Full title of trial	Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy (acronym CLARITY). A Multicentre Phase IIb Randomised Active-Controlled Clinical trial
Short title	CLARITY
Version and date of protocol	Version 4.0 17/SEP /2015
Sponsor:	Moorfields Eye Hospital NHS Foundation Trust
Sponsor protocol number	SIVS1012
Funder (s):	NIHR Efficacy and Mechanism Evaluation (**EME12/66/15**)
EudraCT no	2013-003272-12
ISRCTN no	32207582
ACTIVEINTERVENTION:	Intravitreal Aflibercept
COMPARATOR INTERVENTION:	Panretinal photocoagulation (PRP)
Phase of trial	IIb
Sites(s)	Multi-site

Chief Investigator:
Professor Sobha Sivaprasad
Tel: +447817886759
Fax: +442075662972
email:sobha.sivaprasad@nhs.net

Sponsor Representative:
Mrs Maria Hassard
Tel: 44(0)2075662819
Fax: 44(0)2075662315
e-mail: maria.hassard@moorfields.nhs.uk

Protocol Approval Page

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 investigators agree to conduct the trial in compliance with the approved protocol, 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

Professor Sobha Sivaprasad Moorfields Eye Hospital	Signature	Date

Sponsor Representative

Mrs Maria Hassard Moorfields Eye Hospital	Signature	Date

Contents

List of abbreviations

Abbreviation	Definition	Abbreviation	Definition
ANOVA	Analysis of Variance	MS	Member State
AE	Adverse Event	NetwORC UK	Network of Ophthalmic Reading Centres UK
AR	Adverse Reaction	NICE	National Institute for Health and Care excellence
BCVA	Best Corrected Visual Acuity	NHS	National Health Service
BP	Blood Pressure	NIHR	National Institute of Health Research
CA	Competent Authority	NIMPS	Non-investigational medicinal products
CFP	Colour Fundus Photograph	NV	Neovasularisation
CRF	Case Report Form	NVA	Neovascularisation of the angle
CSRI	Clinical Service Receipt Inventory	NVD	Neovasularisation Disc
CST	Central Sub-field Thickness	NVE	Neovascularisation elsewhere
CTA	Clinical Trial Authorisation	NVG	Neovascular glaucoma
CTU	Clinical Trials Unit	NVI	Neovascularisation of Iris
CTIMP	Clinical Trial of Investigational Medicinal Product	OCT	Optical Coherence Tomography
DMEC	Data Monitoring and Ethics Committee	PDR	Proliferative Diabetic Retinopathy
DMO	Diabetic Macular Oedema	PI	Principal Investigator
DR	Diabetic Retinopathy	PIS	Participant Information Sheet
DSUR	Development Safety Update Report	PP	Per protocol
EASD	European Association for the Study of Diabetes	PRN	Pro Re Nata
EC	European Commission	PRP	Panretinal photocoagulation
EDC	Electronic Data Capture	QA	Quality Assurance
eCRF	Electronic Case Report Form	QALY	Quality-adjusted Life Years
eMC	Electronic Medicines Compendium	QC	Quality Control
EMA	European Medicines Agency	QP	Qualified Person for release of trial drug
EME	Efficacy and Mechanistic Evaluation	RCT	Randomised Control Trial
EQ-5D	Euro Quality of life questionnaire	RCOphth	Royal College of Ophthalmologists
ETDRS	Early Treatment Diabetic Retinopathy Study	R&D	Research and Development
EU	European Union	REC	Research Ethics Committee
EUCTD	European Clinical Trials Directive	RetDQoL	Retinopathy-Dependent Quality of Life Questionnaire
EudraCT	European Clinical Trials Database	RetTSQ	Retinopathy Treatment Satisfaction Questionnaire
FFA	Fundus Fluorescein Angiography	SAR	Serious Adverse Reaction
GCP	Good Clinical Practice	SAE	Serious Adverse Event
GP	General Practitioner	SD-OCT	Spectral-domain optical coherence tomography
HbA1c	Glycosylated Haemoglobin	SDW	Source Data Worksheets
HQoL	Health related quality of life	SE	Study Eye
ICECAP-A	Capability-wellbeing questionnaire	SOP	Standard Operating Procedure
ICF	Informed Consent Form	SPC	Summary of Product Characteristics
IMP	Investigational Medicinal Product	SUSAR	Suspected Unexpected Serious Adverse Reaction
IOP	Intraocular Pressure	TMG	Trial Management Group
ISRCTN	International Standard Randomised Controlled Trial Number	TSC	Trial Steering Committee
ITT	Intention to treat	UK	United Kingdom
KCTU	King's Clinical Trials Unit	VA	Visual Acuity
MA	Marketing Authorisation	VEGF	Vascular Endothelial Growth Factor
MEH	Moorfields Eye Hospital	VEGF-R	Vascular Endothelial Growth Factor Receptor
MHRA	Medicines and Healthcare products Regulatory Agency	VFQ 25	Visual Function Questionnaire

1 Trial personnel

Position	Name	Address	Email, telephone, fax and
Chief Investigator (CI)	Professor Sobha Sivaprasad	NIHR Moorfields Biomedical Research Centre Moorfields Eye Hospital & UCL Institute of Ophthalmology 162,CityRoad, London, EC1V2PD	e: sobha.sivaprasad@nhs.net t: +44(0) 7817886759 f: +44(0) 2075662972
Sponsor's representative	Mrs Maria Hassard	NIHR Moorfields Biomedical Research Centre Moorfields Eye Hospital & UCL Institute of Ophthalmology 162,CityRoad, London, EC1V2PD	e: maria.hassard@moorfields.nhs.uk t: +44(0)2075662819 f: +44(0)2075662315
Co-lead	Mr Phil Hykin	NIHR Moorfields Biomedical Research Centre Moorfields Eye Hospital & UCL Institute of Ophthalmology 162,CityRoad, London, EC1V2PD	e: phil.hykin@moorfields.nhs.uk t: +44 (0) 2075662262 f:+44(0)2075 662972
Co-applicant & Lead Statistician	Professor Toby Prevost	Department of Primary Care and Public Health Sciences King's College London 5thFloor,CapitalHouse 42Weston Street LondonSE13QD	e: toby.prevost@kcl.ac.uk t: +44 (0)2078486799 f: +44 (0) 2078486620
Co-applicant & Operational Director, KCTU at KHP	Ms Caroline Murphy	King's College London PO64,M2.06 Institute of Psychiatry King's College London De Crespigny Park London SE58AF	e: caroline.murphy@kcl.ac.uk t: +44(0) 2078485273 f: +44(0) 2078485229
Co-applicant & Data Management Strategic Lead, KCTU at KHP	Miss Joanna Kelly	King's College London PO64,M2.06 Institute of Psychiatry King's College London De Crespigny Park LondonSE58AF	e: joanna.kelly@kcl.ac.uk t: +44(0) 2078480532 f: +44(0) 2078485229
Co-applicant	Professor James Bainbridge	Institute of Ophthalmology 11-43 Bath Street London, EC1V 9EL	e: j.bainbridge@ucl.ac.uk t: +44 (0) 207608 6889 f: +44 (0)2076086963
Co-applicant	Dr David Hopkins	Clinical Director and Diabetologist King's College Hospital NHS Foundation Trust, Denmark Hill, London SE 5 9RS	e: dhopkins3@nhs.net t: +44 (0)23 8079 5049 f: +44 (0)23 8079 6085
Co-applicant	Professor Phil Luthert	UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL	e:p.luthert@ucl.ac.uk t: +44(0)2076086989 f: +44(0)2076086983

Co-applicant	Prof Rhiannon Tudor-Edwards	Centre for Health Economics & Medicines Evaluation Bangor University Dean Street Building Gwynedd LL57 1UT	e:r.t.edwards@bangor.ac.uk t: +44 1248 383712 f:+44 1248 382153
Trial Manager	Ms Amy Riddell	Kings CTU King's College London PO64,M2.06 Institute of Psychiatry King's College London De Crespigny Park LondonSE58AF	e:Amy.riddell@kcl.ac.uk t:+44 2078486236 f: +442078485229
Trial Statistician	Miss Joana Vasconcelos	Department of Primary Care and Public Health Sciences King's College London 5thFloor,CapitalHouse 42Weston Street LondonSE13QD	e: joana.vasconcelos@kcl.ac.uk t: +442078488225 f: +442078486620

Independent Reading Centre	Ms Clare Newell	Central Angiographic Research Facility NetwORC UK Queen's University of Belfast Grosvenor Road Belfast BT12 6BA Northern Ireland	e:carf@qub.ac.uk t: +44 (0) 28 9063 2516 f: +44 (0) 28 9063 2666
Active intervention Distributor	Ms Nicky Heath	Specialist Pharmacy Technician Clinical Trial Operational Coordinator Royal Free London NHS Foundation Trust Pond Street London NW3 2QG	e:nicky.heath@nhs.net t:+44 (0)20 7317 7531 ext 36890 f: +44 (0)20 7830 2621

DMEC members	
Role in DMEC	**Name and position (address of Chair)**
DMEC Chair	Professor A. Sarah Walker, Professor of Statistics Medical Research Council Clinical Trials Unit (MRC CTU) at UCL, Aviation House, 125 Kingsway, London, WC2B 6NH e: asw@ctu.mrc.ac.uk t: +44 (0)20 7670 4726 f: +44 (0)20 7670 4949

DMEC member	Evelyn Mensah, Consultant Ophthalmic Surgeon
DMEC member	Niral Karia, Consultant Ophthalmic Surgeon

TSC members	
Role in TSC	**Name (address of Chair)**
TSC Chair	Mr Alistair Laidlaw Guy's and St Thomas' Hospital Westminster Bridge Road, London SE1 7EH e: alistair.laidlaw@gstt.nhs.uk t: +44 (0) 207188 2289 f: +44 (0)207 935 1458
Independent Member	Mr Winfried Amoaku
Independent Member	Dr Gillian Hood
Independent Member	Professor Graham Hitman
Patient Representative	Daniel Preese
ServiceUser Representative	Mr Paul Burns
Chief Investigator	Professor Sobha Sivaprasad
Co-lead	Mr Phil Hykin
	Ms Amy Riddell
	Data Manager
	Senior Member(s) of KCTU including statisticians
	Sponsor Representative
	Funder Representative

TMG members	
Role	**Name**
Chief Investigator	Miss Sobha Sivaprasad
Co-Lead	Mr Phil Hykin
Trial Manager	Ms Amy Riddell
LeadStatistician	Professor Toby Prevost
Trial Statistician	Joana Vasconcelos
Data Manager	Data Manager
Senior KCTU personnel	Ms Caroline Murphy(Operational Director) Miss Joanna Kelly(Data Management Strategic Lead)

2 Protocol Synopsis

Title:	**Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy**
Short title:	CLARITY
Trial interventions:	Aflibercept (intervention) Panretinal photocoagulation (comparator)
Phase of trial:	IIb
Objectives:	Primary objective: To evaluate whether mean change in best corrected visual acuity following intravitreal aflibercept therapy is non-inferior to panretinal photocoagulation (PRP) in eyes with proliferative diabetic retinopathy (PDR) at 52 weeks as measured by ETDRS letters. Secondary objectives: 1. To measure the effect of intravitreal aflibercept therapy, relative to panretinal photocoagulation on additional visual functions and quality of life outcomes including i) Unilateral and Binocular Esterman visual fields defects ii) Binocular visual acuity iii) Low luminance visual acuity iv) Visual acuity outcomes in terms of visual gain or loss v) Contrast sensitivity using Pelli Robson charts vi) Vision-related quality of life measured by VFQ-25 and RetDQoL vii) Diabetic retinopathy treatment satisfaction outcomes (RetTSQ) viii) Generic health-related quality of life using the EQ-5D, ICECAP-A, and CSRI. 2. To estimate incremental cost-effectiveness of intravitreal aflibercept versus standard PRP treatment at 52 weeks. 3. To determine the proportions of naïvePDR and non-naïve PDR eyes in both arms that do not require panretinal photocoagulation through 52 weeks after basic treatment of 3 loading doses of aflibercept or initial completion of PRP.

4. To compare between arms the regression pattern at 12 weeks and the regression and reactivation patterns of retinal neovascularisation at 52 weeks.

5. To compare the proportion of patients with 1-step and 3-step improvement or worsening of diabetic retinopathy between treatment arms at 12 and 52 weeks as per schedule of assessment.

6. To explore the difference in safety profile between intravitreal aflibercept and panretinal photocoagulation at 52 weeks, in terms of proportion of patients developing macular oedema (defined as central subfield thickness of >300µm on 3DOCT-1000 (Topcon) SD-OCT due to clinical evidence of macular oedema) or Spectralis OCT >320µmor Cirrus HD-OCT >300 µm or its equivalent if any other OCT devices are used, any de novo or increase in existing vitreous haemorrhage, de novo or increasing tractional retinal detachment, neovascular glaucoma, and requirement for vitrectomy. The indication for vitrectomy will be reported.

Mechanistic evaluation objectives:

1. To explore whether intravitreal aflibercept compared to panretinal photocoagulation causes measurable regression of area of retinal neovascularisation at 12 and 52 weeks.

2. To explore differences in the mean change in retinal vessel oxygen saturation and retinal vessel calibre in eyes treated with intravitreal aflibercept compared to panretinal photocoagulation at 12 and 52 weeks.

3. To explore whether intravitreal aflibercept reduces angiographically quantifiable areas of retinal non-perfusion compared to panretinal photocoagulation through 52 weeks.

Type of trial: A Multicentre Phase IIb Randomised Active-Controlled Clinical Trial

Trial design and methods: A multicentre, prospective, individually randomised, single-masked, controlled trial that will test the non-inferiority of intravitreal aflibercept to standard of care of panretinal photocoagulation at 52 weeks. Participants will either be randomised to receive intravitreal injections of aflibercept or panretinal photocoagulation. Participants in the aflibercept arm will be given a loading phase of three 4-weekly aflibercept injections and then repeated every 4 weeks

based on pre-defined re-treatment criteria according to the level of regression and reactivation. Participants in the arm receiving standard treatment will receive initial repeated PRP sessions until completion and then reviewed 8 weekly and re-treated based on the same pre-defined re-treatment criteria. Comparative tests at 52 weeks will include differences in central visual function (visual acuity), peripheral visual fields, regression of new blood vessels, safety profile, cost-effectiveness, treatment satisfaction and quality of life questionnaires. The trial will also include a mechanistic sub-study of 40 participants who will undergo retinal oximetry and image analysis at baseline, 12 and 52 weeks to explore the effect of aflibercept and PRP on the retina and blood vessels.

Trial duration per participant:	52 weeks
Estimated total trial duration:	104 weeks (recruitment period + follow up period)
Planned trial sites:	Multi-centre study of at least 15 centres
Total number of participants planned:	220 adults
Main inclusion/exclusion criteria:	Main disease area: Proliferative diabetic retinopathy

Inclusion criteria:

1. Subjects of either sex aged 18 years or over.
2. Diagnosis of diabetes mellitus (type 1 or type 2).
3. Best corrected visual acuity in the study eye better than or equal to 54 ETDRS letters (Snellen visual acuity 6/24).
   Please see section 6.3 *Re-screening of patients*
4. Visual acuity in fellow eye ≥ 2/60
5. PDR with no evidence of previous PRP or presence of new or persistent retinal neovascularisation despite prior PRP that (a) requires treatment in the opinion of the investigator and (b) there is sufficient space in the peripheral retina to perform more PRP treatment. In patients with both eye involvement, the eye with no PRP or the least number of PRP burns will be randomised as the study eye. If both eyes have had no PRP before, the eye with the better visual acuity will be randomised as the study eye. However, patients will be offered a choice and can opt for the 'worse seeing eye' to be randomised
6. Media clarity, pupillary dilation and subject cooperation sufficient for

adequate fundus photographs. Eyes with mild pre-retinal haemorrhage or mild vitreous haemorrhage that does not interfere with clear visualisation of the macula and optic disc are eligible for this study.

