evidence of significant cataract as part of their clinical assessment and may undergo cataract surgery at any time up to 10 months. A more formal and thorough assessment for the presence of visually significant cataract should take place at month 9, allowing reasonable time for treatment and recovery before final assessment.

No other experimental or investigational treatments are allowed during this study, including ocular experimental and investigational treatments in the study eye

Study Assessments

A table of procedures by visit is listed below. Written informed consent must be obtained prior to all enrolment events. Investigators must undertake the necessary tests and examinations at each visit and complete the paper source documents in full. Anonymous data from the case report forms (CRF) will be uploaded onto the Castor online database.

PIs at each centre will be setup with a login for the Castor database allowing them to enter anonymous patient data and access the randomisation feature.

10.1 Assignment of Patient Identification

A patient identification (ID) number, which will be assigned at screening, should be used on all study-related documents. To maintain confidentiality, the participant's name should not be recorded on any study document other than the informed consent form. The participant ID will have six digits. The first two digits will identify the site. The following four digits will be assigned to patients sequentially across all sites.

10.2 Subject recruitment

This feasibility trial requires 100 patients to be recruited.

Patients presenting with CIDME who fulfil NICE guidelines for treatment with intravitreal Ranibizumab or Aflibercept will be identified and approached for inclusion in the trial within the first two months of treatment of diabetic macular edema. Patients will be provided with a patient Information sheet (PIS) at this time.

Those fulfilling the trial eligibility criteria (see above) will undergo a total of 3 intravitreal injections in the affected eye at monthly intervals prior to enrolment.

Patients not fulfilling the trial inclusion criteria will be returned to standard NHS care.

10.3 Screening Procedures

Patients will not need to undergo any additional screening procedures. Any tests that may form part of the eligibility criteria are routine tests patients would undergo as part of standard NHS care for the management of DME. Review of notes and routine Investigations are sufficient to identify eligible candidates.

10.4 Consent

Consenting patients with an OCT CMT of at least 350 microns 3 months after initiation of Ranibizumab or Aflibercept therapy will be randomized to the intervention or control arms on a 1:1 basis in blocks of a size unknown to the investigators.

Consent will be obtained by PI or delegate in the clinical setting after their 3rd injection and before their 4th injection. Patients will, therefore, have 12 weeks to decide. 3 consent forms will be signed, 1 copy will be given to the participant; 1 in the researcher site file; and the original kept in the medical notes.

Interpreters will be employed for patients who might not adequately understand verbal explanations or written information given in English, or who have special communication needs.

10.5 Randomisation

Once the patient has completed enrolment, anonymous data will be entered into the online Castor† database. Castor will randomise patients to control or vitrectomy groups at a 1:1 ratio, stratifying for evidence of Vitreomacular Interface abnormality*. Block size will be unknown to the investigators.

Where two eyes of a participant meet inclusion criteria, the more affected eye in terms of BCVA and CMT will be selected for entry into the study.

Where possible, patients will be informed of their randomised group allocation in clinic. If not, patients will be informed by letter after the clinic.

*Vitreomacular Interface abnormality consists of Vitreo macular traction or epiretinal membrane as opposed to vitreo macular adhesion alone. Vitreo macular adhesion alone is defined as persistent adhesion of the hyaloid evident on an SD OCT scan but without any associated local distortion of the retinal surface.

†Anonymous and non-identifiable patient data should be entered onto the Castor platform either during clinic or at the next available opportunity. The Castor platform will then randomise patients to the Treatment or Control arm. Patients will return 4 weeks later either for vitrectomy or injection. It is not possible to mask patients with regards to vitrectomy surgery, therefore it is reasonable to inform the patient if they are having an operation or not.

10.6 Masking & other measures taken to avoid bias

10.6.1 Masking

Ophthalmologists and subjects will not be masked with regards to the performance of vitrectomy. Subjects cannot be masked to the performance of vitrectomy as it is unfeasible to perform a sham operation. Every effort will be made to ensure that outcome assessors (e.g. optometrists measuring visual function, and photographers/technicians/nurses obtaining OCT images) will be masked to the allocated treatment. The investigators obtaining outcome measures will have access to the CRF booklet not to the medical records in which any surgical procedure will be recorded. The CRF booklet will provide no information with regards to the type of treatment to which the patient had been allocated or received

10.7 Radiology

Not applicable.

10.8 End of Study Definition

A 52 week visit is performed regardless of the timing of the last injection visit. On completion of the 52-week visit the patient is returned to standard NHS care with a patient specific follow up date arranged

Schedule Of Treatment

11.1 Weeks -12 to week 0: Standard Ranibizumab or Aflibercept loading treatment and identifying prospective participants

Potentially eligible patients should be identified when first listed for DME treatment, or may subsequently be identified by review of the case notes once listed. This allows sufficient time for patients to read the Patient information sheet, ask questions and provide informed consent. Some patients will not meet the eligibility criteria, some patient's DME will improve to <350 microns and cease to be eligible, and some patients will not wish to participate.

Between weeks -12 – 0 patients will undergo routine tests for DME clinics, typically:

- Complog visual acuity or equivalent
- Macular OCT scan
- Slit lamp assessment
- Intravitreal treatment
- Assessment and treatment of clinically significant PCO

11.2 Week 0: Enrolment

The following assessments will be performed once the patient has consented to enrol in the study. It is preferred the assessments are completed on the same day. However if necessary the assessments may occur over 7 days. The patient is enrolled after all baseline tests are complete, Day 0.

Following enrolment patients will be randomised to treatment or control groups and receive their 4th Anti-VEGF injection with treat and extend follow up.

