Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser (DIAMONDS): A pragmatic, multicentre, allocation concealed, prospective, randomised, non-inferiority double-masked trial

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<tr>
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<td>09th January 2017</td>
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Sources of monetary or material support

| Funder: | National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA). |
| Funders Reference Number: | 13/142/04 |

Sponsor details

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| Ethics Reference Number: | 16/NI/0145 |

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A review of the protocol has been completed and is understood and approved by the following:

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Chief Investigator Name: ___________________________  Signature: ___________________________  Date: __________ / _______/ _______

**Mairead North**

Statistician: ___________________________  Signature: ___________________________  Date: __________ / _______/ _______
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<td>Anti-VEGF</td>
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<td>AR</td>
<td>Adverse Reaction</td>
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<td>BCDVA</td>
<td>Best Corrected Distance Visual Acuity</td>
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<td>CI</td>
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<td>CST</td>
<td>Central Retinal Subfield Thickness</td>
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<td>DM</td>
<td>Diabetes Mellitus</td>
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<td>DMO</td>
<td>Diabetic Macular Oedema</td>
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<td>DR</td>
<td>Diabetic Retinopathy</td>
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<td>DSML</td>
<td>Diode Subthreshold Micropulse Laser</td>
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<td>EQ-5D-5L</td>
<td>European Quality of Life – 5 Dimensions</td>
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<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
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<td>FFA</td>
<td>Fundus Fluorescein Angiography</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HbA1c</td>
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<td>NEI-VFQ-25</td>
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<td>ND: YAG</td>
<td>Neodymium-doped Yttrium Aluminium Garnet</td>
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<td>OCT</td>
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<td>PDR</td>
<td>Proliferative Diabetic Retinopathy</td>
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<td>RCT</td>
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<td>RPE</td>
<td>Retinal Pigment Epithelium</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SAT</td>
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<td>SD-OCT</td>
<td>Spectral Domain Optical Coherence Tomography</td>
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<td>SDV</td>
<td>Source Data Verification</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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### Protocol Title

**DIAbetic Macular Oedema aNd Diode Subthreshold micropulse laser (DIAMONDS)**

### Health condition(s) or problem(s) studied

Diabetic Macular Oedema

### Study Design

A pragmatic, multicentre, allocation concealed, prospective, randomised, non-inferiority double-masked trial

### Study Aim and Objectives

**Aim**

To evaluate the clinical effectiveness and cost-effectiveness of Diode Subthreshold Micropulse Laser (DSML), when compared with standard threshold laser, for the treatment of patients with Diabetic Macular Oedema (DMO) with a central retinal subfield thickness of (CST) of < 400 microns.

**Primary Objective:**

To determine whether DSML is as good or superior to standard laser at improving or preserving vision at 24 months following treatment in patients with DMO.

**Secondary Objectives:**

To determine whether DSML is as good or superior to standard laser at improving or preserving binocular vision and visual field, reducing/clearing DMO, allowing treated patients to achieve driving standards and improving their health and visual related quality of life at 24 months following treatment. The relative cost-effectiveness of DSML when compared with standard laser will also be evaluated, as well as side effects of these treatments, number of laser treatments required and need for additional treatments (other than laser) for both, DSML and standard laser.

### Primary Outcome

- Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to 24 months.

### Secondary Outcomes

- Mean change in best-corrected distance visual acuity (BCdVA) from baseline to month 24
- Mean change in central subfield retinal thickness, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 24
- Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field from baseline to month 24
| Study Intervention | Patients will be randomised to one of two groups:
|                   | Intervention: (i) Diode 577 nm subthreshold micropulse laser (DSML)
|                   | Comparator: (ii) Standard threshold laser (e.g. argon, frequency-doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser, other)

| Inclusion and Exclusion Criteria | Inclusion criteria:
|                                | Patients with diabetic retinopathy and centre involving DMO, as determined by using spectral domain optical coherence tomography (SD-OCT), in one or both eyes with:

1) Central retinal subfield thickness of > 300 but < 400 microns as determined by SD-OCT due to diabetic macular oedema

OR

2) Central retinal subfield thickness of < 300 microns provided that intraretinal and/or subretinal fluid is present in the central subfield (central 1 mm) related to diabetic macular oedema