7. Ability to give informed consent
8. Women should use effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile.

Exclusion Criteria

The following exclusions apply to the study eye only (i.e. they may be present for the non-study eye):

1. Co-existent ocular disease that will affect visual outcome.
2. Moderate or dense vitreous haemorrhage that prevents clear visualisation of the macula and/or optic disc or prevents PRP treatment.
3. Significant fibrovascular proliferation or tractional retinal detachment in the posterior pole.
4. Prior vitrectomy.
5. Presence of macular oedema at baseline confirmed by 3D OCT-1000 (Topcon) SD-OCT as central subfield thickness of more than 300µm due to the presence of morphological evidence of diffuse or cystoid oedema. The equivalent measurement for Spectralis OCT is 320µm and Cirrus HD-OCT is 300µm. Please see rescreening of patients.
6. Other causes of retinal neovascularisation.
7. Iris or angle neovascularisation and neovascular glaucoma.
8. Anticipated need for cataract extraction or vitrectomy within the next 12 months.
9. Known allergy to fluorescein or any components of aflibercept formulation.
10. Previous intravitreal anti-VEGF or steroid treatment for diabetic macular oedema in the last 4 months. (Previous Iluvien therapy is an exclusion).
11. Panretinal photocoagulation within the last 8 weeks.
12. Aphakia.
13. Uncontrolled glaucoma as per investigator's judgement.
14. Severe external ocular infection.

Exclusion criteria also apply to systemic conditions as follows:

15. The participant should not have an HbA1c level of more than 12%. Please see section 6.3 *Re-screening of patients.*
16. The participant should not have a blood pressure of more than 170/110

mmHg. Please see section 6.3 *Re-screening of patients.*

17. A medical condition that, in the opinion of the investigator, would preclude participation in the study.
18. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event within 6 months of randomisation.
19. Dialysis or renal transplant.
20. Pregnant women.
21. Women of child bearing potential who do not agree to use effective contraception during the study and for at least 3 months after the study has finished.
22. Breast feeding women.
23. Males who do not agree to use an effective form of contraception for the duration of the study and for 3 months after the study has finished.
24. Participation in an investigational trial involving an investigational medicinal product within 30 days of randomisation.

Statistical methodology and analysis:

Analyses will be on an intention to treat (ITT) basis. Each continuous outcome will be compared between arms at the 52 weeks point using a linear mixed effects model with patient as a random effect to allow for within-patient correlation of repeated measures over time. The fixed effects will consist of study site in main effect form, and interactions between the full polynomial terms of time with arm, the continuous form of the baseline of the outcome using the missing indicator method, and the remaining minimisation stratifiers. For binary outcomes a corresponding generalised estimating equation approach will be used. Continuous and binary outcomes will be reported as adjusted differences in means or odds ratios respectively. All tests of non-inferiority will be one-sided at the 2.5% significance level. Tests of superiority will be two-sided at the 5% significance level. Safety outcomes will be reported as unadjusted patient proportions and rates within and between arms with 95% confidence intervals using exact methods where appropriate.

For the analysis of the primary outcome, the mixed effects model will be re-fitted in a reduced per protocol (PP) population to compare treatment effects at 12 weeks as well as at the primary time-point of 52 weeks, excluding patients found to be ineligible at entry, and those patients not receiving the full randomised treatment up to and including the 8-week visit (whether due to discontinuation, exclusion or other reason for missing a randomised treatment in this period). Non-inferiority will only be concluded if this is declared by both the ITT analysis and the PP analysis. Sensitivity analysis to missing data and to use of concomitant treatments, and analysis methods for evaluating mechanism, are described in the detailed statistical analysis plan, developed for comment by the Data Monitoring and Ethics Committee (DMEC) prior and

approval by the Trial Steering Committee prior to the availability of primary outcomes. Regular interim reports will be prepared as needed for DMEC meetings.

3 Introduction

3.1 Background

Over 3M people in the United Kingdom (UK) have diabetes. 150,000 people develop diabetes each year. Diabetic retinopathy (DR) is the most common complication of diabetes and is caused by progressive damage to the retinal blood vessels with increasing duration of diabetes (1). The disease progression and severity can be delayed by optimal control of medical risk factors such as hyperglycaemia, hypertension and hyperlipidaemia. However, DR remains a leading cause of blindness in the UK despite reported good uptake of the established national diabetic retinopathy screening programme, improved patient awareness and comprehensive care of the systemic risk factors by multidisciplinary teams of healthcare professionals (2, 3). The two vision threatening complications of DR are diabetic macular oedema (DMO) and proliferative diabetic retinopathy (PDR) (4, 5). DMO is caused by accumulation of excess extracellular fluid in the macula. PDR is characterised by growth of new blood vessels on the retina and if left untreated, these blood vessels can bleed and fibrose to cause severe visual loss due to vitreous haemorrhage, retinal detachment and neovascular glaucoma (NVG). Approximately 110,000 people in the UK have PDR and of these 14,000, have severe visual loss in both eyes highlighting the need to address this prevalent public health problem (6, 7).

Multiple molecular mechanisms are involved in the pathogenesis of DR. However, all lead to a final common pathway of retinal hypoxia and consequent increased levels of vascular endothelial growth factor (VEGF). The retina has the highest oxygen consumption of any tissue of the body and most of the oxygen is consumed by the retinal photoreceptors (8) In the diabetic state, because of the retina's unique demand for oxygen, trivial decreases in oxygen availability results in a hypoxic state (9, 10).Therefore, the aim of treatment options for PDR is to either increase the oxygen availability to the retina or to decrease VEGF levels. Panretinal photocoagulation (PRP) is applied to the peripheral retinal tissue to destroy the peripheral photoreceptors and retinal pigment epithelium to reduce retinal oxygen consumption (10). This reduction in hypoxic drive results in decreased growth factor production especially VEGF, which in turn causes retinal new vessel regression. Response to PRP varies, while it is most desirable to see a regression of new vessels, partial regression with no further growth may also result. Although timely PRP treatment is very effective in reducing visual loss compared to no treatment, PRP treatment is a destructive procedure with well-documented side effects (5, 11). Approximately 13% develop visual loss due to development or worsening of pre-existing macular oedema. In addition, it may lead to transient or permanent loss of visual function, including peripheral visual field defects, night vision loss, loss of contrast sensitivity, and progression of visual loss in nearly 5% of individuals despite appropriate treatment. Non-responders and severe cases may also require vitrectomy. Nine months follow-up of 209 eyes with PDR treated with PRP in the National Health service (NHS) showed that 46% did not reach the driving standard of which 13% had a poor visual acuity outcome of less than or equal to 6/60 (11).

Therefore, there is an unmet need for an alternative treatment option that could either replace or delay the need for PRP treatment for PDR.

New intravitreal treatments targeting VEGF, such as aflibercept, ranibizumab, bevacizumab, and pegaptanib, have introduced a paradigm shift in the treatment of a wide array of ocular diseases; including neovascular age related macular degeneration, DMO and retinal vein occlusions. Anti-VEGF treatment has superseded macular laser treatment and is now the standard of care in patients with centre-involving DMO *(www.nice.org.uk).* However, our therapeutic arsenal for PDR remains limited to PRP despite several clinical and preclinical studies indicating that VEGF is a key causative factor of retinal neovascularisation. Evidence that VEGF is a key stimulus for ocular neovascularisation was demonstrated by the injection of VEGF into the eye of a nonhuman primate that stimulated growth and permeability of new vessels on the retina simulating PDR and it also induced NVG (12). There is also clear evidence that hypoxic retina produces VEGF (13). Levels of VEGF mRNA and protein were shown to be elevated in a manner that is spatially and temporally consistent with the role for VEGF in the growth of new vessels (14). VEGF levels are highest in ocular fluid in patients with PDR compared to other retinal diseases (15). Evidence in support of a direct role of anti VEGF agents blocking retinal new vessel growth have also been reported using soluble VEGF receptor, anti-VEGF aptamers, and VEGFR1-neutralizing antisera (16, 17). Recent evidence also indicates that monthly anti-VEGF treatment can reduce the severity and delay the progression of diabetic retinopathy over 24 months (18). Several case series using different anti-VEGF agents have shown that anti-VEGF therapy is effective in causing transient regression of retinal neovascularisation in PDR. Current evidence points towards the potential for anti-VEGF treatment for PDR to obviate or delay the need of PRP treatment, the efficacy, safety and cost-effectiveness of this treatment relative to PRP coagulation remains unclear (19).

3.2 Implications

Despite better systemic control of risk factors in people with diabetes, a significant proportion still develop PDR and are treated with PRP, an ablative procedure with potential side effects that only stabilises vision. Therefore, there is an unmet need for alternate treatment option for this condition. As anti-VEGF has superseded laser treatment as the treatment of choice for DMO, it is advantageous for both PDR and DMO to be treated with anti-VEGF agents as it will reduce healthcare burden, patient burden and potentially improve patient outcomes. Currently there are two multicentre trials evaluating the efficacy of ranibizumab in PDR (clinicaltrials.gov). However, these studies are evaluating high risk cases only, a group that is less prevalent in the NHS due to prompt referral and treatment of early PDR due to our established screening programmes. The effect of anti-VEGF agents on partial regression and non-responders to previous PRP treatment are also an exclusion criteria for these trials. Therefore, it is necessary to do a similar study in the UK to assess the benefit of anti-VEGF therapy in our patient cohort with PDR. There is enough preclinical and short term clinical data to support an adequately powered trial to compare efficacy, safety and cost-effectiveness of anti-VEGF therapy to PRP (standard of care) in PDR.

3.3 Preclinical data

Information on preclinical and non-clinical studies for aflibercept can be found in the current version of the SPC on the eMC website: http://www.medicines.org.uk/emc/

3.4 Clinical data

The anti-VEGF agents that are currently available include pegaptanib (Macugen, Pfizer, Eyetech Pharmaceuticals), ranibizumab (Lucentis, Novartis, Genentech Inc.), bevacizumab (Avastin, Roche, Genentech Inc.) and Aflibercept (Bayer, Regeneron Inc.). Whilst pegaptanib is a selective VEGF A 165 inhibitor, both ranibizumab and bevacizumab are humanised monoclonal antibodies that inhibit all known isomers of VEGF A.

Aflibercept (previously VEGF Trap-Eye) is a 115 kD decoy receptor fusion protein. Aflibercept is capable of binding both VEGF and placental growth factor (PlGF). The receptor sequences of the aflibercept provide powerful VEGF binding (140 times that of ranibizumab) and the molecule's intermediate size 110 kD (compared to 48 kD for ranibizumab and 148 kD for bevacizumab) create a 1 month intravitreal binding activity that exceeds both ranibizumab and bevacizumab (20). The pivotal phase 3 studies that investigated the efficacy and safety of aflibercept in wet age-related macular degeneration (VIEW 1 and 2 trials) showed that monthly and bimonthly aflibercept were non-inferior to monthly ranibizumab at preventing vision loss (less than 15-letter loss) with comparable vision gains and safety. Year 2 treatment involved both as needed treatment and mandatory injections every 3 months and this regimen maintained vision gains from the first year, with an average of 4.2 injections of aflibercept and 4.7 injections of ranibizumab suggesting a longer durability of aflibercept over ranibizumab (21). Aflibercept has also been evaluated in a Phase 2 study on DMO (Da VINCI study). A total of 221 diabetic patients with clinically significant macular oedema involving the central macula were assigned to 1 of 5 treatment regimens: 0.5 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye every 4 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then every 8 weeks; 2 mg VEGF Trap-Eye for 3 initial monthly doses and then on an as-needed (PRN) basis; or macular laser photocoagulation. Assessments were completed at baseline and every 4 weeks thereafter. Patients in the 4 VEGF Trap-Eye groups experienced significant mean visual acuity benefits ranging +9.7 to +13.1 letters versus -1.3 letters for the laser group (22). Ocular and systemic adverse events in patients treated with aflibercept were generally consistent with those seen with other intravitreal anti-VEGF agents (23). Overall, there is sufficient evidence that aflibercept is as effective and have a longer duration of action than other anti-VEGF agents. Given that PDR is a progressive disease, an agent with a longer duration of action is preferable so aflibercept is the agent of choice for this study. In summary, based on the existing research, we plan to conduct a robust trial with adequate sample-size to evaluate the efficacy, safety and cost-effectiveness of aflibercept in our patient cohort with PDR over 12 months. In addition, the ocular and systemic effects of this drug, the changes induced by the drug on retinal new vessels, capillary non-perfusion and retinal vascular oxygen

saturation and retinal vessel calibre will be the subject of the mechanistic investigation.

3.5 Rationale and risks/benefits

Rationale

PDR is the main cause of severe visual loss in people with diabetes mellitus. Although PRP treatment has been the mainstay of therapy for 40 years, this treatment is inherently destructive and has the potential of permanent adverse effects including severe visual acuity loss, visual field loss with failure to meet the visual standards to drive, night blindness, loss of colour vision and reduced contrast sensitivity. Therefore, an alternative treatment option that can obviate or delay the need for PRP treatment is required. Short duration trials on anti-VEGF therapy in PDR indicate that retinal neovascularisation regresses effectively with this approach. However, the impact of this treatment on visual function and the effects of these agents on retinal neovascularisation compared to PRP remain unclear. Accordingly, we need to investigate this further by conducting a robust multicentre randomised controlled trial comparing the efficacy, safety and cost-effectiveness of repeated intravitreal aflibercept relative to PRP in treating and preventing the recurrence of PDR.

Benefits

There are several attractive benefits to using anti-VEGF agents:

1. PRP is a destructive procedure and any treatment that modulates the disease without destruction of the retina is key to preserve the retina.
2. PDR is driven by VEGF and direct inhibition of VEGF by an anti-VEGF agent is preferable to indirect inhibition of VEGF by PRP.
3. It is possible that this long-acting anti-VEGF agent may be sufficient to preclude the need for PRP treatment as long as the eye continues to receive aflibercept. It may also be likely that infrequent dosing of this agent may be sufficient to delay the need of PRP. This will in turn delay or prevent the complications induced by PRP.
4. Anti-VEGF agent also allows simultaneous treatment of DMO.
5. Unlike PRP treatment, anti-VEGF can be delivered in eyes with hazy media or poor view of the fundus.
6. The societal benefits are decreased rates of certification of visual impairment due to DR, improved visual function outcomes may allow more patients to retain their driving license, be independent, retain employment and depend less on social support.

Risks

1. Risk of aflibercept: Intravitreal aflibercept is well-tolerated in people. More than 5000 people have been treated globally with this drug for retinal vascular diseases and age related macular degeneration. Cumulative safety data to date does not show an increased risk of any ocular or systemic adverse events with this anti-VEGF agent compared to other similar drugs used for these indications. The known adverse events are low risk of arterial thrombo-embolic events as defined by

the Antiplatelet Trialists'Collaboration (APTC). However, the participants who received aflibercept showed no increased risk of either cardiovascular or cerebrovascular events compared to the intravitreal ranibizumab arms in the VIEW studies. It is contraindicated in pregnancy. In the case where the drug is administered in pregnant woman, further injections will be stopped. The pregnancy will be reported using a pregnancy form and followed up until outcome. The collection of study data will continue until the end of the study provided the participant does not withdraw consent. Please see further information in the current version of the SPC on the eMC website: http://www.medicines.org.uk/emc/.