All treatment administered following successful enrolment will be recorded as part of the study.

11.2.1 Baseline measurements

Day 0 is marked by successful enrolment in the study and requires successful completion of baseline measurements.

The following baseline assessments are undertaken and information entered on Form B (Baseline Measurements). These measurements constitute the values for subsequent comparison.

11.2.2 Baseline Visual Function (optician)

To be completed by an optometrist or optician on both eyes

- Best corrected distance visual acuity measured in number of ETDRS letters measured using the COMPlog acuity measurement system
- Contrast sensitivity using COMPlog contrast measuring system, or Pelli Robson contrast test (at participating centres)

11.2.3 Baseline Clinical Assessment (clinician)

To be completed by assessing clinician on both eyes

- Background ocular and medical history – see Form B for details
- Blood pressure
- Slit lamp examination for cataract (Patients with cataract deemed to be visually significant are ineligible)
- Clinical examination to ensure compliance with the inclusion and exclusion criteria
- Heidelberg High resolution SD-OCT macular examination: volume scan centred at the fovea using a 20 × 20 degree cube with 49 raster B-scans each containing 1064 pixels, with a mean of 16 automatic real-time images per scan (or equivalent, see appendix)
    - e 2 macular OCT scans: routine macular cube and High resolution scan
- Hand-held multifocal ERG (St. Thomas' +/- Maidstone sites)

11.2.4 Baseline QOL Questionnaire (patient administered or interview administered)

25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) version 2000. To be completed by the patient and can be either self-administered if the patient is capable or administered with help from a research nurse, optometrist, sub-investigator or principle investigator.

This questionnaire is available free of charge from:

http://www.rand.org/health/surveys_tools/vfq.html

Form B is to be completed as part of baseline assessments.

11.2.5 Form B – Baseline Measures

Field Name	Field Type	Options or Units
Demographics		
Study ID Number	Number	No units
Randomisation Group	Single select	Vitrectomy, Standard
Age	Number	Years
Gender	Single select	Male, Female
Race	Single select	White, Afro-Caribbean, Sub-continental Asian, Oriental Asian, Hispanic-South American, Other
Type of Diabetes	Single select	Type 1, Type 2
Duration of Diabetes	Number	Years
Past Med History (excl DM)	Text	Free text
Past Ocul History (excl DR)	Text	Free text
Drug History	Text	Free text
Allergies	Text	Free text
Baseline Assessment		
HbA1c % (within 2 months)	Number	%
BP systolic	Number	mmHg
BP diastolic	Number	mmHg
BCVA	Number	Measured with complog, numbr of ETDRS letters
Contrast Sensitivity	Number	Pelli-Robson log Units using COMPlog (at participating centres)

Lens Status	Single select	Phakic, Pseudophakic, Aphakic
Presence of visually significant cataract	Single select	Yes/No
OCT Central Subfield	Number	microns
Cystoid Spaces on OCT	Single select	Yes, No
Subretinal Fluid on OCT	Single select	Yes, No
Epiretinal membrane	Single select	Yes, No
Macular pucker	Single select	Yes, No
Vitreomacular traction	Single select	Yes, No
Contiguous traction	Single select	Yes, No
PVD present	Single select	Yes – complete, Yes – partial, No
Grading of retinopathy	Single select	Mild NPDR, moderate NPDR, severe NPDR, very severe NPDR, active PDR, inactive DR See reference photos and descriptions
(Light adapted) ERG	Single select	Yes, No
QoL Score	Number	0-100

11.3 Randomisation

Once all baseline tests have been completed patients may be enrolled in the trial and randomised on the same day. Randomisation takes place as outlined above.

11.4 4th Ranibizumab or Aflibercept

Following Randomisation patients should receive their 4th Anti-VEGF injection. This should fall approximately 90 days after their 1st injection.

Aflibercept patients should receive a scheduled 5th Injection 1 month after their 4th.

Subsequent follow up is in line with Treat and Extend pathway as outlined in Form G.

Any delay in randomisation should not prevent patients receiving their scheduled Anti-VEGF treatment on time. Randomisation takes place through the Castor platform and if, in the context of a busy clinic, this is delayed until after the clinic is finished patients may still proceed with treatment and be randomised later that day.

11.5 Week 0-4: Vitrectomy group

Pars plana vitrectomy with ILM peel +/- PRP laser will be performed on the Vitrectomy group within 4 weeks of randomisation. Specifics regarding the procedure are listed above.

Post-operative follow up should take place at 2 weeks. Thereafter patients will be reviewed regularly in clinic as part of treat and extend follow up.

11.6 Repeat Measurements

At follow-up visits (month 1 to month 12) Form E (Follow Up) is completed by the principle investigator or a sub-investigator. This involves:

- COMPlog visual acuity with habitual correction and pinhole.
- OCT macular volume scan to determine central sub field thickness
- Slit lamp examination for visually significant cataract (dilated slit lamp exam) and to determine safety of treat and extend injection.
- Recording of the treatment performed as per the Form G Treatment Protocol
- Recording of trial related complications
- Determination of follow up visit timing

A more formal and through assessment for the presence of visually significant cataract should take place at Month 9.