AND

3) Visual acuity of > 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent > 20/320)
4) Amenable to laser treatment, as judged by the treating ophthalmologist
5) Over 18 years of age
Exclusion criteria:

Eyes of patients will not be included in the study if:

1) The macular oedema is due to causes other than diabetic macular oedema such as epiretinal membrane, vitreomacular traction, vein occlusion, or others
2) The eye is ineligible for macular laser treatment, as judged by the treating ophthalmologist
3) The eye has DMO and central subfield retinal thickness (CST) of > 400 microns.
4) The eye has active proliferative diabetic retinopathy (PDR) requiring treatment.
5) The eye has received intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapy within the previous two months.
6) The eye has received macular laser treatment within the previous 12 months.
7) The eye has received intravitreal injection of steroids.
8) The eye has received cataract surgery within the previous six weeks
9) The eye has received panretinal photocoagulation within the previous 3 months

The patient is
10) Patients on pioglitazone and the drug cannot be stopped 3 months prior to entering into the trial and for the duration of the study
11) The patient has chronic renal failure requiring dialysis or kidney transplant
12) The patient has any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study)
13) The patient has very poor glycemic control and started intensive therapy within the previous 3 months
14) The patient will use an investigational drug during the study

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<td>Target Sample Size</td>
<td>266 patients</td>
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<td>Study Duration</td>
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## STUDY TEAM

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The Wellcome-Wolfson Institute for Experimental Medicine  
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97 Lisburn Road BT9 7BL |
3. BACKGROUND AND RATIONALE

3.1 Background Information

Laser has been the treatment of choice for people with Diabetic Macular Oedema (DMO) since its beneficial effects were demonstrated by the ETDRS in 1985 [1]. In a recent appraisal [2], The National Institute of Health and Care Excellence (NICE) recommended the continued use of standard threshold laser to treat people with DMO and central retinal thickness of < 400 microns because laser treatment is clinically effective and cost-effective in this patient group. However, conventional laser treatment may have side effects including paracentral scotomas (areas around the central vision in which patients do not see; these may affect the ability to read and drive), enlargement of the laser scar over time with potential visual loss, reduced colour vision and epiretinal membrane/subretinal fibrosis. If conventional laser is accidentally applied to the centre of the retina, profound visual loss would ensue.

Small case series and small randomised trials suggested DSML has comparable or superior efficacy but may have less side effects than conventional laser. Thus, Lavinsky and collaborators [3], in a trial where participants were randomised to receive standard threshold laser (n=42), normal density DSML (n=39) or high density DSML (n=42) showed superiority of the latter with regards to visual acuity improvement and reduced retinal thickness at 12 months follow-up [3]. In a randomised trial with 50 patients with DMO, Vujosevic and colleagues [4] found no differences in terms of visual acuity or central retinal thickness between standard threshold laser and DSML, but a statistically significant increased retinal sensitivity, as measured with microperimetry was achieved following DSML with no laser scars present in the retina, as disclosed by fundus examination and autofluorescence images at 12 months follow-up [4]. Similarly, randomised trials by Kumar and associates [5], Figueira and coworkers [6] and Laursen and associates [7] included 20, 53 and 16 patients respectively, and a follow-up duration of 18 weeks, 12 months and 5 months respectively, found no differences in visual acuity and central retinal thickness between conventional threshold laser and diode subthreshold laser. A recently published review [8] concluded that available data suggested similar or superior efficacy of DSML (when compared with standard threshold laser) with less or no retinal damage. It is possible that DSML may allow for a more standard delivery of treatment to all patients given that it is applied to the entire macular area in a confluent manner, rather than to zones that the treating ophthalmologist may perceive as thickened or to areas of suspected leakage or extrathecal ischaemia based on fluorescein angiography, reducing/minimising possible variability in the results obtained.

Although published data suggest that DSML may be superior to conventional threshold laser, current knowledge is based on results of randomised trials with small numbers of patients followed for no more than 12 months. Furthermore, important outcomes such as cost-effectiveness of the treatment, effects of the laser on the visual field and patient reported outcomes were not evaluated in these previous studies. Stronger evidence is required to support policy-making and investment decisions.