2. Risk of intravitreal injections: The procedure is the most common surgical procedure done in ophthalmology with minimal adverse events. The reported adverse events are allergy to anaesthetic drops or povidone iodine, subconjunctival haemorrhage, discomfort and pain that last up to 24 hours, transient elevation of intraocular pressure and mild inflammatory reaction that resolves spontaneously or requires treatment with topical steroids. The serious adverse events are endophthalmitis (intraocular infection) that may occur in 1:3000 injection, retinal detachment (incidence is less than 1%) and vitreous haemorrhage (incidence is less than 1%). Endophthalmitis requires vitreous tap and intravitreal antibiotics and there is a risk of permanent visual loss with this complication. However, this complication is very rare.
3. Risk of panretinal photocoagulation: This treatment may cause peripheral field loss and affect driving. It may also cause transient or permanent central visual loss, night blindness, loss of colour vision and contrast sensitivity. If indirect PRP is necessary, this requires retrobulbar or peribulbar anaesthetic injections.
4. Risk of macular laser: Complications are rare (less than 1:1000) and these include foveal burns, scotoma, decreased vision, choroidal neovascularisation and poor response to this treatment.
5. Risk of ancillary tests: Allergy to topical medications including anaesthetic drops and mydriatic drops. Complications of fundus fluorescein angiography (FFA) are transient nausea and vomiting, yellow discoloration of skin and urine and very rarely allergic reaction.

3.5.1 Mechanistic evaluation

Preclinical and clinical data suggest that the pathophysiology of PDR is mediated by hypoxia induced release of VEGF which in turn leads to further retinal ischemia in addition to retinal neovascularisation. Thus, inhibition of intraocular VEGF by an anti-VEGF agent should cause regression of retinal new vessels, slow the progression of retinopathy and potentially improve retinal perfusion.

In the mechanistic evaluation, we will explore whether repeated intravitreal aflibercept and PRP retards the progression of PDR by:

i) causing regression of retinal neovascularisation.
ii) improving vessel calibre and oxygen saturation within retinal vessels and
iii) reducing quantifiable areas of retinal non-perfusion.

All participants recruited to the study at Moorfield's Eye Hospital will be invited to take part in the mechanistic sub-study. As retinal oximetry is not widely available, we have limited the study to 40 consecutive consenting participants from Moorfield's Eye Hospital who will be agreeable to additional

tests (n=20 in the PRP arm and n=20 in the aflibercept arm) and followed up to 52 weeks.

3.6 Assessment and management of risk

Please see section 3.5for risks of the study and their management. In addition, we have also factored in a poor initial acceptance rate despite our experience suggesting good compliance with this treatment in other retinal diseases.

This trial is categorised as Type B

4 Objectives

4.1 Trial objectives

To compare the efficacy, safety and cost-effectiveness of intravitreal aflibercept with standard of care, PRP for PDR for 52 weeks in a phase IIb randomised active-controlled clinical trial.

4.2 Primary Objective

To evaluate whether mean change in best corrected visual acuity following intravitreal aflibercept therapy is non-inferior to PRP in eyes with PDR at 52 weeks as measured by ETDRS letters.

4.3 Secondary objectives

1. To measure the effect of intravitreal aflibercept therapy, relative to panretinal photocoagulation on additional visual function and quality of life outcomes including:
   - i) Uniocular and binocular Esterman visual fields defects
   - ii) Binocular visual acuity
   - iii) Low luminance visual acuity
   - iv) Visual acuity outcomes in terms of visual gain or loss
   - v) Contrast sensitivity using Pelli Robson charts
   - vi) Vision-related quality of life measured by VFQ-25 and RetDQoL.
   - vii) Diabetic retinopathy treatment satisfaction outcomes (RetTSQ)
   - viii) Generic health-related quality of life using the EQ-5D, ICECAP-A and CSRI
2. To estimate incremental cost-effectiveness of intravitreal aflibercept versus standard PRP treatment at 52 weeks.
3. To determine the proportions of naïve PDR and non-naïve PDR eyes that do not require panretinal photocoagulation through 52 weeks after basic treatment of 3 loading doses of aflibercept in the aflibercept arm and after initial completion of PRP in the panretinal photocoagulation arm.
4. To compare between arms the regression pattern at 12 weeks and the regression and reactivation patterns at 52 weeks.
5. To compare the proportion of patients with 1-step and 3-step improvement or worsening of diabetic retinopathy between treatment arms at 12 and 52 weeks as per schedule of assessment.
6. To explore the difference in safety profile between intravitreal aflibercept and PRP at 52 weeks, in

terms of proportion of patients developing macular oedema (defined as central subfield thickness of >300µm on 3D OCT-1000 (Topcon) SD-OCT or Spectralis OCT >320µm and Cirrus HD-OCT > 300µm or its equivalent if any other OCT devices are used. on SD-OCT due to clinical evidence of macular oedema), any de novo or increase in existing vitreous haemorrhage, denovo or increasing tractional retinal detachment, NVG, and the requirement for vitrectomy. The indication for vitrectomy will be reported.

4.4 Objectives for sub-study on mechanistic evaluation

1. To explore whether intravitreal aflibercept compared to PRP causes measurable regression of retinal neovascularisation at 12 and 52 weeks.
2. To explore differences in the mean change in retinal vessel calibre and oxygen saturation in eyes treated with intravitreal aflibercept compared to PRP at 12 and 52 weeks.
3. To explore whether intravitreal aflibercept reduces angiographically quantifiable areas of retinal non-perfusion compared to panretinal photocoagulation through 52 weeks.

Participants for the mechanistic evaluation sub-study will be selected from the participants referred into Moorfields Eye Hospital only.

5 Trial design

5.1 Overall design

This is a non-commercial multicentre, prospective, individually randomised, single-masked, active-controlled trial that will test the non-inferiority of intravitreal aflibercept to the standard of care of PRP at 52 weeks. The optometrist assessing the primary outcome will be masked to the treatment arm. Other masked personnel are all outcome assessors such as OCT technicians, visual field technicians and the reading centre staff.

The trial design has been formulated in consultation with the accredited CTU at King's College London, a trial statistician, a methodologist from the Research Design Service, diabetes research networks, service users and a group of ophthalmologists specialising in diabetic retinopathy.

The basic study design and the associated clinical measurements are well established. The non-inferiority study design and the non-inferiority margin of 5 letters have also been successfully used in numerous previous clinical trials on anti-VEGF agents (24). Patients cannot reliably detect this difference, it does not equate to altered visual function (25). A non-inferiority margin of < 5 letters may give an inconclusive result [IVAN study: 3.5 letters] (26).

220 adult patients with PDR will be randomised 1:1 to receive intravitreal aflibercept or standard care of PRP for a period of 52 weeks. The primary outcome which is the change in best corrected visual acuity will be measured using validated ETDRS vision charts employing standard operating procedures for trials

in DR (4, 23, 27). Refracted visual acuity testing will be done at screening, 12 and 52 weeks and at the point of withdrawal.

The secondary outcome measures are also measured using well-established and validated tools including Pelli Robson charts for contrast sensitivity (28, 29), Esterman driving visual field test (30, 31), colour fundus photography, OCT and fundus fluorescein angiography (FFA). Vision related quality of life data using VFQ 25 will be collected at screening and 52 weeks. VFQ 25 is a validated tool for vision related quality of life (32). RetDQoL is a validated questionnaire specific for diabetic retinopathy (33). RetTSQ is a diabetic retinopathy treatment satisfaction questionnaire that has taken both anti-VEGF and PRP treatment into account when it was designed (34). The EQ-5D is a generic health-related quality of life measure, which will be collected at screening and week 52 for health economics analysis (35). The ICECAP-A is a brief questionnaire which measures the ability of an individual to carry out activities (36). A client service receipt inventory (CSRI) will be included to collect data on health and social care service use frequency.

5.2 Design of the mechanistic evaluation sub-study

40 willing participants (20 in each arm) from participants referred into Moorfields Eye Hospital will undergo retinal oximetry as part of this sub-study. Independent grading of retinopathy and changes in retinal neovascularisation will be performed by graders in reading centres within the Network of Ophthalmic Reading Centres UK (NetwORC UK). Graders are trained and quality assured to grade DR. Changes in intravascular oxygen saturation and vessel calibre at baseline, 12 and 52 weeks and at the point of withdrawal will be measured using the retinal oximeter. The area of retinal neovascularisation, at screening, 12 and 52 weeks and capillary non-perfusion and foveal avascular zone on early venous phase on FFA at screening, week 52 and at the point of withdrawal will also be analysed using computational image analysis using automated segmentation program in Matlab (MatLab R2012b; The MathWorks., Cambridge, UK) and compared with results obtained from composite images containing overlays of aligned angiographic images created on Adobe Photoshop.

6 Selection of Subjects

6.1 Inclusion criteria

1. Subjects of either sex aged 18 years or over.
2. Diagnosis of diabetes mellitus (type 1 or type 2).
3. Best corrected visual acuity in the study eye better than or equal to 54 ETDRS letters (Snellen visual acuity 6/24). Please see section 6.3*Re-screening of patients.*
4. Visual acuity in fellow eye ≥ 2/60.
5. PDR with no evidence of previous PRP or presence of new or persistent retinal neovascularisation despite prior PRP that (a) requires treatment in the opinion of the investigator and (b) and there is sufficient space in the peripheral retina to perform more PRP treatment. In patients with both eye involvement, the eye with no PRP or the least number of PRP burns will be randomised as the study eye. If both eyes have had no previous PRP, the eye with the better visual acuity will be

randomised as the study eye. However, patients will be offered a choice and can opt for the 'worse seeing eye' to be randomised.

6. Media clarity, pupillary dilation and subject cooperation sufficient for adequate fundus photographs. Eyes with mild pre-retinal haemorrhage or mild vitreous haemorrhage that does not interfere with clear visualisation of the macula and optic disc are eligible for this study.
7. Ability to give informed consent.
8. Women should use effective contraception, be post-menopausal for at least 12 months prior to trial entry, or surgically sterile.

6.2 Exclusion criteria

The following exclusions apply to the study eye only (i.e. they may be present for the non-study eye):

1. Co-existent ocular disease that may interfere with visual outcome.
2. Moderate or dense vitreous haemorrhage that prevents clear visualisation of the macula and/or optic disc or prevents PRP treatment.
3. Significant fibrovascular proliferation or tractional retinal detachment in the posterior pole.
4. Prior vitrectomy.
5. Presence of macular oedema at baseline confirmed by 3D OCT-1000 (Topcon) SD-OCT as central subfield thickness of more than 300µm due to the presence of morphological evidence of diffuse or cystoid oedema. The equivalent measurement for Spectralis OCT is 320µm and Cirrus HD-OCT is 300µm. (*please see section 6.3 Re-screening of patients*)
6. Other causes of retinal neovascularisation.
7. Iris or angle neovascularisation and neovascular glaucoma.
8. Anticipated need for cataract extraction or vitrectomy within the next 12 months.
9. Known allergy to fluorescein or any components of aflibercept formulation.
10. Previous intravitreal anti-VEGF or steroid treatment for diabetic macular oedema in the last 4 months (Previous Iluvien therapy is an exclusion).
11. Panretinal photocoagulation in the last 8 weeks.
12. Aphakia.
13. Uncontrolled glaucoma as per investigator's judgement.
14. Severe external ocular infection.

Exclusion criteria also apply to systemic conditions as follows:

15. The participant should not have an HbA1c level of more than 12%. As a precautionary measure, normal healthcare providers will be informed if any patient with HbA1cof more than 8%, is identified during a standard letter, directing the provider to the current NICE guidelines on the management of diabetes to ensure optimal follow-up (please see section 6.3*Re-screening of patients*).
16. The participant should not have a blood pressure of more than 170/110 mmHg.If either systolic BP is >170mmHg or diastolic BP is >110mmHg at screening, the patient should be excluded. As a precautionary measure, normal healthcare providers will be informed if any patient with a blood pressure > 150/90mmHg is identified. A standard letter will be provided directing the provider to

the current NICE guidelines on the management of hypertension in patients with diabetes to ensure optimal follow up of these patients (please see section 6.3 *Re-screening of patients*).

17. A medical condition that, in the opinion of the investigator, would preclude participation in the study.
18. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event within 6 months of randomisation.
19. Dialysis or renal transplant.
20. Pregnant women.
21. Women of child bearing potential who do not agree to use effective contraception during the study and for at least 3 months after the study has finished. Effective contraception is defined as one of the following:
    a. Barrier method: condoms or occlusive cap with spermicides.
    b. True abstinence: When it is in line with the preferred and usual lifestyle of the subject Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    c. Permanent Contraception: have had tubal ligation or bilateral oophorectomy (with or without hysterectomy).
    d. Male partner sterilisation. The vasectomised male partner should be the only partner for the female participant.
    e. Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device.
22. Breast feeding women.
23. Males who do not agree to use an effective form of contraception for the duration of the study and for 3 months after the study has finished. Effective contraception is defined as one of the following:
    a. Barrier method: condoms or occlusive cap with spermicides.
    b. True abstinence: When it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence and withdrawal are not acceptable methods of contraception.
    c. Male sterilisation (vasectomy).
    d. Female partners using contraception.
24. Participation in an investigational trial involving an investigational medicinal product within 30days of randomisation.

6.3 Re-screening of patients

1. Patients that do not meet the inclusion criteria at initial screening because of the presence of centralretinal sub field thickness>300µm on3D OCT-1000 (Topcon) SD-OCT or Spectralis OCT > 320µm and Cirrus HD-OCT > 300µm. SD-OCT with clinical evidence of macular oedema, can be re-screened if central subfield thickness is <300µm on3D OCT-1000 (Topcon) SD-OCT or Spectralis OCT < 320µm and Cirrus HD-OCT < 300µm or its equivalent if any other OCT devices are used either spontaneously or after treatment with macular laser or anti-VEGF therapy. Patients must wait4 months after their last treatment.
2. Individuals that do not meet the inclusion criteria because of BP or HbA1c may be re-screened

twice if these parameters are brought under control. For patients with hypertension, re-screening can occur at least one month after the last screening visit. For patients with high HbA1c, re-screening can take place 3 months after the last screening visit. If a patient failed screening because of both parameters, then the longer waiting period must be used before the patient is re-screened.

3. Individuals that do not meet the inclusion criteria because of their best corrected visual acuity can be rescreened if visual acuity becomes better than or equal to 54 ETDRS letters in the study eye. Re-screening can occur one month after their last screening visit.

All assessments performed at the screening visit should be repeated during the rescreening visit. Fluorescein angiography does not need to be repeated if the re-screening is done within 2 months.
If a patient is found to be eligible on re-screening and is randomised, their initial entry on the eCRF system should be updated rather than creating a 'new' patient on the system. This will avoid 'double counting the patients in the CONSORT diagram.'

7 Recruitment

Patients may be identified from medical retina clinics and laser databases and may be contacted using an invitation letter with a view to a pre-screening visit at which clinical examination and discussion of study will be carried out. Patient identification sites may be used for this study.

8 Study procedures and schedule of assessments

8.1 Informed consent procedure

The Principal Investigator or designee (must be a clinician) will be responsible for ensuring that a patient is fully consented following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Patients will be advised that any data collected will be held and used in accordance with the Data Protection Act 1998.

Patients will be given at least 24 hours after receiving the patient information sheet to consider taking part. The PI or designee must record when the patient information sheet (PIS) has been given to the patient.

The PI or designee will explain that patients are under no obligation to enter the trial and that they can withdraw at any time, without giving a reason and without their future medical care being affected.

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

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

8.2 Randomisation procedures

A patient identification number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro), after consent has been signed. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study.

Randomisation will be via a bespoke web based randomisation system hosted at the KCTU.

Authorised site staff will be allocated a username and password for the randomisation system by the Trial Manager. An authorised staff member will log into the randomisation system (www.ctu.co.uk and click 'randomisation – advanced' and select CLARITY) and enter the patients details using the unique PIN.

Once a patient is randomised, the system automatically generates emails to key staff within the study. Emails sent to site pharmacies will alert them to a patient's treatment group -aflibercept or PRP therapy. The pharmacy department should use the alert to cross check the trial prescription to ensure that aflibercept is being dispensed for the correct patient. Additional emails will be generated from the randomisation system to key trials staff, with or without treatment allocation information, depending on their role in the study.