11.6.1 Form E – Follow-up Visits

Follow-up Visits		
Patient ID	Number	001-100
Follow up visit	Number	1-
Weeks post randomization	Number	0-52
Habitual correction and pinhole COMPlog VA	Number	Measured COMPlog acuity in number of ETDRS letters
BCVA last visit	Number	Lookup number of ETDRS letters
Best previous VA	Number	Lookup number of ETDRS letters
Change in VA from last visit	Number	Calculated number of ETDRS letters
Change in VA from best post randomization value	Number	Calculated number of ETDRS letters
Lens Status	Single select	Phakic, Pseudophakic, Aphakic
Cataract surgery required	Single select	Y/N
Cataract surgery since last visit	Multi select	Yes/no, routine/complex, adjuvant VEFG/ no adjuvant Rx, date
OCT CSF Thickness	Number	Measured OCT ETDRS grid average CSFMT microns
OCT CSF Thickness last visit	Number	Lookup OCT CSF Thickness
Best previous OCT CSF Thickness	Number	Lookup OCT CSF Thickness
Change from previous OCT CSF Thickness	Number	Calculated number of microns
Change from best post recruitment OCT CSF Thickness	Number	Calculated number of microns
Complications from Trial Treatment	Text	Free text
Management Plan	Single select	Criteria A-H from Follow Up Criteria Definition Table
Treatment given	Single select	Ranibizumab, Aflibercept, Ozurdex, Iluvian, Avastin, Triamcinolone, none
Follow up interval weeks	Select	4, 8, 12, (covid19 extension:)
Date of next follow up appointment	Date	

11.7 Final Measurements

At the final visit at week 52, Form F (Final Measurements) and the following assessments are completed

Final Visual Function

- Best corrected distance visual acuity measured in number of ETDRS letters measured using the COMPlog acuity measurement system
- Contrast sensitivity using COMPlog contrast measuring system, or Pelli Robson contrast test (at participating centres)

Final Clinical assessment

- Slit lamp examination
- Heidelberg High resolution SD-OCT macular examination: volume scan centred at the fovea using a 20 × 20 degree cube with 49 raster B-scans each containing 1064 pixels, with a mean of 16 automatic real-time images per scan (or equivalent, see appendix)
- Hand-held multifocal ERG (St. Thomas's and Maidstone sites)

Section 3 – Final QOL Questionnaire

To be completed by the patient and can be self-administered or administered by a research nurse, optometrist, sub-investigator or principle investigator.

11.7.1 Form F – Final Measurements

Final Visit 12 months		
BCVA	Number	COMPlog number of ETDRS letters
Contrast Sensitivity	Number	Pelli-Robson log Units using COMPlog (at participating centres)
Lens Status	Single select	Phakic, Pseudophakic, Aphakic
Presence of visually significant cataract?	Single select	Yes/No
Cataract surgery since trial recruitment	Multi select	Yes/no, routine/complex, adjuvant VEFG/adjuvant steroid/no adjuvant Rx, date
OCT CSF Thickness	Number	microns
Cystoid Spaces on OCT	Single select	Yes, No
Subretinal Fluid on OCT	Single select	Yes, No
Epiretinal membrane	Single select	Yes, No
Macular pucker	Single select	Yes, No
Vitreomacular traction	Single select	Yes, No
PVD present	Single select	Yes – complete, Yes – partial, No
Grading of retinopathy	Single select	Mild NPDR, moderate NPDR, severe NPDR, active PDR, inactive DR See reference photos and descriptions
(Light adapted) ERG	Single select	Yes, No
Complications from Trial Treatment since Recruitment	Text	none
QoL score	Number	0-100

1.8 Withdrawal of Participants and Treatment Stopping Rules

Participants have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Patients will be offered follow up in routine DME clinic.

For patients that have undergone vitrectomy, they will be offered routine post-operative follow up in conjunction with follow up in the DME clinic.

Covid-19 Trial Amendment

The COVID-19 pandemic in December 2019 has had a significant impact on outpatient ophthalmology services in the UK.

Due to concerns for patient safety, staffing provisions and and in-line with Royal College of Ophthalmologists guidelines, outpatient clinic capacities have been reduced and patients, with conditions such as DMO, have been seen less frequently and with increasing treatment intervals.

Therefore, we understand and appreciate the difficulties of following the protocol for the treatment of VIDEO patients as outlined within this document.

As sites begin to the process of increasing outpatient capacity and trial patients are able to be seen again, we hope the following amendment provides guidance on how to manage patients who have deviated from the initial trial protocol as a consequence of the unprecedented COVID-19 pandemic.

12.1 Treatment guidance

We anticipate patients will fall into 1 of 4 categories:

1. Patients have been seen as per the trial protocol throughout:

Continue treatment as per the protocol

2. Patients who have missed a scheduled appt and **deteriorated**:

Return to last successful treatment interval

i.e. if previously patients were stable at an 8/52 interval then treat and return to 8/52 Intervals. Patients can subsequently be managed as per the treat and extend pathway.

3. Patients who have missed scheduled appointments and are **stable:**

a. If last treatment was less than 6 months ago, consider this an ‘opportunistic extension’ and continue to treat and review patient at this interval until the final (week 52) visit.

The interval can be reduced in 4 week blocks If there are subsequent signs of deterioration.

b. If treatment was more than 6 months ago (so patient has missed the equivalent of 2 x 12/52 appointments) then patients should be considered stable without treatment and enter a monitoring

cycle. The subsequent monitoring visit should take place at ½ the interval time.

i.e. reviewed in 3/12 times, if last treated 6/12 ago, or at the final (week 52) visit.

Criteria for stability and deterioration remain unchanged and as outlined above.