3.2 Rationale for the Study

Diabetic Macular Oedema (DMO) is the most common cause of irreversible blindness among people with diabetes mellitus and Diabetic Retinopathy (DR). It was estimated that in England alone, the prevalence of DMO in one or both eyes was 166,325 or 7% of all people with diabetes, of whom 40% had some reduction in visual acuity [9]. DMO represents accumulation of fluid in the macula, the area responsible for central detailed vision. As fluid accumulates, visual loss ensues. NICE [2] has recommended the use of standard threshold laser to treat people with DMO and retinal thickness of < 400 microns, as measured using an imaging technique called optical coherence tomography (OCT), because it dominated when
compared with anti-VEGF (ranibizumab or aflibercept) treatment. Randomised trials demonstrated the efficacy of laser to prevent visual loss in people with DMO. The ETDRS found a 50% reduction in visual loss 3 years following laser and recent randomised trials have shown that as much as 35% of patients experience an improvement in vision of at least 10 ETDRS letters following laser. Furthermore, approximately 50% of people undergoing anti-VEGF therapy still require macular laser within the first two years of treatment.

Laser thus remains an effective option for people with DR and DMO. However, side effects of laser include paracentral scotomas, which may affect the ability to undertake tasks that require precise near vision, such as reading, and the ability to drive; enlargement of the laser scar over time with a potentially associated visual loss; reduced colour vision; epiretinal membrane and subretinal fibrosis formation, among others. If the laser is accidentally applied to the centre of the macula, marked central visual loss would occur.

Standard threshold laser is performed using a continuous wave laser that produces a visible burn (a “grey” mark) in the retina. Retinal cells at the site of the burn are killed. The laser energy is absorbed by one of the layers of the retina, the retinal pigment epithelium (RPE), and converted into heat. Although the mechanisms of action of conventional threshold laser are not completely understood, it is believed that it has its effect by acting upon still viable RPE cells around the site of the laser spot. As heat spreads by conduction, a damaging effect in retinal layers overlying the RPE, including the photoreceptors (visual cells) may also occur. Standard laser requires considerable expertise by the clinician in order to identify areas involved to which the laser should be aimed. Affected areas requiring laser may be determined by slit-lamp biomicroscopy using a contact lens, with the help of optical coherence tomography and/or fluorescein angiography.

Recently, DSML was introduced. In DSML, a series of repetitive short laser pulses are applied (“micropulse”), instead of a continuous wave emission, each separated by a long off-time which reduces the increased temperature in the tissue that follows conventional laser. In this manner, a sublethal effect on the RPE is achieved with preservation of the overlying neurosensory retina and visual cells. Small case series and randomised trials including relatively small number of patients have shown that subthreshold tissue-sparing micropulse laser may have comparable or higher efficacy than standard laser, even in the absence of a visible burn, with reduced side effects. This laser may be easier to deliver because it is applied to the entire macular area and, thus, may be less dependent on surgeon’s skills.

An adequately powered randomised trial comparing standard laser versus DSML, such as DIAMONDS, would benefit patients by providing strong evidence to advise whether one or the other should be preferred. This is important because it is likely that laser will remain an option to patients with DMO for many years to come. Furthermore, because DIAMONDS is a pragmatic randomised trial conducted in a National Health Service (NHS) setting, its findings are likely to be of relevance and practical use to the NHS for some time. Several measures of visual function will be obtained from the DIAMONDS trial to gain further knowledge on the effects of conventional and DSML in the retina. The knowledge gained might also be applicable to other retinal disorders.
4. STUDY AIMS AND OBJECTIVES

4.1 Research Hypothesis

The hypothesis is that DSML is non-inferior to standard laser for the treatment of patients with DMO and a central subfield thickness of < 400 microns.

4.2 Study Aim

DIAMONDS aims to determine the clinical effectiveness and cost-effectiveness of DSML compared with standard laser for the treatment of people with DMO and central retinal subfield thickness of < 400 microns, for which laser treatment is currently recommended by NICE [2].

4.3 Study Objectives

4.3.1 Primary Objective:

The primary objective of DIAMONDS is to determine whether DSML is as good or superior to standard laser at improving or preserving vision at 24 months following treatment in patients with DMO.