8.3 Masking

The research optometrists are the primary outcome assessors and will conduct the visual acuity tests at screening, 12 and 52 weeks. They will be masked to treatment allocation throughout the study. The optometrists will receive the participants into the visual acuity lanes with a visual acuity specific source data worksheet which will include their PIN number and details of the study eye and non-study eye to be refracted, but with no previous records or case report forms by which the patient's treatment arm could be identified. The optometrists will also assess the secondary outcome measure of contrast sensitivity and will use the same technique of masking as above. At all other visits, visual acuity examiners will be provided with a copy of the refraction log to conduct an open aperture visual acuity test in both eyes with the previous refraction. At these time-points, the visual acuity tests may be conducted by unmasked professionals. The other tests of secondary outcome measures of visual fields and OCT scans will be done by masked technicians. The technicians will receive the patients into the visual field and OCT room using the specific source data worksheet that provides details of the patient's PIN number and eye to be examined. After every visit, the completed source data worksheets should be kept with the Principal Investigator's team.

The participants will be advised at enrolment that they must not discuss the study arm they are in with these assessors.

The retinal photographs at screening, 12 and 52 weeks and FFA at screening and 52 weeks will be graded by masked graders in the Independent Reading Centres within NetwORC UK. The photographers will be trained to take the photographs as per the SOP for this study. The graders in the

Reading Centre are trained and quality assured to grade diabetic retinopathy based on Early Treatment Diabetic Retinopathy Study (ETDRS) grading system as required for this study. These masking procedures will avoid both performance and detection bias. We will describe the completeness of outcome data for each outcome, including reasons for attrition and exclusions from the analysis.

8.4 Unmasking

This is a single masked study. Only optometrists and OCT technicians will be masked to the treatment allocation. Both participants and the Principal Investigators and delegated clinical investigators will be aware of the treatment group. Therefore this study will not incorporate any unmasking procedures.

8.5 Screening Period

All sites will receive an operating manual for the study.

Screening must be performed no more than 15 days before randomisation. Screening and baseline can be performed on the same day provided all test results are available. Participants that do not meet the inclusion criteria for blood pressure, HbA1c, the presence of central retinal sub-field thickness>300µm on 3D OCT-1000 (Topcon) SD-OCT or Spectralis OCT >320µm and Cirrus HD-OCT >300µm or its equivalent if any other OCT devices are used or best corrected visual acuity will have the opportunity to be rescreened. Please see section 6.3 *Re-screening of patients*.

All participants will be consented prior to any study specific procedures being carried out.

Please see section 8.8 *Flowchart of assessments*.

8.6 Baseline assessments

Please see section 8.8 *Flowchart of assessments*.

8.7 Subsequent assessments

Please see section 8.8 *Flowchart of assessments*.

8.7.1 Visit window for study appointments

Sites should aim to bring participants in for their study visit within 10 days after or before the scheduled visit, however:

a. If the visit is outside the window, the visit should be classed as “missed” and the participant should be brought in under the next scheduled visit.

b. **The dosing interval between two doses of aflibercept cannot be shorter than one month. One month for the purpose of this study is considered as four weeks.**

A within window flexibility to complete the assessments and treatment is permitted. However, the randomisation visit, 4, 8 and 12 weeks are fixed visits with minimal flexibility to allow for prompt loading phase and milestone data collection.

8.8 Flowchart of study assessments:

8.8.1 PRP arm

	Screening	Baseline	Week 4	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52 (final visit)	Withdrawal
Visit window	(Day -15 to Day 0)	Day 0	± 10 days	±10 days	± 10 days	±10 days	±10 days	±10 days	±10 days	
Visit No	1	2	3	4	5	6	7	8	9	
Informed consent	x									
Inclusion/Exclusion Review	x									
Medical and Ocular History	x									
Blood test – HbAIc[1]	x								x	x
Pregnancy test[2]	x									
Standard ophthalmic examination + tonometry in both eyes	x	x	x	x	x	x	x	x	x	x
Blood Pressure[3]	x			x	x	x	x	x	x	x
ETDRS visual acuity tests in both eyes[4]	x (+R)	x	x	x (+R)	x	x	x	x	x (+R)	x (+R)
Low luminance visual acuity in both eyes	x								x	x
Binocular vision acuity	x								x	x
Pelli Robson contrast sensitivity tests in both eyes	x								x	x
Esterman driving visual fields tests - Uniocular (study eye) and binocular	x								x	x
Questionnaires: VFQ 25, RetTSQ, RetDQoL,EQ-5D ICECAP-A, & CSRI	x								x	x
SD-OCT macular thickness protocol in both eyes	x			x					x	x
Colour Fundus Photographs (CFP) - 7-field or wide-field [5]	x			x					x	x
Fluorescein Fundus Angiography7-field or wide-field (FFA) [5]	x								x	x
Colour Fundus Photography (CFP) – 4-field or wide-field[5]in study eye only					x	x	x	x		
Concomitant medication review	x	x	x	x	x	x	x	x	x	x
Adverse Event review	x	x	x	x	x	x	x	x	x	x
Randomisation[6]		x								
Review of regression in study eye only		x		x	x	x	x	x	x	x
PRP treatment in study eye only		x	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)		
Treatment allocation guess form[7]									x	x
Study completion form[8]									x	x
Mechanistic Evaluation Sub-study (Moorfields Eye Hospital only)										
Retinal oximetry in both eyes[9]		x		x					x	x

(R) - Refraction assessment (+/-) – Activity should be performed depending on re-treatment criteria;

[1]Test can be performed on day and according to local practice. If test was done in last 3 months it does not need to be repeated. Patients that have HbA1c> 12% at screening are excluded but can be rescreened.

[2]Urine dipstick should be used. It must be performed on day of screening. Principal Investigators can perform subsequent pregnancy tests in accordance with local practice but not for the study

[3] BP must be ≤ 170/110mmHg to be eligible. BP > 150/90 mmHg should be followed up with the normal healthcare provider

[4]Should be performed in both eyes. Patients will also have a refraction assessment at screening, week 12 and week 52.

[5]. Further photographic fields and FFA can be taken to determine the presence or absence of NV as per local practice. However this will not be recorded as research data. wide-field imaging may also be done.

[6]Must be last activity performed at baseline but **BEFORE** intervention. Patient should be informed what treatment arm they are in, but reiterated that the assessors must remain masked to that information.

[7]Form to be completed by masked optometrists only at week 52 or at the point of withdrawal

[8]If a patient withdraws from the study, the form should be completed at the withdrawal visit only.

[9]Patients that have consented for the sub-study at Moorfields Eye Hospital only.

8.8.2 Aflibercept arm

	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52 (final visit)	Withdrawal
Visit window	(Day -15 to Day 0)	Day 0	± 10 days	± 10 days	± 10 days	± 10 days	± 10 days	±10 days	±10 days	±10 days	± 10 days	±10 days	± 10 days	±10 days	±10 days	
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Informed consent	x															
Inclusion/Exclusion Review	x															
Medical and Ocular History	x															
Blood test – HbAIc[1]	x														x	x
Pregnancy test[2]	x															
Standard ophthalmic examination and tonometry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood Pressure[3]	x				x	x	x	x	x	x	x	x	x	x	x	x
ETDRS visual acuity tests in both eyes[4]	x (+R)	x	x	x	x (+R)	x	x	x	x	x	x	x	x	x	x (+R)	x (+R)
Binocular vision acuity	x														x	x
Low luminance acuity in both eyes	x														x	x
Pelli Robson contrast sensitivity tests in both eyes	x														x	x
Esterman driving visual fields tests - uniocular (in study eye) and binocular	x														x	x
Questionnaires: VFQ 25, RetTSQ, RetDQoL,EQ-5D ICECAP-A& CSRI	x														x	x
SD-OCT macular thickness protocol in both eyes	x				x										x	x
Colour Fundus Photography (CFP) - 7-field or wide-field5	x				x										x	x
Fundus Fluorescein Angiography 7-field or wide-field (FFA)[5]	x														x	x
Colour Fundus Photographs (CFP) 4-field or wide-field [5]in study eye			x	x		x	x	x	x	x	x	x	x	x		
Concomitant medication review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Event review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomisation[6]		x														
Review of regression in the study eye			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Aflibercept injection in study eye only		x	x	x	x ±L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)	x ± L (+/-)		
Post injection check[7]		x	x	x	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)	x(+/-)		
Treatment allocation guess form[8]															x	x
Study completion form[9]															x	x
Mechanistic Evaluation Sub-study (Moorfields Eye Hospital only)																
Retinal Oximetry[10] Both eyes		x			x										x	x

(R) - Refraction assessment; (+/-) – Activity should be performed based on re-treatment criteria; x ±L - Aflibercept injection with or without PRP

[1]Test can be performed on day and according to local practice. If test was done in last 3 months it does not need to be repeated. Patients that have HbA1c> 12% at screening are excluded but can be rescreened.

[2]Urine dipstick should be used. It must be performed on day of screening. Principal Investigators can perform subsequent pregnancy tests in accordance with local practice but not for the study
[3]BP must be ≤ 170/110mmHg to be eligible. BP > 150/90 mmHg should be followed up with the normal healthcare provider.
[4]Should be performed in both eyes. Patients will have a refraction assessment at screening, week 12 and week 52.
[5] Further photographic fields and FFA can be taken to determine the presence or absence of NV as per local practice. However this will not be recorded as research data.wide field imaging may also be done.
[6]Must be last activity performed at baseline but **BEFORE** intervention. Patient should be informed what treatment arm they are in, but reiterated that the assessors must remain masked to that information.
[7]Following aflibercept injection, the treating physician may check vision, intraocular pressure and optic nerve head perfusion in accordance with local practice.
[8]Form to be completed by masked optometrist only at week 52 or at the point of withdrawal
[9]If a patient withdraws from the study, the form should be completed at the withdrawal visit only.
[10]Patients that have consented for the sub-study at Moorfields Eye Hospital only

8.8.3 Participant demographics and other baseline characteristics

This information can be retrieved from the participant, hospital medical records or general practitioner. Data will include age and gender. Data will also be collected on diabetic history and management, ocular history and treatment, other clinically relevant medical history and their management in the last 12 months, and concomitant medication.

8.8.4 Visual acuity tests

The visual acuity tests are done using the validated ETDRS vision charts using standard operating procedures. Refracted visual acuity will be done in both eyes at screening, weeks 12 and 52 and at the point of withdrawal by masked optometrists. Binocular visual acuity and low luminance acuity will be done at screening and 52 weeks and at the point of withdrawal. Please refer to the operation manual. For all other visits, the visual acuity will be tested with the previous protocol refraction. .The visual acuity tests in these visits may be recorded by unmasked visual acuity examiners. The worksheets used for the visual acuity tests should be retained in a file held with the Principal Investigators team. The total visual acuity score will be recorded in the eCRF and the raw visual acuity data will be recorded at screening, 12 and 52 weeks..

8.8.5 Contrast sensitivity tests

The Pelli Robson chart will be used to test contrast sensitivity in both eyes at screening, week 52 and at the point of withdrawal as per SOP. The total contrast sensitivity score in both eyes will be recorded in the eCRF.

8.8.6 Driving fields tests

Uniocular (study eye) and binocular Esterman fields will be done at screening, week 52 and at the point of withdrawal. The field charts should be filed with the source data worksheets with the Principal Investigator's team. Please refer to operations manual.

8.8.7 Standard ophthalmic examination

A standard ophthalmic examination using slit lamp biomicroscopy, tonometry and dilated fundus examination is done in both eyes at all visits. Gonioscopy is indicated if NVA or NVI or NVG is suspected. The grade of diabetic retinopathy and the presence or absence of macular oedema is assessed by the investigator. .

8.8.8 Spectral Domain Optical Coherence Tomography (SD- OCT)

Masked OCT technicians will perform the SD-OCT. The central sub-field thickness in both eyes will be recorded from SD-OCT thickness map at screening, 12 and 52 weeks and at the point of withdrawal. This test may be repeated at any visit at the investigator's discretion. If treatment of DMO is planned, OCT may be done for confirmation of DMO and monitoring treatment. Any SD-OCT machine may be used for the study but the same model of SD-OCT should be used for each individual throughout the period of the study.

8.8.9 Colour Fundus Photography (CFP),and Fundus Fluorescein Angiography (FFA).

7-field or wide-field CFP will be performed to assess the severity level of diabetic retinopathy and area of retinal neovascularisation at screening, weeks 12 and 52 and at the point of withdrawal. FFA will be done at screening, week 52 and at the point of withdrawal. 4-field photography or wide field imaging in the study eyeare done at all other visits to evaluate regression and reactivation patterns. In the PRP arm, these include visits at week 20, 28, 36 and 44 weeks and in the aflibercept arm week 4, 8, 16, 20, 24, 28, 32, 36, 40, 44 and 48 weeks. Additional fields for colour photographs and FFA may be performed to determine the presence or absence of NV in either eye at any of these visits as per local practice or investigator discretion. The 7-field or wide-field photographs and FFA performed at screening, weeks 12 and 52 and withdrawal will be read by masked graders at the Independent Reading Centres in NetwORC UK. Please see operation manual for details.

8.8.10 Blood pressure

Blood pressure will be performed at each study visit except baseline and week 4 for both arms and week 8 for the aflibercept arm.

Eligible patients must not have a blood pressure of >170 systolic or >110mmHg diastolic at screening.

If the blood pressure is >170/110mmHg, the patient may be re-screened, at least one month after the last screening visit, if the parameter is brought under control and the other inclusion-exclusion criteria are met.

If the blood pressure is above 150/90 mmHg but ≤ 170/110, the participant is eligible but the normal healthcare provider will be informed via a standard letter directing the provider to the NICE guidance of management of blood pressure in patients with diabetes.

If the blood pressure is ≤ 150/90 mmHg, the participant is eligible.

All randomised patients will continue to be followed up by their normal healthcare provider and remain in the study and undergo all study assessments and treatment as per protocol.

8.8.11 Pregnancy test

Pregnancy test using urine dipstick should be performed before randomisation. Principal Investigators can perform subsequent pregnancy tests in accordance with local practice but not for the study

8.8.12 Questionnaires

The following satisfaction, generic health and quality of life questionnaires will be administered at screening, week 52 and at the point of withdrawal: RetTSQ, VFQ-25, RetDQoL, EQ-5D; ICECAP-A and CSRI.

8.8.13 Mechanistic tests (Moorfield's Eye Hospital only)

40 participants (20 in each arm) who consent for the mechanistic evaluation will undergo oximetry tests in both eyes at baseline, weeks 12 and 52 and at the point of withdrawal. A within-visit flexibility of + 10 days is allowed for patients to complete these tests. The site should aim to complete the additional tests on the same day as the main study visits.

8.8.14 HbA1c

Please see Laboratory procedures section.

8.8.15 Independent Reading Centres in NetwORC UK

The NetwORC will provide each site with a manual giving instructions and guidance on how to acquire and transfer the colour retinal photographs completed at screening, weeks 12 and 52 and at the point of withdrawal. The FFA done at baseline, week 52 and at point of withdrawal will also be transferred to the Reading Centre. The images will be anonymised to study PIN, and will include the time-point at which the image was collected. The images should be transferred to the reading centre via CD, SFTP or another suitably secure media agreed by the reading centre and the Chief Investigator. The images will be accompanied by a transmittal log which will require the patient's date of birth as an identifier. Sites must ensure that all PINs and dates on images, compliment the information recorded on the transmittal log and that all images are captured, exported and submitted in accordance with the requirements of the study imaging protocol (see operations manual). Sites should aim to transfer the images to the reading centre within 2 weeks post capture. The reading centre will send reports regularly to KCTU throughout the study with an overview of what has been received and what is currently outstanding from each of the sites. The reading centres will evaluate the images and the results will be transferred to the Trial Manager in KCTU. The Trial Manager will transfer the data to the study statisticians necessary.

8.8.16 Treatment allocation guess form

Masked optometrists will be asked to complete a treatment allocation guess form to assess how well assessor masking worked for the study at week 52 or at the point of withdrawal.