12.2 Figure 2 Flow diagram of COVID-19 outcomes

Clinical Parameters

Ophthalmic assessments will include COMPlog best corrected VA, contrast sensitivity (at participating centres), wide field colour fundus photography and optical coherence tomography. Maidstone and St. Thomas' sites will also perform a hand held ERG. The number of anti-VEGF injections will also be recorded. Whenever possible, the same person should perform the evaluations specified by the protocol at each study visit. Except where otherwise indicated, ocular assessments should be performed on the study eye only.

13.1 ETDRS Best-corrected visual acuity

Optometrist or Optician performs manifest refraction and VA measurements at baseline and final visit using COMPlog VA software. Trained member of staff completes VA at follow up visits using COMPlog software. See appendix.

13.2 Optical coherence tomography (OCT)

Spectral domain OCT will be utilised to assess central subfield thickness, cystoid edema, subretinal fluid, epiretinal membrane, vitreomacular traction, macular pucker, and PVD.

Investigating units will perform grading.

Copies of the high resolution baseline and final visit OCT scans will be transferred to the central unit, in accordance with safe data transfer policies.

At each of follow up visit the Investigator will review the participant's OCT. At baseline and final visit higher resolution macular scans will also be taken and transferred to the reading centre.

OCTs will be taken by qualified technicians, acquired and transferred in a timely manner, using the protocol specified by the reading centre.

Follow-up-visit OCT images are not sent for central review and should be captured using the same approved device, technician, and technique of image acquisition. The OCT scan should be centred on the fovea, in the same position each visit. The OCT software will provide an objective thickness reading in the central 1 mm subfield. This reading is recorded each visit as part of the study. It may also be used, alongside other criteria, to determine appropriate management.

This automated reading should be checked for errors as it is possible that the OCT software fails to correctly identify the inner and outer neural retina limits correctly.

If there are segmentation errors then a manual adjustment should be made, by repositioning all the central segmentation lines and re-reading the central 1mm subfield value. This corrected value should be recorded in the source documents and eCRF, and it should also be recorded that a manual adjustment was made.

Baseline and final visit OCT scans will be exported anonymously in accordance with safe data transfer policies for central review. Reviewers will assess scans for pre and post treatment inner and outer retinal change.

13.3 Vitreomacular Interface classification

Vitreomacular Interface abnormality consists of Vitreo macular traction or epiretinal membrane as opposed to vitreo macular adhesion alone. Vitreo macular adhesion alone is defined as persistent adhesion of the hyaloid evident on an SD OCT scan but without any associated local distortion of the retinal surface.

13.4 Wide field photography and retinopathy grading

Wide field photography for assessment of retinopathy should take place in all patients at baseline and final visit. Photography may be repeated during follow up visits if the examining clinician feels it to be necessary.

Wide field colour photography is recommended where available, which can capture >200 degrees of the retina. E.g. Optos 200tx. If not available 4 field colour stereo fundus photography should be used. Images and retinopathy should be graded in line with the EDTRS Retinopathy Severity Grading score. See appendix.

Laboratories

Not applicable

Health Economic And Quality Of Life Questionnaire

The health economic component of VIDEO will estimate the relative cost-effectiveness of Vitrectomy and help determine whether Vitrecomy in conjunction with Anti-VEGF provides value for money for the NHS. The main outcome measure will be quality of life, which will be used to calculate a cost per quality-adjusted life year (QALY) gained for vitrectomy plus Ranibizumab or Aflibercept versus Ranibizumab or Aflibercept alone.

Participants will complete the National Eye Institute 25 Item Visual Function Questionnaire (VFQ-25) at enrolment and at week 52. The questionnaires, with instructions, are provided in the source documents.

This provides some indication of the baseline quality of life (in terms of visual function) and a change in response to treatment of the population compared on a common scale with other trial populations.

Costing will aim to estimate the cost of performing vitrectomy alongside Ranibizumab or Aflibercept in routine clinical practice. The number of Anti-VEGF injections, monitoring consultations and ocular imaging procedures will be collected on standard trial forms

Analysis of costs and cost-effectiveness will follow standard NICE guidelines.

Assessment Of Safety

16.1 Definitions:

16.1.1 Adverse Events (AE):

An adverse event (AE) includes any untoward sign, symptom, disease, or condition associated with the use of the study treatment (Vitrectomy or Anti-VEGF) regardless of the suspected cause. Conditions or diseases that are chronic but stable should not be recorded on the CRF.

16.1.2 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)

16.1.3 Serious Adverse Events

An AE should be classified as a serious adverse event (SAE) and reported as such, if it meets one or more of the following criteria:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life threatening (i.e., the AE places the participant at immediate risk of death)
- It results in hospitalization or prolongation of hospitalisation
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the participant's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- The investigator considers it an important medical event because, based on medical judgment, it may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above
- It is considered sight-threatening by the investigator.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolongation of hospitalization for diagnostic, medical or surgical procedures for pre-existing conditions;
- Hospitalization or prolongation of hospitalization required to allow outcome measurement for the study;
- Hospitalization or prolongation of hospitalization for treatment of the target disease of the study.

16.1.4 Sight threatening events

- An event is considered sight-threatening and should be reported as an SAE if it meets one or more of the following criteria:
- It is associated with a decrease in visual acuity of >30 ETDRS letters (compared with the assessment of visual acuity at the last visit)
- It is associated with a decrease in visual acuity to the level of Light Perception or worse
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of antibiotics, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)
- In the opinion of the investigator it may require medical or surgical intervention to prevent permanent loss of sight.

16.2 Adverse event assessment

All participants who have been exposed to the study treatment will be evaluated for AEs at each visit. All AEs, regardless of severity or seriousness and whether or not they are ascribed to the study treatment, will be recorded in the source documents and eCRF using standard medical terminology.