4.3.2 Secondary Objectives:

The secondary objectives of DIAMONDS are to determine whether DSML is as good or superior to standard laser at improving or preserving binocular vision and visual field, reducing / clearing DMO, allowing treated patients to achieve driving standards and improving their health and visual related quality of life at 24 months following treatment. The relative cost-effectiveness of DSML when compared with standard laser will also be evaluated, as well as side effects of these treatments, number of laser treatments required and use of additional treatments (other than laser) for both, DSML and standard laser.

5. OUTCOME MEASURES

5.1 Primary Outcome Measure

The primary outcome measure is:

- Mean change in BCdVA in the study eye at 24 months (for definition of study eye, see section 7.2).

5.2 Secondary Outcome Measures

There are a number of secondary outcomes, which will be measured at 24 months and include:

- Mean change in binocular BCdVA from baseline to month 24
- Mean change in central subfield retinal thickness in the study eye, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 24
- Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field in the study eye from baseline to month 24
- Change in the percentage (%) of people meeting driving standards from baseline to month 24
- Mean change in EQ-5D 5L, NEI VFQ25 and VisQoL scores from baseline to month 24.
- Incremental cost per QALY gained
- Side effects
- Number of laser treatments needed
- Use of additional treatments (other than laser)

6. STUDY DESIGN

6.1 Study Design

A pragmatic, multicentre, allocation concealed, prospective, randomised, non-inferiority double-masked trial.

6.2 Study Setting

Specialist Hospital Eye Services (HES) in the UK. All centres involved have extensive experience with the management of patients with diabetic retinopathy and specifically DMO.

6.3 Study Schematic Diagram

![CONSORT diagram for DIAMONDS](image)

Figure 1: CONSORT diagram for DIAMONDS
6.4 End of Study

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

- Mandated by the REC
- Mandated by the Sponsor (e.g. following recommendations from Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC)
- Funding for the trial ceases

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

7. PATIENT ELIGIBILITY

7.1 Eligibility Criteria

Patients will be screened for eligibility based on the inclusion and exclusion criteria outlined below. Eligibility will be confirmed by a medically qualified doctor and documented on the eligibility checklist form.

7.1.1 Inclusion criteria:

Patients with diabetic retinopathy and centre involving DMO, as determined by using spectral domain optical coherence tomography (SD-OCT), in one or both eyes with:

1) Central retinal subfield thickness of \( \geq 300 \) but \( < 400 \) microns as determined by SD-OCT due to diabetic macular oedema

OR

2) Central retinal subfield thickness of \( < 300 \) microns provided that intraretinal and/or subretinal fluid is present in the central subfield (central 1 mm) related to diabetic macular oedema

AND

3) Visual acuity of \( > 24 \) Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Snellen equivalent \( > 20/320 \))
4) Amenable to laser treatment, as judged by the treating ophthalmologist
5) Over 18 years of age

7.1.2 Exclusion criteria:

Eyes of patients will not be included in the study if:

1) The macular oedema is due to causes other than diabetic macular oedema such as epiretinal membrane, vitreomacular traction, vein occlusion, or others
2) The eye is ineligible for macular laser treatment, as judged by the treating ophthalmologist
3) The eye has DMO and central subfield retinal thickness (CST) of \( > 400 \) microns.
4) The eye has active proliferative diabetic retinopathy (PDR) requiring treatment.
5) The eye has received intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapy within the previous two months.
6) The eye has received macular laser treatment within the previous 12 months.
7) The eye has received intravitreal injection of steroids.
8) The eye has received cataract surgery within the previous six weeks.
9) The eye has received panretinal photocoagulation within the previous 3 months.

The patient is:
10) Patients on pioglitazone and the drug cannot be stopped 3 months prior to entering into the trial and for the duration of the study.
11) The patient has chronic renal failure requiring dialysis or kidney transplant.
12) The patient has any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study).
13) The patient has very poor glycemic control and started intensive therapy within the previous 3 months.
14) The patient will use an investigational drug during the study.