8.9 Treatment procedures

8.9.1 Active interventionarm

Aflibercept (Bayer plc, Regeneron, Inc.) is approved by the FDA and EMA for wet age related macular degeneration and macular oedema due to central retinal vein occlusion. The physical, chemical, and pharmaceutical properties and formulation of aflibercept are provided in the current version of the SPC. The drug will be delivered in exactly the same dose and formulation as notified in the marketing authorisation for wet age related macular degeneration and macular oedema due to central retinal vein occlusion.

8.9.1.1 Interval between injections

The interval between two doses of aflibercept should not be shorter than one month. One month for the purpose of this study is considered as four weeks.

8.9.1.2 Loading phase

All study eyes randomised to receive aflibercept will receive an intravitreal injection of aflibercept 2 mg/0.05ml at baseline, 4 and 8 weeks. Regression patterns of retinal neovascularisation will be assessed using 4-field or wide angle fundus photography (please see Table 1 for definitions of regression patterns).

8.9.1.3 Week 12 re-treatment

Further treatment at week 12 is determined by the degree of regression of neovascularisation (NV) of disc and elsewhere on clinical examination with adequate visualisation of entire retina and compared to 7-field colour or wide-field photographs at screening. The patients will be categorised according to treatment response into three groups: (1) No regression (2) Partial regression and (3) Total regression as defined in table 1.
Please see flow chart 1 for re-treatment regimen.

Table 1: Classification of retinal neovascularisation and definition of regression patterns and regression pattern defined re-treatment for the aflibercept arm at 12 weeks.

Regression pattern	***Definitions of regression patterns (compared to screening visit)***	***Treatment regimen***
No Regression	Any one or more of the following: (a) No decrease in size or density of active NV; (b) Increase in area of active NV (c) De novo active NV (flat or elevated) in an eye with pre-existing active NV observed at screening that have not regressed or partially regressed. (d) iris or angle neovascularisation and NVG	Aflibercept and supplemental PRP should be undertaken. Supplemental PRP is only deferred if there is insufficient space to perform further laser. Follow-up in 4 weeks.
Partial Regression	(a) Persistent active NV but decrease in size or density of NV from screening visit. (b) De novo active NV (flat or elevated) in an eye with complete regression of active NV observed at screening.	Intravitreal aflibercept injection Panretinal photocoagulation is not allowed. Follow-up in 4 weeks
Total regression	Any one or more of the following: (a) Complete regression of NVE/D. (b) Regression of NV tissue to avascular fibrotic tissue. (c) Quiescent NV defined as inactive NV that in the opinion of the investigator does not require any further treatment.	No aflibercept injection Panretinal photocoagulation is not allowed. Follow-up in 4 weeks.

8.9.1.4 Week 16 to week 48 re-treatment

All patients in the aflibercept arm will be reviewed 4 weekly. From week 16, further treatment is determined by

both regression and reactivation of NV on clinical examination with adequate visualisation of entire retina and by comparing the 4-field colour photographs or wide-field imaging done in the previous visit. The treatment response will be categorised into 4 groups: (1) No regression (2) Partial regression and (3) Total regression (4) Reactivation as shown in table 2 and flowchart 2.

Further fields of colour retinal photographs or fluorescein fundus angiography may be performed at any visit if there is any doubt that a clinical feature represents retinal neovascularisation.

Table 2: Classification of retinal neovascularisation and definition of regression patterns and re-treatment in the aflibercept arm from week 16-48

Regression pattern	***Definitions of regression patterns (compared to previous visit)***	***Treatment regimen***
No Regression	Any one or more of the following: (a) No decrease in size or density of active NV; (b) Increase in area of active NV (c) De novo active NV (flat or elevated) in an eye with pre-existing active NV that have not regressed or partially regressed since previous visit. (d) iris or angle neovascularisation and NVG	Aflibercept and supplemental PRP should be undertaken. Supplemental PRP is only deferred if there is insufficient space to perform further laser. Follow-up in 4 weeks.
Partial Regression	Persistent active NV but decrease in size or density of NV from previous visit.	Intravitreal aflibercept injection Panretinal photocoagulation is not allowed. Follow-up in 4 weeks
Total regression	Any one or more of the following: (a) Complete regression of NVE/D. (b) Regression of NV tissue to avascular fibrotic tissue. (c) Quiescent NV defined as inactive NV that in the opinion of the investigator does not require any further treatment.	No aflibercept injection Panretinal photocoagulation is not allowed. Follow-up in 4 weeks.
Reactivation	Reactivation can occur at any visit from week 16 and is defined as one or more of the following : (a) Recurrence of NV (b) De novo NV (flat or elevated) following total regression.	Intravitreal aflibercept injection Panretinal photocoagulation is not allowed. Follow-up in 4 weeks

Fluorescein fundus angiography may be performed at any visit if there is any doubt that a clinical feature represents retinal neovascularisation.

8.9.1.5 Deferred aflibercept treatment

1. If an eye has experienced adverse effects from prior intravitreal injection, retreatment with intravitreal aflibercept is at the discretion of the investigator. In addition, if any future treatment with aflibercept is contraindicated based on a previous adverse reaction, treatment with panretinal photocoagulation for PDR is at the investigator's discretion.
2. Treatment with aflibercept or PRP may be deferred in cases of total vitreous haemorrhage with no clear view of the fundus until the fundus can be sufficiently well visualised to permit subsequent intraocular injection.
3. Aflibercept injections may be deferred in an eye that developed a rhegmatogenous retinal detachment or requires surgical intervention for tractional retinal detachment threatening the fovea. Aflibercept injections may be resumed following surgical repair.
4. Aflibercept injections may be deferred if the interval between injections is less than 4 weeks.
5. Aflibercept injection may be deferred in a visit where IOP remains above 30mmHg despite iopidine eye drops or other anti-glaucoma eye drops. The participant may be prescribed iopidine eye drops or other glaucoma drops for a week and rescheduled for aflibercept injection within a week if IOP is less than 30 mmHg. Participants with elevated IOP at any visit will be managed as per investigator discretion and local hospital policy.

8.9.1.6 Deferral of PRP in the aflibercept 'no regression' category

1. Hazy media that prevents PRP.
2. PRP may be deferred in a participant in the 'no regression' groups if in the opinion of the investigator it is not deemed necessary at that visit.

8.9.2 Comparator Intervention arm

Panretinal photocoagulation (PRP) therapy, the current standard of care, will be the comparator and will be delivered as per routine clinical practice as shown below.

8.9.2.1 Initial treatment

Naïve PDR patients requiring PRP treatment will for the first time be initiated on it and completed in fractionated 2 weekly sessions up to and may include week 4 and then reviewed at week 12.

Participants with persistent active new vessels that have had PRP previously and are randomized to the PRP arm will receive fill-in PRP in 1-2 two-weekly sessions.

From week 12, all patients in the PRP arm will be assessed for treatment response every 8 weeks and categorised exactly as the aflibercept arm. Table 3and flowchart 2gives the summary of further treatment in the PRP arm.

Table 3: Classification of retinal neovascularisation and definition of regression patterns and re-treatment in the PRP arm.

Regression pattern	***Definitions of regression patterns (compared to previous visit)***	***Treatment regimen as per routine clinical practice***
No Regression	Any one or more of the following: (a) No decrease in size or density of active NV; (b) Increase in area of active NV (c) De novo active NV (flat or elevated) in an eye with existing active NV that have not regressed or partially regressed since previous visit. (d) iris or angle neovascularisation and NVG	Repeat PRP. Fractionated 2 weekly PRP sessions are allowed to complete the treatment. Follow-up in 8 weeks.
Partial Regression	Persistent active NV but decrease in size or density of NV from previous visit.	Repeat PRP at investigator discretion Follow-up in 8 weeks.
Total regression	Any one or more of the following: (a) Complete regression of NVE/D. (b) Regression of NV tissue to avascular fibrotic tissue. (c) Quiescent NV defined as inactive NV that in the opinion of the investigator does not require any further treatment.	No PRP indicated. Follow-up in 8 weeks
Reactivation	Reactivation can occur at any visit from week 16 and is defined as one or more of the following : (a) Recurrence of NV (b) De novo NV (flat or elevated) following total regression.	Repeat PRP at investigator discretion Follow-up in 8 weeks.

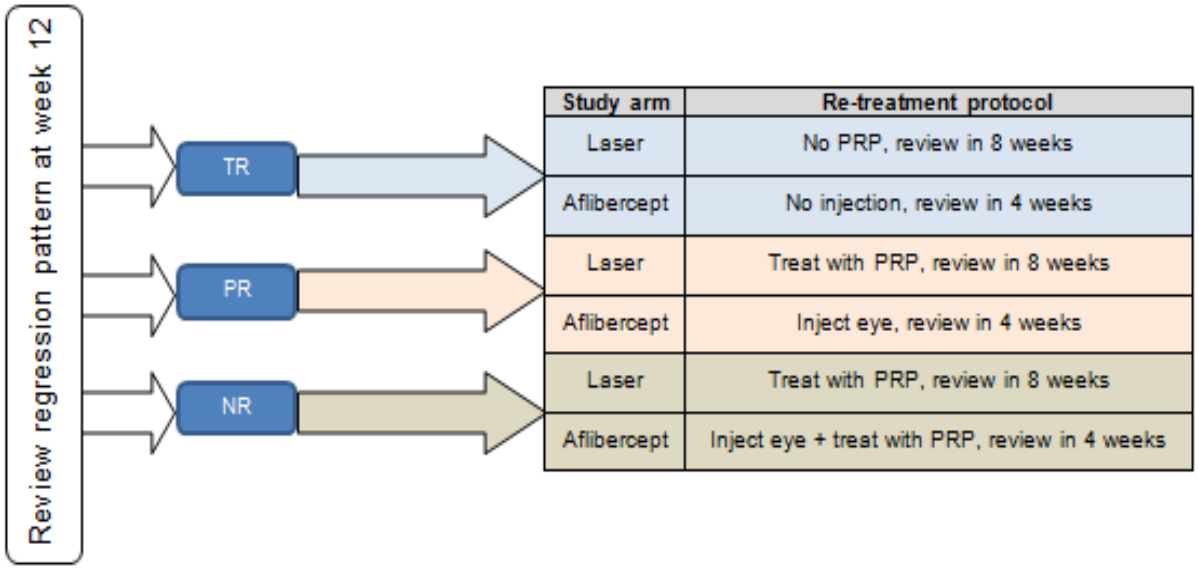
Fluorescein fundus angiography may be performed at any visit if there is any doubt that a clinical feature represents retinal neovascularisation.

PRP treatment can be done using any PRP delivery system including indirect PRP. If PRP has to be done as a day case, this should not be recorded as a serious adverse event despite hospitalisation.

8.9.2.2 Deferred PRP in PRP arm

1. PRP may be deferred if the media is too hazy to perform the procedure.
2. PRP may be deferred in the 'no regression category' if in the opinion of the investigator, the eye has had adequate PRP and there is insufficient space for further fill-in PRP.

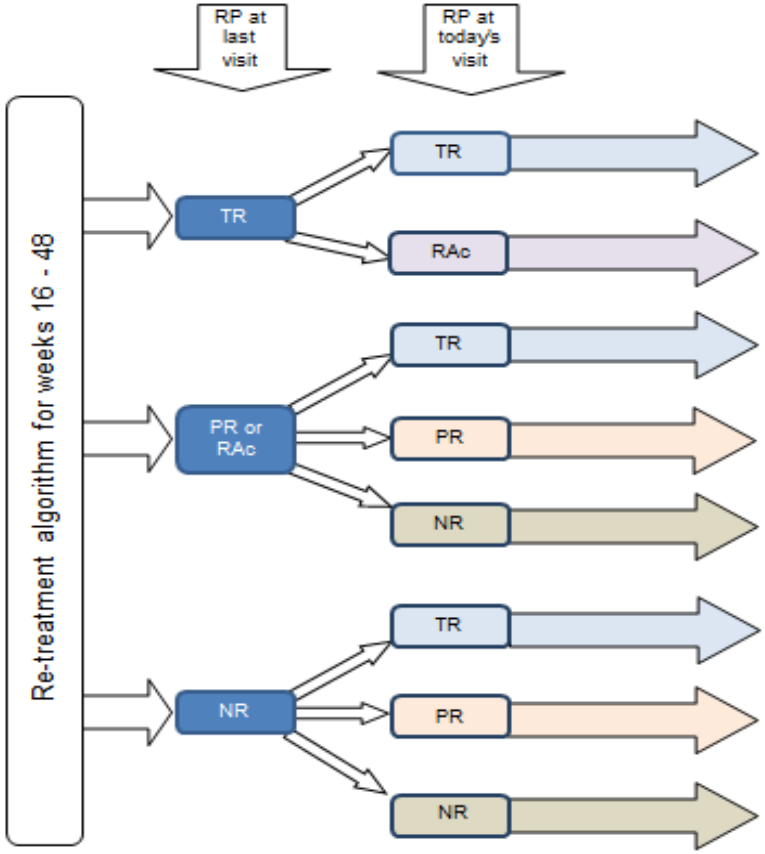
Flow chart 1: Summary of retreatment plan at week 12 following the first review of regression pattern



Study arm	Re-treatment protocol
Laser	No PRP, review in 8 weeks
Aflibercept	No injection, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye + treat with PRP, review in 4 weeks

Key: NR - No regression TR - Total regression PR - Partial regression

Flowchart 2: Summary of retreatment plan from week 16-48.
(Please see table 2 and 3 for details-PRP in PR and RAc may be as per investigator discretion)



Study arm	Re-treatment protocol
Laser	No PRP, review in 8 weeks
Aflibercept	No injection, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye, review in 4 weeks
Laser	No PRP, review in 8 weeks
Aflibercept	No injection, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye + treat with PRP, review in 4 weeks
Laser	No PRP, review in 8 weeks
Aflibercept	No injection, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye, review in 4 weeks
Laser	Treat with PRP, review in 8 weeks
Aflibercept	Inject eye + treat with PRP, review in 4 weeks

Key: RP - Regression pattern NR - No regression TR - Total regression PR - Partial regression RAc - Reactivation

8.10 Methods

8.10.1 Laboratory procedures

The following blood sample will be processed at local labs or in accordance with local practice: HbA1c
HbA1c will be performed at screening and final visit. If the test has been performed within 3 months of the visit, it does not need to be repeated.

For new participants:
Participants that have a HbA1c of more than 12% at the start of the study can be re-screened after 3 months, if the parameter is brought under control and the other inclusion criteria are met. Any patients identified with a result of >8%will be referred for follow up with their normal healthcare provider. A standard letter directing the healthcare provider to the NICE guidelines for management of diabetes will be provided.

For existing participants at final visit:
If HbA1c is >8%, their normal healthcare provider should be informed to ensure prompt and optimal management of these participants. A standard letter directing the provider to the NICE guidelines for management of diabetes will be provided. If in the opinion of the Principal Investigator the result is classed as clinically and significantly abnormal, this should be recorded as an adverse event and followed up accordingly.

8.11 Definition of end of trial

Patients will be in the trial for around 52 weeks from the point of randomisation. End of trial will be defined as last participant and last participant visit. This definition also applies to the mechanistic evaluation sub-study.

8.12 Discontinuation/withdrawal of participants and 'stopping rules'

Discontinuation
The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Chief Investigator, Data Monitoring and Ethics Committee (DMEC) and/or Trial Steering Committee (TSC), Sponsor, regulatory authority or Research Ethics Committee concerned.

Discontinuation of injections in the aflibercept arm

Patients will be discontinued from aflibercept for the following reasons:

1. In the event of pregnancy. The participant should remain in the study and study data collected until week 52 unless consent is withdrawn. Panretinal photocoagulation of active PDR is advised.
2. Patients that are lost to follow-up.

3. Significant medical condition based on clinical judgement that prevents the participant from attending visits until end of study. The participant should remain in the study and study data collected until week 52 unless consent is withdrawn.
4. Any ocular or systemic disease that according to the investigator is a contraindication for aflibercept injection. Panretinal photocoagulation for active PDR is advised.