All AEs will be evaluated beginning with onset, and evaluation will continue until resolution is noted, or until the investigator determines that the participant's condition is stable. The investigator will take appropriate and necessary therapeutic measures required for resolution of the AE. Any medication or other intervention necessary for the treatment of an AE must be recorded on the concomitant medication section of the source documents and eCRF.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Expectedness
- Outcome
- Treatment or action taken.

16.3 Adverse Event Terms

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used. Only one medical concept, preferably a diagnosis instead of individual symptoms, should be recorded as the event.

If more than one distinct AE occurs, each event should be recorded separately.

However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the eCRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnoea, rales, and cyanosis). If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. If a diagnosis is subsequently established, this information should be reported on the source documents and eCRF as follow-up information.

Signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as a separate AE).

AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE.

If a participant is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event. For example, if a participant is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass.

16.4 Adverse Event Intensity/Severity

All AEs should be graded on a three-point scale (mild, moderate, severe) for intensity/severity. Unless otherwise defined in the protocol, these definitions are as follows:

Mild: Transient; no medical intervention/therapy required and does not interfere with daily activities.

Moderate: Low level of concern and only mild to moderate limitation in daily activities; some assistance may be needed; minimal or no medical intervention/therapy required.

Severe: Severe limitation in daily activities, significant assistance required; significant medical intervention/therapy required.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a serious adverse event (SAE). For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs listed in the section Serious Adverse Events, above.

16.5 Treatment or Action Taken

The intervention taken to treat an AE is defined as:

- None
- Medical intervention
- Surgical intervention
- Other (specify).

16.6 Adverse Event Outcome

The clinical outcome of an AE will be characterized as follows:

- Resolved without sequelae
- Resolved with sequelae (specify)
- Ongoing (i.e. continuing at time of study discontinuation)

16.7 Adverse Event Follow up

All AEs and SAEs will be followed through to resolution or 30 days after the participant terminates from the study, whichever occurs first.

The Sponsor or its designee may follow-up with the site by telephone, fax, email, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

16.8 Reporting Adverse Events

Serious Adverse Events must be reported to the Chief Investigator/Trial Manager within 96 hours of learning of their occurrence.

Immediately after the trial personnel become aware of any SAE the Principal Investigator with responsibility at each research site must report them to the Chief Investigator or the organizing research team on the form specified. The Principal Investigator or his/her research team must also follow all through to outcome, and report to the Chief Investigator, or to the organising research team on the form specified.

In addition, the Investigator should expeditiously notify the Chief Investigator of any of serious adverse events that occurs after a participant has completed or discontinued from study participation.

Contact details for submission to:

Chief Investigator (DAH Laidlaw) or Trial Manager (Eme Chan)

The initial report can be made by completing the SAE form, emailing or faxing to:

Eme Chan

Email: eme.chan@gstt.nhs.uk

Tel: 02071884885

A record of this notification (including the date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, a follow up report should be provided as soon as the information becomes available

16.8.1 Reports to Ethics Committee

Please see Appendix 1 “Information with regards to Safety Reporting in Non-CTIMP Research”

The Chief Investigator will provide an annual report of all SAEs which will be distributed to the Data Monitoring and Ethics Committee (DMEC) or the REC, as appropriate

16.8.2 Expectedness

All AEs will be evaluated as to whether they are expected or unexpected.

Expected (anticipated): An AE is expected if it is identified in the list of expected adverse events below, or in the latest Ranibizumab or Aflibercept Summary of Product Characteristics, or the Patient Information Sheet.

Unexpected (unanticipated): An adverse event is unexpected if it is not identified in the list of adverse events below or in the latest Ranibizumab or Aflibercept Summary of Product Characteristics or the Patient Information Sheet.

16.8.3 Expected (anticipated adverse) events

- Post injection endophthalmitis
- Post vitrectomy endophthalmitis
- Vitreous or choroidal Haemorrhage
- Cataract
- Inflammation
- Retinal tear or detachment

- Intraocular pressure of ≥ 45 mmHg
- Worsening of Cystoid Macular Oedema
- acute post injection visual loss ≥ 30 ETDRS letter (post injection here is

defined as within 30 minutes of the injection)sight-threatening adverse event: e.g. central retinal vein occlusion, retinal detachment, sterile endophthalmitis

16.9 Relatedness

- Serious adverse events should be assessed in terms of the causality or relatedness to the following events:
- Ranibizumab drug
- Aflibercept drug
- Ranibizumab or Aflibercept injection procedure
- Vitrectomy surgery
-
- This relationship should be classified as follows:
- Not related
- Remote
- Possible
- Probable
- Definite

16.10 Trial Steering Committee (if applicable)

Due to the size of the trial and as a small feasibility trial there is no TSC for this study.

16.11 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

The Medicines and Healthcare products Regulatory Agency (MHRA) has reviewed the VIDEO protocol. They have determined that the trial is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) as defined by the EU Directive 2001/20/EC and that no submission to the Clinical Trials Unit at the MHRA is required.

The protocol and related documents have been reviewed and approved by a UK Research Ethics Committee (REC) prior to trial commencement. The details of the REC will be provided to participants and study sites by the Sponsor.

Annual progress and safety reports and a final report at the conclusion of the trial will be submitted to the REC within the timelines defined in the Regulations.

Prior to recruitment of any participants into the study at each participating site, Site Specific Approval (SSA) and NHS Research and Development approval must also be obtained.

Any changes to the protocol must be discussed and approved by Sponsor in writing unless the change is made to assure the safety of the participant.