7.2 Definition of Study Eye

If both eyes are eligible for the study based on the above inclusion and exclusion criteria, the ‘STUDY EYE’ will be considered as the eye with the best visual acuity at randomisation. If the visual acuity is the same in both eyes, the eye with less CST, as determined by SD-OCT, will be selected as the ‘STUDY EYE’. If both eyes are eligible for the study, both will receive the same type of laser treatment (i.e. if patient is randomised to receive DSML, both eyes will receive this type of laser).

7.3 Co-enrolment Guidelines

Patients enrolled in observational studies are potential candidates for this randomised trial. This is at the Principal Investigator’s (PI) discretion and should be considered when the burden on participants is not expected to be onerous. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

8. PATIENT SCREENING, CONSENT AND RECRUITMENT

8.1 Screening Procedure

The NICTU will provide screening logs which must be completed by the PI or designee to document all patients screened for the study and all patients recruited. Patients screened and not recruited on to the study should also be documented on the screening log, including the reason for not being enrolled on the study. The PI or designee will be required to submit screening logs to the NICTU every month.

8.2 Informed Consent

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki [10]. Eligible patients may only be included in the trial after written informed consent is obtained. Informed consent must be obtained prior to conducting any trial specific procedures and the process for obtaining informed consent must be
documented in the patient’s medical records (source documents will be reviewed at the time of on-site monitoring visits).

Informed Consent Forms (ICF) approved by the REC will be provided by the NICTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each patient prior to any trial treatment being administered. This requires that the ICF be signed and personally dated by the patient prior to any trial treatment proceeding. If no consent is given, a patient cannot be recruited into the trial.

The NICTU will provide patient information sheets (PIS) approved by the REC. The PI or designee is responsible for ensuring that all patients are given a copy of the PIS and are allowed adequate time to review this and the opportunity to ask any study related questions. All patients should have the capacity to self-consent. This should be judged by the PI or the designated member of the study team who will have the responsibility for taking consent.

Two copies of the ICF must be signed and personally dated by the patient and the individual taking consent. A copy of the signed ICF will be filed in the patient’s medical records, whilst the originals will be retained by the patient and by the PI in the Investigator Site File (ISF).

Following the recruitment of a patient onto the study, the PI or designee will issue a letter to the patient’s General Practitioner (GP) to inform them that their patient is participating in the DIAMONDS trial. The patient will be advised that this contact will be made with their GP on the PIS.

8.3 Withdrawal of Consent
Patients may withdraw from the trial at any time without prejudice. In the event of consent withdrawal, patients will be asked for their permission to use the data already collected to date. If this permission is declined, then any data collected to date on that patient will not be used into the trial analysis. Withdrawal of consent will be recorded on the Case Report Form (CRF).

8.4 Recruitment

8.4.1 Patient Recruitment

The DIAMONDS trial requires 266 participants to be recruited. Using an electronic database from a typical UK centre serving a population of 600,000 we confirmed that 75 patients with DMO of < 400 microns were evaluated at this centre in one year. Based on this, we estimate that the centres participating in DIAMONDS, which serve a total population of more than 6,000,000 people, will assess at least 900 people with DMO < 400 microns during the recruitment period. Based on our clinical experience, we anticipate that most of these patients will be eligible to participate in DIAMONDS. Estimating, conservatively, that 50% of eligible patients will be identified in time for treatment and that 70% of those asked if they wish to participate will agree, the research group should be able to recruit the targeted 266 individuals in approximately 15 months, with each centre recruiting an average of 2 participants per month.

Potential participants will be identified through patient electronic databases at each of the participating centres, through referrals to Hospital Eye Services or while in the clinic. If identified through search of electronic databases (e.g. Medisoft, an electronic database in routine use in Ophthalmic Clinics) or through letters of referral to the Hospital Eye Services the potential participants may be approached to participate in the study by phone or via an invitation letter. When approached by phone, the potential participants will be informed about the study before they come to their Hospital appointment; if willingness to participate is demonstrated, a patient information leaflet will be sent to them prior to the clinical appointment. Then, at their clinical appointment and if agreeable to participate, informed
consent will be obtained and the patient will be recruited in the study while in clinic. If they are approached by letter, a letter of invitation to participate in the study and a patient information leaflet will be provided to the potential participant prior to their clinical appointment. Then, as above, when the patient comes to their clinical appointment, if willing to participate, they will be consented and enrolled in the study. Under the above circumstances, potential participants will have a minimum of 24 hours to decide whether or not they wish to participate in the study.