Stopping rules

The DMEC will review data quality and accumulating safety data throughout the trial. There is no expectation of a formal interim analysis or the use of formal statistical stopping rules in this trial, but if there is any change to this plan, the DMEC will document this via the DMEC charter.

Withdrawal of Subjects

Participants have the right to withdraw from the study at any time and for any reason, without providing a reason. The investigator also has the right to withdraw participants from the study in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations or other reasons. Should a participant decide to withdraw from the study, they will be asked to volunteer a reason for withdrawal but are at liberty not to do so.

Should a participant withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the participant. Subjects who withdraw from treatment early will be encouraged to return to the study site for early termination assessments, and those who terminate early will continue to have follow-up until week 52, providing that consent is not withdrawn.

The visit window process described in *section 8.7* should be followed for withdrawn participants.

9 Name and description of all drugs used in the trial

9.1 Treatment of subjects

Investigational product/treatment

9.1.1 Aflibercept

Aflibercept will be supplied in "kits" of 15 vials by Bayer Pharma who holds the marketing authorisation for this drug. Aflibercept will be shipped from Bayer to The Clinical Trials Manufacturing and Supplies Department, Pharmacy Production Department, Royal Free Hospital NHS Foundation Trust.

The secondary packaging will have two labels; the first will be affixed by Bayer before being dispatched to the manufacturing unit. This label will not be removed. The second label will be annex 13 compliant and will be affixed by the manufacturing unit before being distributed to sites. Sites should follow instructions on this label. The manufacturing unit will also affix an annex 13 compliant label to each of the primary packaging within the kits (the vials). Labelling will be completed prior to QP release and distribution to sites."

Aflibercept should be kept at 2-8^{0}C and therefore will be shipped and stored under temperature controlled conditions to ensure stability. All processes will be conducted in accordance with Good Manufacturing Practice.

The physical, chemical, and pharmaceutical properties and formulation of aflibercept are provided in the current version of the SPC via the eMC website (http://www.medicines.org.uk/emc). The drug will be delivered in exactly the same dose and formulation as notified in the marketing authorisation for wet age related macular degeneration and macular oedema due to central retinal vein occlusion.

9.1.2 PRP

PRP treatment will be delivered as specified in section 8.9 *Treatment Procedures.* Sites should use PRP delivery systems in accordance with local practice. The type of PRP machine used will be recorded.

9.2 Concomitant medication

All concomitant medication, including current and past therapies in the last 12 months will be recorded at screening. Any change in concomitant medications will be recorded at each visit. Eye drops for dilating the pupils at each visit, topical antibiotics and anaesthetic, topical fluorescein and local antiseptics used during the injection procedure and topical anaesthetic and lubricant gel used during PRP treatment are not considered as concomitant medications.

9.3 Permitted and prohibited procedures

9.3.1 Macular oedema in study eye (both arms)

Macular laser may be applied for de novo macular oedema during the study period. An OCT should be done prior to macular laser treatment and monitored with further OCT at each visit. FFA can be done at any visit. Anti-VEGF and steroid treatment for DMO are to be avoided in both arms unless significant visual impairment is expected before the end of the study.

9.3.2 *Vitrectomy*

A study eye in either arm may develop sight-threatening vitreous haemorrhage or traction retinal detachment. These conditions will be recorded as serious adverse events. Vitrectomy may be performed at the discretion of the investigator. Vitrectomy may also be done in the non-study eye if indicated.

9.3.3 Treatment of macular oedema in fellow eye

It is advocated that macular laser treatment is the first choice offered to the non-study eye if treatment is required for DMO. However, the participant can be treated with intravitreal anti-VEGF therapy or steroid therapy if the central macular sub-field thickness is above 400µm due to clinical evidence of macular thickening and as per discretion of the treating physician. If anti-VEGF therapy is contemplated due to anticipated visual impairment related to DMO, intravitreal aflibercept is the drug of choice.

9.3.4 Panretinal photocoagulation in fellow eye

PRP to fellow eye is permitted if retinal or disc neovascularisation is observed in any visit. The patient should then be seen at two weekly intervals until sufficient PRP is applied. The participants will also continue to attend all study visits until end of study. PRP done as a day case will not be recorded as a serious adverse event although it will be a hospitalisation.

9.3.5 Change in control of diabetes and hypertension

Changes in medications related to diabetes or hypertension will be recorded within concomitant medications.

9.3.6 Cataract surgery

Anticipated need for cataract surgery in the study period is an exclusion criterion. Randomised patients that require cataract surgery in the study will be allowed to continue in the study. Cataract surgery in the study eye will not be recorded as a serious adverse event although it may be a hospitalisation. Cataract surgery is allowed in non-study eye.

9.3.7 Endophthalmitis

This is a serious adverse event. Diagnosis and treatment of endophthalmitis is based on investigator judgement and local hospital policy. However, vitreous and aqueous cultures must be obtained and the intravitreal antibiotics used should be recorded as concomitant medications.

9.3.8 Neovascular glaucoma, angle or iris neovascularisation

Diagnosis and management of these complications of diabetic retinopathy is based on investigator discretion and local practice. However, other anti-VEGF agents in the study eye should be avoided.

9.3.9 Management of diabetes and systemic complications and other co-morbidities

This will remain under the participant's medical care provider.

10 Investigational Medicinal Product

10.1 Name and description of investigational medicinal product(s)

10.1.1 Aflibercept

Bayer Pharma is the manufacturing authorisation holder for aflibercept (EU/1/12/797/002). Aflibercept is commercially provided as Eylea 40mg/ml solution for injection in a vial (type I glass) with a stopper (elastomeric rubber) and an 18G filter needle. Each vial contains 100 microlitres which is equivalent to 4mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2mg aflibercept. It is aclear colourless to pale yellow and iso-osmotic solution.

The dose and delivery of aflibercept will be in line with the marketing authorisation recommendations for wet age macular degeneration and macular oedema due to central retinal vein occlusion. All patients randomised to receive aflibercept will be given a 2 mg/0.05ml intravitreal injection at each dosing visit.

10.1.2 Panretinal photocoagulation (PRP)

This is standard care for treatment of proliferative diabetic retinopathy. The laser machine used to deliver the PRP will be in accordance with local practice.

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

Prophylactic antibiotic eye drops can be prescribed post injection by any treating physician as per routine NHS practice and will be recorded as a concomitant medication for the study. Dose, duration and frequency will be in accordance with local practice. Normal NHS prescribing practice in both primary and secondary care will apply with no special arrangements.

Intravenous fluorescein dye used to visualise the retinal circulation by obtaining retinal photographs is one of the secondary outcome measures and will be recorded as a concomitant medication for the study. Normal prescribing practice within secondary care will apply with no special arrangements.

10.3 Summary of findings from non-clinical studies

Please see section 3.3 Preclinical data and refer to the current version of the SPC on the eMC website: http://www.medicines.org.uk/emc/.

10.4 Summary of findings from clinical studies

Please see section 3.4 Clinical data and refer to the current version of the SPC on the eMC website: http://www.medicines.org.uk/emc/.

10.5 Summary of known and potential risks and benefits

Please see section 3.5 Rationale and risks/benefits and 3.6 Assessment and management of risks. Further information is available in the current version of the SPC on the eMCwebsite:http://www.medicines.org.uk/emc/.

10.6 Description and justification of route of administration and dosage

Intravitreal Aflibercept 2mg/0.05ml injection is performed under sterile conditions in a designated treatment room as per SPC and/or each trial centre's treatment policy. Prior to injection, the aflibercept vial will be supplied from each local pharmacy clinical trial stock. There will be no change to the licensed dose or technique of administration. After the drug administration, the empty vial and box should be returned to site pharmacy for reconciliation.

10.7 Dosages, dosage modifications and method of administration

Aflibercept 2 mg/0.05ml will be administered by intravitreal injection into the study eye at baseline, week 4 and week 8.At week 12 and further visits, the study eye will be assessed to determine the level of regression that has taken place and re-treated based on the pre-defined re-treatment criteria shown under section 8.9*Treatment procedures*. The interval between two doses of aflibercept should not be shorter than one month. One month for the purpose of this study is considered as four weeks.

10.8 Preparation and labelling of Investigational Medicinal Product

Aflibercept will be supplied by Bayer plc and shipped to The Clinical Trials Manufacturing and Supplies Department, Pharmacy Production Department, Royal Free Hospital NHS Foundation Trust, who will be responsible for packaging, labelling and QP releasing the drug prior to distribution to site. The Trial Manager will support centralised tracking of IMP. Local pharmacies at participating sites will be responsible for storing, dispensing, recalls and destruction of aflibercept during the study.

10.8.1 Prescribing, dispensing and ordering procedures

Study medication will be prescribed by an authorised study physician according to the protocol, using a trial specific prescription. Medication will be dispensed according to local pharmacy practice. Participants will be informed of potential adverse reactions and advised to seek medical help and contact the research team, if required. Documentation of prescribing, dispensing and return of study medication shall be maintained for study records in the pharmacy file and reconciled with the investigator site file at end of study. A study specific prescription must be submitted to pharmacy as early as possible after randomisation. The pharmacy will have received an email from the randomisation service at the time of randomisation, which must be printed and filed with the dispensing records and which will be referred to by the dispensing pharmacist to confirm whether the participant is correctly randomised to receive aflibercept.

Pharmacy will be responsible for maintaining adequate stock levels of aflibercept and should notify the Trial Manager when stocks are running low using a trial specific order request form. The Trial Manager will place the orders with the manufacturing unit on behalf of the sites. The manufacturing unit will deliver directly to the sites. Sites will be provided a study specific drug order request form. A maximum of three orders will be permitted throughout the duration of the study.

10.9 Drug accountability

Research staff will be asked to return any surplus study drug and empty vials to the site pharmacy, who will verify and document returns on the patient specific accountability log. In the event that an injection is not given as scheduled, reasons must be documented in the patients' notes and also on the patient specific accountability log. With the permission of the Trial Manager, returned and expired aflibercept vials should be destroyed in accordance with local practice and recorded on the trial specific destruction log. The completed log should be retained in the pharmacy site file. Please refer to pharmacy instructions for more details.

All records will be reconciled at the end of the study with the Investigator Site File.

10.10 Source of active intervention and comparator

Aflibercept will be provided by Bayer Healthcare Ltd. in accordance with its marketing authorisation. The Clinical Trials Manufacturing and Supplies Department, Pharmacy Production Department, Royal Free Hospital NHS Foundation Trust, will be responsible for packaging, labelling and QP releasing the drug prior to distribution to site.

Laser machine needed to complete the comparative treatment, PRP, will be sourced by the local site.

10.11 Dose modifications

Participants randomised to receive aflibercept will receive an intravitreal injection of (2 mg in 0.05ml) at baseline, week 4 and week 8 before being categorised on response to treatment (please see section 8.9*Treatment procedures*). Participants will receive further doses depending on the level of regression of neovasularisation observed.

Naïve PDR participants randomised to receive PRP treatment will receive PRP in fractionated session two-weekly and then reviewed 8 weekly. Participants will be re-treated based on the retreatment criteria based on routine clinical practice (please see section 8.9*Treatment procedures*).

10.12 Assessment of compliance

10.12.1 Protocol compliance

The study will run in accordance with the approved protocol. To ensure a standard approach to study conduct, site personnel will be trained in the protocol prior to starting recruitment at the site initiation visit. Local sites should also contact the Chief Investigator or Trial Manager should any queries relating to the conduct arise.

Trained ophthalmologists and nurses will be administering aflibercept. Trained ophthalmologists will perform PRP. Date of assessment, lot or batch number and expiry date of aflibercept will be recorded to monitor compliance clinically. Date of assessment and whether the PRP treatment has been successfully delivered will be used to confirm compliance for patients in the PRP arm of the study.

10.12.2 Participant compliance

Clinical trials on DMO that require regular monthly follow-up visits showed that the approximately 5% withdraw consent and 5% are lost to follow-up in similar sample-sized studies. Based on previous clinical trial experience of these patients at various sites selected for this study, the compliance rates of these patients to attend intervention and assessment schedules are good because of their fear of visual loss. The usual cause of non-compliance with visits for this type of study is due to other co-morbidities.

Sites will be instructed to follow up all participants for outcome data. Participants who withdraw from the study intervention should be encouraged to attend their visits and complete study data as per the protocol schedule for their allocated arm.

If a participant withdraws from the study, section 8.12under *Withdrawal of Subjects* should be followed.

10.13 Post-trial active intervention arrangements

Aflibercept will not be available to participants after the trial has finished for treatment of PDR. PRP treatment will be offered, which is the standard care for this condition, if the condition recurs.

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 study intervention and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a subject to a study intervention which **is related** to any dose administered to that subject.

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: 1. results in death, 2. is life-threatening, 3. requires hospitalisation or prolongation of existing hospitalisation 4. results in persistent or significant disability or incapacity, or 5. 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 study intervention in question set out in the summary of product characteristics (aflibercept) and RCOphth Diabetic Retinopathy guidelines (PRP).
SUSAR	Suspected Unexpected Serious Adverse Reaction.

11.2 Recording adverse events

Adverse events occurring subsequent to consent will be recorded in the source data worksheets and eCRF.

All serious adverse events will be recorded with diagnosis, where a diagnosis has been made, or with clinical symptoms where a diagnosis has not been made and accompanied with a simple, brief description of the event, including dates as appropriate. Non-serious adverse events will be recorded with no detailed description.

If the investigator suspects that the subjects' disease has progressed faster due to the administration of either study intervention, then he will record and report this as an adverse event.

HbA1c will be recorded as an adverse event if the result has clinically and significantly worsened since commencing the trial and is deemed clinically and significantly abnormal in the opinion of the Principal Investigator.

Planned cataract surgery and PRP therapy completed as a day case will not be recorded as a serious adverse event.

All serious adverse events will be reportable to the Chief Investigator up to 30 days post last administration of either study intervention.

11.3 Assessments of Adverse Events

Each adverse event will be assessed for the following criteria:

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.

11.3.1 Causality

The assessment of relationship of adverse events to the administration of either study intervention is a clinical decision based on all available information at the time of the completion of the source data worksheets and eCRF and should be performed by the Principal Investigator or delegate (must be a clinician). .

Whilst the Principal Investigator is responsible for resolving any queries that arise during the completion of the AE log and eCRF, queries can also be directed to the Chief Investigator and Trial Manager.

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 either study intervention. 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 either study intervention). 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.

11.3.2 Expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the study intervention listed in the SPC (aflibercept), RCOphth Diabetic Retinopathy guidelines(PRP) **or defined in this protocol.**
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about either study intervention in the SPC (aflibercept), RCOphth Diabetic Retinopathy guidelines (PRP).

The reference documents to be used to assess expectedness against the study intervention are the SPC (aflibercept) and RCOphth Diabetic Retinopathy guidelines (PRP). The protocol will be used as the reference document to assess disease related and/or procedural expected events.

Expected adverse events may be classified into ocular (study eye and non-study eye will be reported separately) and non-ocular. Ocular adverse events may be due to disease progression, injection procedure related, study intervention related or any other related event that the investigator deems clinically significant.

Disease progression may include cataract progression, retinal detachment, vitreous haemorrhage, increase severity of diabetic retinopathy, neovascular glaucoma, iris or angle neovascularisation, macular oedema.

Injection related events may include conjunctival haemorrhage, conjunctival hyperaemia, eye pain, transient reduced visual acuity, raised intraocular pressure. Endophthalmitis is a serious adverse event.

Symptoms related to rhegmatogenous detachment or vitreous haemorrhage occurring within 12 hours of injection or PRP may be reported as related to procedure.

Other related adverse events include allergic reaction to the fluorescein dye. Any APTC events will also be documented. These include vascular deaths, non-fatal myocardial infarction, non-fatal stroke, other thrombo-embolic events, non-ocular haemorrhage.