Signed consent forms must remain in each participant's study file and must be available for verification by study monitors at any time.

Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

1. The incidence or severity of adverse events in this or other studies indicates an unacceptable potential health hazard to participants.
2. Patient enrolment is unsatisfactory.
3. Data recording is inaccurate or incomplete.

Compliance And Withdrawal

18.1.1 1Subject compliance

Patients will be seen at outpatient clinic and injections administered by clinician. Therefore compliance will be documented in patient notes and on proforma. Compliance can be measured by their attendance to clinic.

Vitrectomy will be performed by operating surgeon and compliance will be recorded in patient notes and proforma.

As a real world study non-attendance is anticipated to some degree, as in all NHS clinics.

18.2 Withdrawal / dropout of subjects

Patients will be withdrawn from the trial if they withdraw consent at any stage. They will then return to standard NHS care without prejudice. Any collected data will be taken as last observation carried forward.

18.3 Protocol Compliance

Investigators should make every attempt to not deviate from the protocol. Deviations can ultimately affect the scientific soundness of the protocol, as well as the rights, safety and welfare of the participants. An Investigator who feels that a deviation from the protocol is necessary must submit a request to the Chief Investigator or Trial Manager by email.

Prior approval of a protocol deviation is not required for clinically urgent actions that are undertaken to protect participants, if the delay needed for prior approval would increase the risk to the participant. A protocol deviation form must be sent to the Chief Investigator for all deviations that occur.

The Sponsor will authorise all changes to the protocol as an amendment to the protocol, and approval will be sought from the REC and HRA prior to implementation.

Data

19.1 Data to be collected

Data collected will include eligibility criteria, patient history and examination findings. The consulting clinician will collect these at clinic visits.

A member of the nursing staff, optometry department or direct care team will perform visual acuity tests on all patients at all outpatient visits. This will be obtained using standardised COMPlog visual acuity software and recorded in the CRF.

Investigations will also include an OCT scans of the retina performed at each outpatient visit and obtained using standardised OCT recording software by a trained member of the direct care team. These images will be stored on a single unit, password protected OCT machine. Measurements from these scans, such as central macular thickness, will be recorded in the CRF and as anonymous data on the Castor Platform.

Wide field photography of the retina and retinopathy grading will be performed at the beginning and end of the study. A trained member of the direct care team will obtain these images and the images will be stored on a password-protected computer.

A Standardised Quality of Life Questionnaire (see above) will be performed by the patient at baseline and end of the trial in the clinic. The results will be stored in the CRF.

We do not anticipate any investigations to be obtained outside the clinical setting.

All the data collected is routine data that is collected as part of standard treatment for DME. All images are also routine and will be stored securely and routinely on hospital computers.

19.2 Data handling and record keeping

The local investigator must maintain the following accurate, current, and complete records relating to his/her participation in the study:

- All correspondence with another local investigator, REC, Sponsor, monitor, including required reports
- Records of each participant's source documents including signed and dated consent forms and medical records, progress notes, hospital or clinical charts and nurses' notes
- All relevant observations, including records concerning adverse surgical or drug effects, information and data on the condition of the participant upon entering and during the course of the study, including information about relevant previous medical history and the results of all diagnostic tests
- The protocol, with documents showing the dates of and reasons for each deviation from the protocol
- Source documents

- Fundus photography, OCT images

All study records should be maintained in a locked, limited-access area.

The local Investigator will act as custodian for the trial data at each site. The following guidelines will be strictly adhered to:

- Patient data will be anonymised before sharing with the central study team
- All anonymised data will be stored on a password protected computer
- All trial data will be stored and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006.

The local Principal Investigator shall maintain all study records for 5 years or until notified by the Chief Investigator that retention is no longer required, whichever occurs soonest. If the local Investigator moves from the site at which he/she conducted the study and/or maintained the study records, the local Investigator shall notify the Chief Investigator in writing whether the records will remain at the site at which the study was conducted or be moved to another location, and if another location, where and under whose custody. The Investigator shall notify the Sponsor as soon as possible in the event of destruction or loss of any study records.

The chief investigator will have access to the final trial dataset.

19.3 Data management

All study data will be initially entered onto paper source documents and then transferred into the online Castor platform. All requested information must be entered on the castor platform. If an item is not available or not applicable this fact should be indicated. Data management must comply with the Data Protection Act 1998. The data management team and study monitors may raise queries using the electronic system, and the study site Investigator must provide a response in a timely manner.

To ensure the quality of clinical data across all participants and sites, data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol. To resolve any questions arising from the clinical data, data queries and/or site notifications will be created in the database for resolution

Statistical Considerations

Statistician: Dr. Pirro Hysi

This is a small prospective randomised controlled feasibility trial seeking to recruit 100 patients.

The primary outcome is best corrected visual acuity.

Secondary outcomes include Number of injections, Rate of recruitment, Rate of completed follow up, OCT ETDRS Central Sub Field Macular thickness, Area under the curve of CMT

Area under the curve of BCVA, (Best corrected visual Acuity)

Rate of loss of 15 or more letters from baseline, Rate of rescue therapy, Rate of cataract surgery

Rate of complications.

Descriptive and summary statistics at baseline and final visit. Classical hypothesis testing between control and intervention group on parametric and non-parametric data as appropriate. Correlation analysis as appropriate.

We hope to be guided by this trial on the feasibility of sample size scaling to power a larger definitve randomised control trial of the same question.

Ethical Considerations

The study has been Peer reviewed by Fight for Sight UK, and PIS have been reviewed by the Macular Disease Society UK. Members of the public have reviewed patient information sheets.

The Health Research Authority (HRA) and Research Ethics Committee (REC) have reviewed all trial documents and given approval for this study.

Translators will be sought in cases of non-english speaking eligible patients.

Those lacking capacity will not be eligible for this study.

Patients may withdraw at any stage of the trial, free from prejudice.

The Principal Investigators (PI) at each site must comply with the signed Statement of Activities. The PI must have and maintain current good clinical practice (GCP) training, and ensure that all trial staff do likewise. He or she may delegate tasks to appropriately trained staff, but he or she maintains responsibility for their conduct. The PI shall ensure that there is a delegation log detailing all staff involved in the conduct of the trial at his or her site.

Protocol amendments will be disseminated, with approval from sponsor’s R&D department, to trial units via email. Relevant and accompanying documentation will be included.

Informed Consent

The Investigator is responsible for obtaining the legally effective informed consent of the participant. In carrying out this responsibility, the investigator (and other involved team members) should recognise that informed consent is not just a signature on an informed consent form, but a process during which the participant and those with whom the participant wishes to consult (such as family members, friends,

and personal physicians) are provided with sufficient information about the study under circumstances that allow the participant to consider whether or not to participate and to minimize the possibility of undue influence or coercion.

Once the REC has approved the Patients Information Sheet and Informed Consent Form, the form should be used as the basis of the information presented to the participant during the informed consent process. The form should be provided to the participant early in the process, so that he/she has ample time to read it and discuss it with others if he or she wishes to do so.

Each of the following key elements must be discussed with the participant:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the participant.
- A description of any benefits to the participant or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
- A statement describing the extent, if any, to which confidentiality of records identifying the participant will be maintained and that notes the possibility that regulatory authorities and external monitors may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research participants' rights, and whom to contact in the event of a research-related injury to the participant.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.
- A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or foetus, if the participant is or may become pregnant) which are currently unforeseeable.
- Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent.
- Any additional costs to the participant that may result from participation in the research.
- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.

Once the informed consent process is complete and the participant has reached a decision as to whether to participate, the investigator should record the decision in the case history form. A participant who decides to participate should be asked to sign the Informed Consent Form. A copy of the signed form should be given to the participant, and the signed form should be included with the participant's study records.

If there is any new information which may affect a participant's willingness to continue participating in the trial, he or she will be re-consented with an amended or supplementary Patient Information Sheet and Consent Form

Financing And Insurance

Funding is supplied by Fight for Sight.

Insurance is provided by KCL.

Reporting And Dissemination

We aim to publish the data and trial findings in peer-reviewed journals and at national and international meetings.

The named authors will comprise researchers who have made a significant contribution to study design, clinical or statistical analysis, and manuscript preparation.

Funders will not be responsible for the study design, collection, management of data or publication.

Useful reading/websites

Integrated Research Application System (IRAS)

https://www.myresearchproject.org.uk/

Health Research Authority (HRA)

www.hra.nhs.uk

HRA Guidance for Patient Information Sheet and Informed Consent

http://www.hra.nhs.uk/research-community/before-you-apply/participant-information-sheets-and-informed-consent/

CONSORT statement

A set of recommendations for improving the quality of reports of parallel group randomised trials

http://www.consort-statement.org/

ICH Harmonised Tripartite Guidelines for Good Clinical Practice (1996)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Martin Bland et al, Statistical guide for research grant applications

http://www-users.york.ac.uk/~mb55/guide/guide.htm

Includes detailed information and definitions of many aspects required for a research protocol as well as information about randomisation software and services

Martin Bland, Directory of randomisation software and services

http://www-users.york.ac.uk/~mb55/guide/randsery.htm

Declaration of Helsinki

(http://www.wma.net/en/30publications/10policies/b3/index.html)

Abbreviations

AE	Adverse Event
AMD	Age Related Macular Degeneration
AR	Adverse Reaction
ASR	Annual Safety Report
BCVA	Best Corrected Visual Acuity
CA	Competent Authority
CI	Chief Investigator
CIDME	Centre Involving Diabetic Macular eEdema
CMT	Central macular thickness
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee

DME	Diabetic Macular Oedema (interchangeable with DMO)
DMO	Diabetic Macular Oedema (interchangeable with DME)
EC	European Commission
ERG	Electroretinography
ERM	Epiretinal Membrane
FFA	Fundus Fluorescein Angiogram
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ILM	Internal Limiting Membrane
ISRCTN	International Standard Randomised Controlled Trial Number
logMAR	Logarithm of the Minimal Angle of Resolution (visual acuity test)
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NICE	National Institute for health and Clinical Excellence
NHS R&D	National Health Service Research & Development
OCT	Ocular Coherence Tomography
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
Participant	An individual who takes part in a clinical trial
PCO	Posterior Capsular Opacification
PPV	Pars Plana Vitrectomy
PRP	Pan Retinal Photocoagulation
PVD	Posterior Vitreous Detachment

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SD – OCT	Spectral Domain Ocular Coherence Tomography
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
VEGF	Vascular Endothelial Growth Factor
VMT	Vitreomacular Traction