Any planned procedure completed as a day case, for example, cataract surgery or PRP therapy, does not need to be reported as a serious adverse event.

11.3.3 Seriousness

Collection, recording and reporting of adverse events (including serious and non-serious events and reactions) to the sponsor will be completed according to the study specific SOPs.

11.4 Procedures for recording and reporting Serious Adverse Events

All SAEs, SARs & SUSARs shall be recorded and reported on the serious adverse event form to the Chief Investigator / delegate within 24 hours of learning of its occurrence. The initial report can be made by completing the serious adverse event form, and faxing or emailing to the KCTU (Fax: 020 7848 5229, email: ctu@kcl.ac.uk). A record of this notification (including 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. The site will respond promptly to any queries raised by the Chief Investigator /delegate.

Relationship of the SAE to either study intervention should be assessed by the Principal Investigator/delegate (must be a clinician) at site. The CI will assess the expected or unexpected nature of any serious adverse reactions

The Chief Investigator/delegate with the support of the KCTU will ensure that Moorfields Eye Hospital, as Sponsor is made aware of any SUSARs and SAEs that occur. The Chief Investigator/delegate in conjunction with the Sponsor will be responsible for reporting all SUSARs to the MHRA and relevant ethics committee.

Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

All Principal Investigators will be informed of all SAEs assessed as fulfilling criteria as a SUSAR (i.e.possibly, probably or definitely related to either study intervention and unexpected as per the SPC (aflibercept) or RCOphth Diabetic Retinopathy guidelines (PRP).

11.4.1 Notification of deaths

Death will be treated as an SAE and should be reported in the same format as described in section 11.4 *Procedures for recording and reporting Serious Adverse Events*.

11.4.2 Reporting SUSARs

The Chief Investigator/delegate, in conjunction with the sponsor, will notify the main REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

11.4.3 Development Safety Update Reports

The Chief Investigator/delegate will prepare and submit a Development Safety Update Reports (DSUR) to the main REC and the MHRA in conjunction with 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.

11.4.4 Annual progress reports

The Chief Investigator/delegate will prepare and submit an annual progress report (APR) 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.

11.4.5 Pregnancy

In the event a female participant becomes pregnant, this should be reported to KCTU via fax or email (Fax: 020 7848 5229, email: ctu@kcl.ac.uk)using a pregnancy form as soon as the Investigator becomes aware of it. The pregnancy will be monitored to determine outcome. Any information related to the pregnancy following the initial report should be reported as follow up information on a separate pregnancy form.

Further treatment of aflibercept should be stopped on becoming aware of pregnancy but collection of outcome data should continue to the end of the study provided the participant is willing to do so.

Pregnancies in the PRP treatment arm should be reported as above but treatment should not be withdrawn. Collection of outcome data should continue to the end of the study provided the participant is willing to do so.

Participants who wish to withdraw should be withdrawn as described in section 8.12 *Withdrawal of participants/discontinuation and stopping rules* under *Withdrawal of subjects*

Any SAEs experienced during the pregnancy must be reported on an SAE form as described in *Procedures for recording and reporting Serious Adverse Events* above.

SAE data will not be collected for partners of patients taking part in the study.

11.4.6 Overdose

In the event that a higher does is given to a participant, the site should notify the Chief Investigator/delegate. Follow up action will be decided on a case by case basis. Participants do not need to be withdrawn from the study and should remain on treatment and in follow up. Sites will be instructed to complete the adverse event form if such an event occurs.

11.4.7 Reporting Urgent Safety Measures

Any urgent safety measures taken should be immediately reported to the Chief Investigator or her assignee. Any queries that arise should be promptly resolved by the site to ensure reporting timelines are adhered to. The Chief Investigator /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.

11.5 Type and duration of the follow-up of subjects after adverse events

Any AEs during the patient's participation in the study will be followed up.AEs, ARs, SAEs, SARs and SUSARs will be reportable for up to 30 days after the last intervention session.

11.5.1 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 inwriting 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 Principal Investigator should notify the Chief Investigator/delegate if a serious breach in GCP/protocol is thought to have occurred as soon as he/she becomes aware of it. The Chief Investigator shall notify the sponsor as soon as she becomes aware of any case where the above definition applies during the trial conduct phase. The Chief Investigator will also notify the Trial Steering Committee and Data Monitoring Committee of serious breaches, throughout the course of the study. The Chief Investigator/delegate and the sponsor will be responsible for notifying the MHRA of serious breaches in GCP/protocol to the MHRA within the required timeframe and in line with Sponsor requirements.

12 Data management and quality assurance

12.1 Confidentiality

Data will be handled, computerised and stored in accordance with the Data Protection Act 1998.Participants will be identified via a unique code and their initials. Identifiable information will not be stored in the eCRF and will not leave the site. Any participant contact information will be stored within the site on password protected computers.

12.2 Data collection tools and source document identification

Written informed consent will be obtained prior to screening and any other study specific procedures are performed.

SAE data will be collected on paper SAE report forms and faxed to the KCTU. Summary details of SAEs will be transcribed to the adverse event section of the eCRF. For all other data collected, source data worksheets will be used for each patient and data will be entered onto the eCRF database. Source data worksheets will be reconciled at the end of the trial with the patients NHS medical notes in the recruiting centre. During the trial, critical clinical information will be written in the medical notes to ensure informed medical decisions can be made in the absence of the study team. Trial related clinical letters will be copied to the medical notes during the trial. The Principal Investigator will provide an electronic signature for each patient Case Record Form once all queries are resolved and immediately prior to database lock.

It will be the responsibility of the Principal Investigator and his team to ensure the accuracy of all data entered in the worksheets in accordance with Good Clinical Practice. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database. The Principal Investigator will be responsible for ensuring that source data worksheets are filed in a suitably secure location to ensure source data verification can be undertaken throughout the study.

12.3 Data handling and analysis

All study data and site files will be kept at site in a secure location with restricted access.
The study will employ an eCRF created using the InferMed MACRO database system. Data will be managed via this system. The eCRF will be created in collaboration with the trial statistician and the CI and maintained by the KCTU. It will be hosted on a dedicated secure server within KCL.

This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive) and will have a full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting.

The Trial Manager will be responsible for providing usernames and passwords to permitted local study personnel. Only those authorised by the Trial Manager wil lbe able to use the system.

Database Website Address:

Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

12.3.1 Quality assurance

The study incorporates a range of data management quality assurance functions. The eCRF system will contain a range of validations that will alert sites to inconsistencies in the data being entered which will be monitored by the Trial Manager. The Trial Manager will provide study training, ongoing study support and conduct regular monitoring visits at each centre, checking source data for transcription errors. Any necessary alterations to entered data will be date and time stamped within the eCRF.

A detailed monitoring plan and data management plan will be developed and updated as the trial progresses, detailing the quality control and quality assurance checks to be undertaken.

12.3.2 Database lock

Prior to database lock, the Trial Manager will review any outstanding warnings on the eCRF and resolve or close these as appropriate before database lock. Local study personnel should resolve any queries that arise promptly. Once all queries have been resolved no further changes will be made to the database unless specifically requested by the Study Office in response to the statistician's data checks. The study PI will review all thedataforeachparticipantandprovideelectronicsign-offtoverifythatallthedataarecompleteand correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with the eCRF for the centre on a CD-ROM. This will be filed locally for any future regulatory inspection or internal audit.

13 Record keeping and archiving

The Chief Investigator will be custodian for the data generated from the study. The Chief Investigator will be responsible for archiving the original data. All data will be archived for at least 5 years from the end of the trial and will be archived in accordance with Sponsor and regulatory requirements. Investigators will be responsible for securely archiving local data generated, essential documents and source data in accordance with local requirements, but for at least 5 years from the end of the study. Investigators should provide archiving details to the Chief Investigator/delegate and will be instructed that authorisation from the Chief Investigator should be obtained before study data or study documentation is destroyed.

Essential documents held by the KCTU will be returned to the Chief Investigator for archiving by the Sponsor organisation. eCRF data will also be exported and provided to the Chief Investigator for archiving.

14 Statistical Considerations

Toby Prevost, Lead Statistician, with the support of Joana Vasconcelos as the trial statistician will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

14.1 Outcomes

14.1.1 Primary outcomes

Change in best corrected visual acuity from screening to 52 weeks in the study eye measured in ETDRS letter score at 4 metres: difference in means.

14.1.2 Secondary outcomes

To measure the effect of intravitreal aflibercept therapy, relative to panretinal photocoagulation on additional visual function and quality of life outcomes including:

i) Percentage of uniocular and binocular Esterman efficiency scores at 52 weeks: difference in proportions.
ii) Binocular visual acuity at 52 weeks: difference in means.
iii) Low luminance visual acuity at 52 weeks: difference in means.
iv) Visual acuity outcomes in terms of visual gain or loss: difference in proportions.
v) Contrast sensitivity measured using Pelli Robson chart at 52 weeks: difference in means.
vi) Change from baseline in vision related quality of life measured using VFQ-25 and RetDQolat 52 weeks: difference in means.
vii) Change from baseline in Diabetic retinopathy treatment satisfaction questionnaire (RetTSQ) scores at 52 weeks: difference in means.
viii) Change from baseline in health related quality of life at 52 weeks (EQ-5D, ICECAP-A and CSRI): difference in means.

Cost-effectiveness:
Incremental cost-effectiveness of intravitreal aflibercept versus conventional panretinal photocoagulation at 52 weeks. The incremental costs and consequences of alternative arms will be compared and expressed in cost per quality-adjusted life years (QALYs) where possible. National unit costs will be used to calculate health and social care service usage costs. The intervention arms will be costed using published unit costs. From a methodological perspective, we will compare the performance of the EQ-5D (a generic, preference based HQoL measure) with the vision loss specific HQoL measures. To understand how sight loss has an impact on daily life we will analyse the activities of daily living questionnaire.

Anatomical outcomes:
1. To compare between arms the regression patterns of new vessels at 12 weeks and the regression and reactivation patterns at 52 weeks: means and proportions.
2. To compare the proportion of patients with 1-step and 3-step improvement or worsening of diabetic retinopathy between treatment arms at 12 and 52 weeks: difference in proportions.

Treatment related outcomes:
3. To determine the proportions of naïve PDR and non-naïve PDR eyes that do not require panretinal photocoagulation through 52 weeks after basic treatment of 3 loading doses of aflibercept in the aflibercept arm and after initial completion of PRP in the PRP arm: difference in proportions.

Safety profile:

To explore the difference in safety profile between intravitreal aflibercept and PRP at 52 weeks, in terms of proportion of patients developing macular oedema (defined as central subfield thickness of >300µm on3D OCT-1000 (Topcon) SD-OCT or Spectralis OCT > 320µm and Cirrus HD-OCT > 300µmor its equivalent if any other OCT devices are used due to clinical evidence of macular oedema), any de novo or increase in existing vitreous haemorrhage, denovo or increasing tractional retinal detachment, NVG, and the requirement for vitrectomy for various indications: difference in proportions.

Mechanistic evaluation:

1. To explore whether intravitreal aflibercept compared to PRP causes measurable regression of retinal neovascularisation at 12 and 52 weeks in terms of decimal disc area units in 4- field colour photographs and FFA: difference in means.
2. To explore differences in the mean change in retinal vessel calibre and oxygen saturation in eyes treated with intravitreal aflibercept compared to PRP at 12 and 52 weeks: difference in means.
3. To explore whether intravitreal aflibercept reduces angiographically quantifiable areas of retinal non-perfusion compared to panretinal photocoagulation through 52 weeks: means and proportions.

All image sets of the study including colour photographs, fluorescein angiography and OCT images may be analysed to validate observations noted in the mechanistic sample.

14.2 Sample size and recruitment

14.2.1 Sample size calculation

The sample size calculation was performed using nQuery Advisor 4.0 software. The primary outcome is the change in best corrected visual acuity ETDRS letter score from baseline to 52 weeks. Based on the objectives of this study and the potential deleterious effects on visual function by panretinal photocoagulation, a non-inferiority margin of 5 letters was judged to be clinically acceptable (24-26, 37) In addition, this margin is less than the lower limit of the 95% confidence interval for the comparison of immediate panretinal photocoagulation with observation. This helps ensure that aflibercept is superior to observation alone in the event that it is found to be non-inferior to panretinal photocoagulation. Therefore, in the wider patient population, if aflibercept is no more than five letters worse then it will be defined to be non-inferior. The sample size is based on providing a 95% confidence interval for the between-arm difference in mean change in visual acuity that will be sufficiently narrow to detect non-inferiority (by the confidence interval lying entirely above the margin) with high power, while keeping a false declaration of non-inferiority to 5% through use of a statistical test applied at the two-sided 5% level of significance.

The standard deviation of the change in visual acuity, after adjustment for baseline, is anticipated to be 10.3, based on the estimate from a relevant trial (37).

With 110 patients randomised per arm (total 220), 182 will be followed up to 52-week outcome (allowing for 17% dropout or per protocol exclusion). This provides 90% power to detect non-inferiority using a two-sided

95% confidence interval from an analysis of covariance test with adjustment for baseline visual acuity.

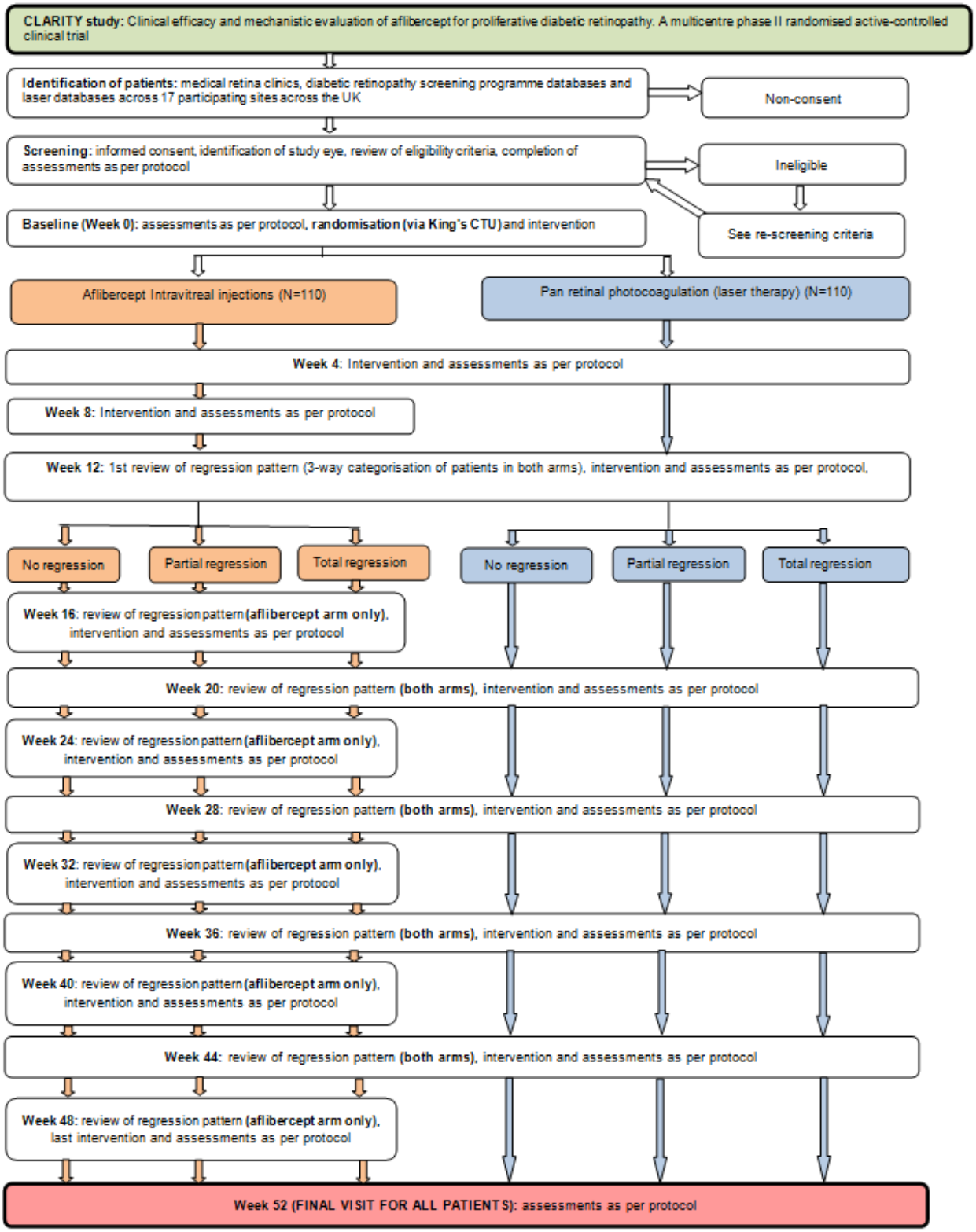
14.2.2 Planned recruitment rate

At least 15 sites will be opened for this study. It is anticipated that 220 participants will be recruited over a 12 month period. The DMEC will receive recruitment updates and based on committee recommendations new sites will be added as needed.

Statistical analysis plan

A detailed statistical analysis plan will be developed for comment from the DMEC and for approval by the TSC prior to the availability of primary outcome data.

14.2.3 Summary of baseline data and flow of patients



A detailed statistical analysis plan will be developed for approval by the Trial Steering Committee prior to the availability of primary outcome data being supplied to the study statisticians.

14.2.4 Primary outcome analysis

Analyses will be on an intention to treat (ITT) basis. The primary outcome will be compared between arms primarily at the 52-week point and secondarily at the 12-week point using a linear mixed effects model with patient as a random effect to allow for within-patient correlation of repeated measures over time. The fixed effects will consist of study site in main effect form, and interactions between the full polynomial terms over time with arm, the continuous form of the baseline of the outcome using the missing indicator method, and the remaining minimisation stratifiers. The test for non-inferiority will be one-sided at the 2.5% significance level, and presented as an estimated effect with two-sided 95% confidence interval compared against the non-inferiority margin.

For the analysis of the primary outcome, the mixed effects model will be re-fitted in a reduced per protocol (PP) population, excluding patients found to be ineligible at entry, and those not receiving the full randomised treatment up to and including the 8-week visit (whether due to discontinuation, exclusion or other reason for missing a randomised treatment in this period). Non-inferiority will only be concluded if this is declared by both the ITT analysis and the PP analysis at 52 weeks. Non-inferiority will also be assessed in ITT and PP populations at 12 weeks.

14.2.5 Secondary outcome analysis

Secondary outcome analyses will be on an ITT basis only, and assessed with tests at the two-sided 5% level of significance. Continuous outcomes will be compared between arms using a linear mixed effects model, as specified for the primary outcome ITT analysis, incorporating prior measurements of the outcome over time. Binary outcomes will be compared between arms using a corresponding generalised estimating equation approach. Continuous and binary outcomes will be reported as adjusted differences in means or odds ratios respectively. All tests will be two-sided at the 5% significance level and interpreted cautiously with a focus on interpreting effect sizes with 95% confidence intervals. Safety outcomes will be reported as unadjusted patient proportions and rates within and between arms with 95% confidence intervals using exact methods where appropriate.

14.2.6 Sensitivity and other planned analyses

Sensitivity to the missing at random assumption made in the primary outcome analysis will be undertaken to assess sensitivity to the handling of missing 52-week data, and to the use of concomitant treatments, and will be detailed in the statistical analysis plan.

If non-inferiority is concluded, superiority will be assessed, and also the effect on the primary outcome will be presented with 95% confidence interval within baseline retinopathy status subgroups: naïve PDR and non-naïve PDR.

14.3 Randomisation methods

Randomisation will be via a bespoke web based randomisation system hosted at the KCTU on a secure server. 220 adult patients with proliferative diabetic retinopathy will be randomised 1:1 at the level of the individual using the method of minimisation incorporating a random element. The minimisation factors will be proliferative diabetic retinopathy status (naïve PDR and non-naïve PDR),HbA1c (<8%, 8-10%, >10%), diastolic blood pressure (>90mmHg versus ≤90mmHg), best corrected visual acuity (54-69 versus ≥70 letters),and trial site.

14.4 Interim analysis

Formal interim analysis of the primary outcome for early stopping is not planned for this study. Regular interim reports will be prepared as needed for DMEC meetings.

14.5 Other statistical considerations

Please see section 14.1.
A detailed statistical analysis plan will be developed for approval by the Trial Steering Committee prior to the availability of primary outcome data being supplied to the study statisticians.

15 Name of Committees involved in trial

15.1 Trial Steering Committee (TSC)

The TSC's key purpose will be to 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 communication from the TMG. Ultimate responsibility for any decision required on the trial's continuation will lie with the TSC. The Committee will consist of at least an independent Chair, two other independent members, one or two principal investigators and, where possible, a patient representative. TSC meetings will take place at least annually and these will be arranged by the Chief investigator and the Trial Manager in conjunction with the Chair. Increased frequency of meetings will be arranged depending on the requirements of the study DMEC and TSC recommendations. An NIHR MRC EME representative and Moorfields Eye Hospital representative (Sponsor) may also be invited.

15.2 Data Monitoring and Ethics Committee (DMEC)

An independent data monitoring and ethics committee (DMEC) will be responsible for monitoring the safety and efficacy of the study and will advise the TSC of any follow up recommendations. The committee will have a DMEC chair and will consist of: a Professor in statistics who will be the independent chair and two independent ophthalmic physicians. The DMEC meeting will aim to occur at least 3 weeks prior to the TSC meeting. Only the DMEC will have access to masked study data, if deemed necessary. The trial statistician will provide the DMEC with an in depth report prior to each meeting and will also be responsible for finalising the DMEC charter with the DMEC members.

15.3 Trial Management Group (TMG)

The TMG will be responsible for monitoring the delivery of the trial on a day to day basis and will be supported and managed via the KCTU. The TMG membership will consist of: Chief Investigator, Co-Lead, Trial Manager, Data Manager, the trial statistician(s) and senior members of KCTU. Other members of the wider research team may be invited to a meeting depending on the scope covered.

16 Direct Access to Source Data/Documents

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be under taken by the Trial Manager. The main areas of focus will include consent, serious adverse events, and essential documents in study site files.

Site monitoring will include:

- Reviewing all consent forms within the site file and medical notes.
- Source data verifying serious adverse events against medical records and a proportion of the primary outcome measure.
- Checkingessentialdocumentsintheinvestigatorsitefileandstudyfiles.

Central reviews will include:

- Ensuring accuracy and completeness of all applications for study authorisations and submissions of progress/ safety reports, prior to submission
- Ensuring all documentation essential for study initiation are in place prior to site authorisation
- Reporting and following up all monitoring findings with the appropriate persons in a timely manner.

The investigator(s)/ institution(s) will also 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

17.1 Ethical issues

The main ethical issues in relation to this study are the use of intravitreal injections. However, this is now standard of care for wet age related macular degeneration, diabetic macular oedema and retinal vein occlusion. There are at least 5extra visits that the participants need to undergo in excess of standard of care. The precise risks and benefits of participating in the clinical study will be outlined in patient information sheets, formulated with service user involvement.

Participants in the mechanistic sub-study have to undergo retinal oximetry, an additional non-invasive imaging of the retina at baseline, 12 and 52 weeks and at the point of withdrawal. There are no known risks for retinal oximetry.

Participants will be treated with standard of care (PRP treatment) if the disease recurs after they have completed the study. This information is reflected in the patient information sheet.

Any breach of confidentiality will be minimised by adherence to the UK Data Protection Act 1998 and the approved protocol.

17.2 Approval requirements

The Chief Investigator with the support of KCTU and 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 REC, 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. 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 11.4on reporting urgent safety measures).

Within 90 days after the end of the trial, the Chief Investigator/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 Chief Investigator 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.

18 Monitoring requirement for the trial

The Trial Manager will conduct source data verification as described in section 16 *Direct Access to Source Data/Documents*.

19 Finance

The study is funded through the MRC and NIHR Efficacy and Mechanism Evaluation Programme. Bayer Pharma is supplying aflibercept free of charge and has provided additional funding to support the conduct of the study.

20 Insurance

The participating NHS Trusts have liability for clinical negligence that harms individuals towards whom they have a duty of care. NHS indemnity covers NHS staff and medical academic staff with honorary contracts conducting the trial. There are no arrangements for non-negligent compensation.

21 Publication policy

The data will be the property of the Chief Investigator. Publication will be the responsibility of the Chief Investigator. It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their website. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering CommitteeandFunderpriortosubmission.Individualswillnotbeidentifiedfromanystudyreport.

A copy of the results of the study will also be available to participants if a copy is requested. No personal data of participants will be detailed in any publication submitted.

22 Statement of compliance

The trial will be conducted in compliance with the approved protocol, the UK Regulations and as amended and GCP.

23 References

1. Abbate M, Cravedi P, Iliev I, Remuzzi G, Ruggenenti P. Prevention and treatment of diabetic retinopathy: evidence from clinical trials and perspectives. Curr Diabetes Rev. 2011; 7(3):190-200.
2. Bunce C, Xing W, Wormald R. Causes of blind and partial sight certifications in England and Wales: April 2007-March 2008. Eye (Lond). 2010; 24(11):1692-9.
3. Scanlon PH. Why do patients still require surgery for the late complications of Proliferative Diabetic Retinopathy? Eye (Lond). 2010; 24(3):435-40.
4. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. Ophthalmology. 1991; 98 (5 Suppl):766-85.
5. The Diabetic Retinopathy Study Research Group. Preliminary report on effects ofphotocoagulation therapy. Am J Ophthalmology. 1976; 81(4):383-96.
6. Sivaprasad S, Gupta B, Gulliford MC, Dodhia H, Mann S, Nagi D, Evans J. Ethnic variation in the prevalence of visual impairment in people attending diabetic retinopathy screening in the United Kingdom (DRIVE UK). PLoS One.2012; 7(6):e39608.
7. Sivaprasad S, Gupta B, Gulliford MC, Dodhia H, Mohamed M, Nagi D, Evans JR.Ethnic variations in the prevalence of diabetic retinopathy in people with diabetes attending screening in the United Kingdom (DRIVE UK). PLoS One. 2012; 7(3):e32182.
8. Arden GB, Sivaprasad S. Hypoxia and oxidative stress in the causation of diabetic retinopathy. Curr Diabetes Rev. 2011; 7(5):291-304.
9. Stefánsson E. Ocular oxygenation and the treatment of diabetic retinopathy. Surv Ophthalmology. 2006; 51(4):364-80
10. Aiello LM. Perspectives on diabetic retinopathy. Am J Ophthalmology. 2003; 136(1):122-35.
11. Bailey C etal.The National Diabetic Retinopathy Laser Treatment Audit. III. Clinical outcomes. Eye. 1999; 13:151-9.
12. Shima DT, Adamis AP, Ferrara N, Yeo KT, Yeo TK, Allende R, Folkman J, D'Amore PA. Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. Mol Med. 1995; 1(2):182-93.
13. Lange CA, Stavrakas P, Luhmann UF, de Silva DJ, Ali RR, Gregor ZJ, Bainbridge JW. Intraocular oxygen distribution in advanced proliferative diabetic retinopathy. Am J Ophthalmology. 2011; 152(3):406-412.
14. Miller JW, Adamis AP, Shima DT, D'Amore PA, Moulton RS, O'Reilly MS, FolkmanJ, Dvorak HF, Brown LF, Berse B. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994; 145(3):574-84.
15. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med.1994; 331(22):1480-7.
16. Adamis AP, Shima DT, Tolentino MJ, Gragoudas ES, Ferrara N, Folkman J, D'Amore PA, Miller JW. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris

neovascularization in a nonhuman primate. Arch Ophthalmology. 1996; 114(66-71).
17. Aiello LP, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, Ferrara N, King GL, Smith LE. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins ProcNatlAcadSci USA. 1995; 92(23):10457-61.
18. Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmology. 2012; 130(9):1145-52.
19. Salam A, D'Costa J, Sivaprasad S. Treatment of proliferative diabetic retinopathy with anti-VEGF agents. Acta Ophthalmology. 2011; 89(5):405-11.
20. Golik P, Tońska K. Comparison of the biological principles underlying the action of monoclonal antibody (mAb) and decoy receptor anti-VEGF agents--on the example of ranibizumab (anti-VEGF-A mAb) and aflibercept (decoy VEGFR1-2 receptor). KlinOczna. 2012; 114(1):79-83.
21. Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups*. Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration. Ophthalmology. 2012 Oct 17. doi: pii: S0161-6420(12)00865-2.10.1016/j.ophtha.2012.09.006.
22. Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R, Berliner AJ, Gao B, Zeitz O, Ruckert R, Schmelter T, Sandbrink R, Heier JS; DA VINCI Study Group. One-year outcomes of the DA VINCI Study of VEGF Trap-Eye in eyes with diabetic macular edema. Ophthalmology. 2012; 119(8):1658-65.
23. Michaelides M, Fraser-Bell S, Hamilton R, Kaines A, Egan C, Bunce C, Peto T, Hykin P. Macular perfusion determined by fundus fluorescein angiography at the 4-month time point in a prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (Bolt Study): Report 1. Retina. 2010; 30(5):781-6.
24. Martin DF et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results, CATT Research Group. Ophthalmology 2012;119:1388-98.
25. Rosser DA et al. How sensitive to clinical change are ETDRS logMAR visual acuity measurements ?, IvestOphthalmol Vis Sci 2003; 44:3278-81.
26. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology. 2012 Jul;119(7):1399-411. Erratum in: Ophthalmology. 2012 Aug;119(8):1508. Ophthalmology. 2013 Sep;120(9):1719.
27. Ferris FL 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982 Jul;94(1):91-6.
28. Elliott DB, Bullimore MA, Bailey IA. Improving the reliability of the Pelli-Robson contrast sensitivity test. Clin Vis Sci 1991;6:471–5.
29. Mackie SW, Walsh G. Contrast and glare sensitivity in diabetic patients with and without pan-retinal photocoagulation. Ophthalmic Physiol Opt. 1998 Mar;18(2):173-81.
30. EstermanB . Functional scoring of the binocular field. Ophthalmology 1982;89:1226–34.
31. Muqit MM, Wakely L, Stanga PE, Henson DB, Ghanchi FD. Effects of conventional argon panretinal laser photocoagulation on retinal nerve fibre layer and driving visual fields in diabetic retinopathy. Eye (Lond). 2010 Jul;24(7):1136-42.
32. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD; National Eye Institute Visual Function Questionnaire Field Test Investigators. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001 Jul;119(7):1050-8.
33. Brose LS, Bradley C. Psychometric development of the individualized Retinopathy-Dependent Quality of Life Questionnaire (RetDQoL). Value Health. 2010 Jan-Feb;13(1):119-27.
34. Brose LS, Bradley C. Psychometric development of the retinopathy treatment satisfaction questionnaire (RetTSQ). Psychol Health Med. 2009 Dec;14(6):740-54.
35. Janssen MF, Birnie E, Bonsel GJ. Quantification of the level descriptors for the standard EQ-5D three-level system and a five-level version according to two methods. Qual Life Res. 2008 Apr;17(3):463-73.
36. Al-Janabi H, Peters TJ, Brazier J, Bryan S, Flynn TN, Clemens S, Moody A, Coast J. An investigation of the construct validity of the ICECAP-A capability measure. Qual Life Res. 2013 Sep;22(7):1831-40.
37. González VH, Giuliari GP, Banda RM, Guel DA. Intravitreal injection of pegaptanib sodium for proliferative diabetic retinopathy. Br J Ophthalmology. 2009; 93(11):1474-8.
38. Diabetic Retinopathy Guidelines 2012 www.rcophth.co.uk