Figures

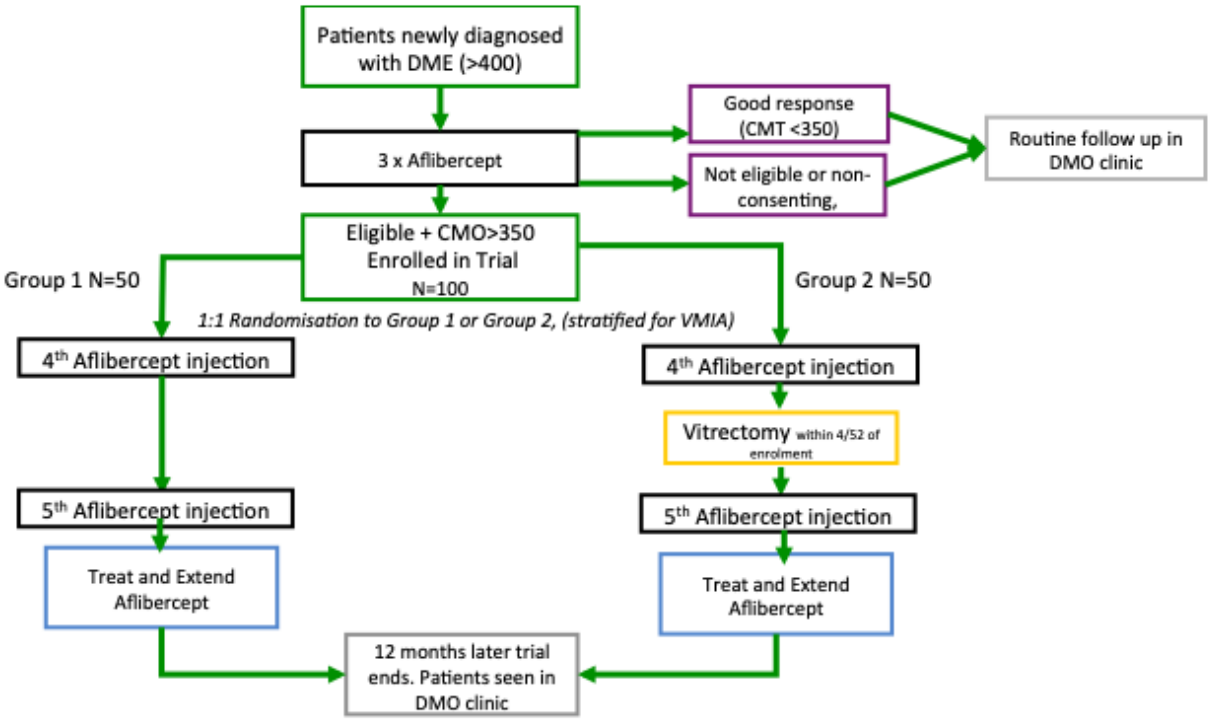

Figure 1

Trial summary

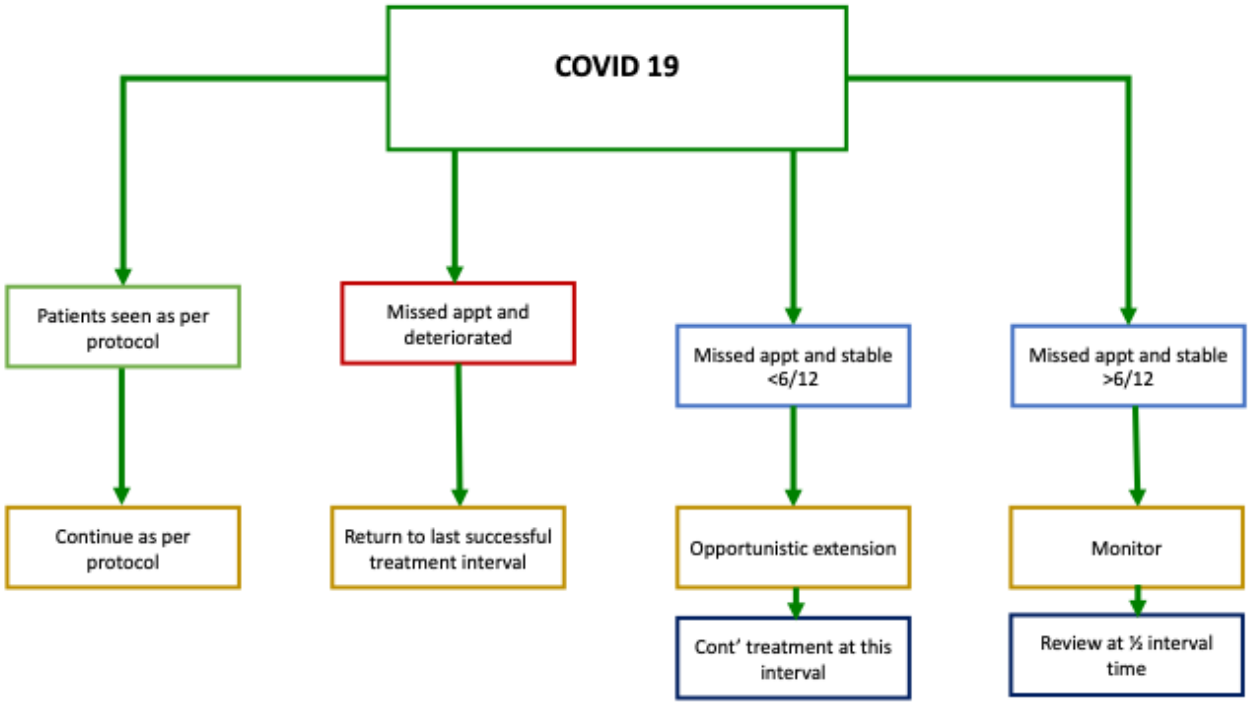

Figure 2

Flow diagram of COVID-19 outcomes

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1.pdf
- 13.image4.docx
- PIS.docx
- SpiritChecklist.doc
- consentform.doc