Potential participants may be also identified while in the clinic. In this case, information about the study will be given there and then, including a patient information leaflet. Under these circumstances, patients will be asked whether they wish to have time to think about their participation in the study once information has been provided to them and once they have had time to ask questions about it. It is envisaged that some patients would like to have time to think about their potential participation in the study, in which case a further visit will be organise for them; if at this further visit they are willing to participate, then they will be recruited. It is envisaged also that some patients may not wish to delay their laser treatment (i.e. having 24 hours to think about it and then having to arrange an additional visit) but may wish to participate in the study. Under these circumstances, patients will be given the time they wish to think about the study and, if willing to be recruited on the same day, following informed consent, they will be recruited into the trial.

The recruitment progress will be monitored by the TMG.

8.4.2 Pilot Study

An internal pilot study to assess feasibility will be undertaken. This will run until month 4 of the recruitment period, by which time it is expected to have recruited 50 patients. Recruitment feasibility milestones will be as follows. If recruitment rates achieve 75-100% recruitment, we will progress with the trial; if we achieve 50-75% recruitment, we will progress with the trial following review of screening logs and the protocol and after barriers to achieving adequate recruitment are addressed; if we recruit 25-50% of the required number, the trial will be progressed only after screening logs and the protocol are reviewed and following approval by NIHR HTA, additional sites are opened. Should recruitment be <25%, it is not expected the trial will progress. The decision to stop the trial will be made by the TSC and the NIHR HTA.

8.4.3 Study Within A Trial

In order to help achieve the targeted recruitment, the research group will conduct one or more SWAT (Study Within A Trial) in the early months of the main trial to assess different recruitment strategies [11, 12]. SWAT provides an opportunity to embed methodology research within clinical research, to resolve uncertainties about the optimal methods to use in the current and future trials. In DIAMONDS, the SWAT are likely to include comparisons of different approaches to potential participants in the different sites (for example, by different types of clinician) to determine their relative effects on recruitment to the trial and retention through the intervention and follow-up procedures. This will allow us to identify the most effective strategies, which might then be implemented across the trial as a whole in its later months. This would allow the research group to maximise recruitment across the trial as a whole and help ensure that DIAMONDS reaches its target recruitment on time.

8.4.4 Randomisation – Treatment Allocation

Once consent has been obtained from patients meeting the eligibility criteria they will be recruited to the study.
On the day the laser procedure is going to be performed, participants will be randomised 1:1 to receive DSML or standard laser using an automated randomisation system. The local ophthalmologist will be the person interacting with the automated randomisation system to generate the random allocation sequence. The laser procedure should be performed within 2 weeks of the baseline visit. If the laser treatment is not being performed on the same day as the baseline visit, eligibility should be confirmed again prior to undertaking the laser treatment.

A minimisation algorithm will be used to ensure balanced allocation of patients across the two treatment groups for the following important prognostic factors: centre, distance BCdVA at presentation [≥ 69 ETDRS letters (Snellen equivalent of ≥ 20/40; logMAR ≥ 0.3); 24-68 ETDRS letters (Snellen equivalent ≤20/50; logMAR 0.4-1.2) previous use of anti-VEGF therapies in the study eye, previous use of macular laser treatment in the study eye.

When a patient is ready to be randomised, the site should access the automated randomisation system and complete all requested information. The randomisation service will assign a unique trial identifier to each patient and issue the treatment allocation, ensuring that each patient’s allocation remains concealed up to the time that it is issued. The randomisation service will confirm randomisation details by email to the site and the NICTU.

The unique trial identifier assigned at the time of randomisation will be used throughout the trial for the purposes of patient identification.

**8.4.5 Masking of Treatment Allocation**

This randomised trial is designed to be a pragmatic trial so that its results would be applicable immediately in a NHS setting. For this reason, ophthalmologists undertaking laser treatments for DMO at each of the participating centres will also deliver the treatment for the trial. Although, for obvious reasons, ophthalmologists delivering the treatment will not be masked with regards to the laser used, every effort will be made to ensure that participants and outcome assessors (e.g. optometrists measuring visual function, photographers/technicians/nurses obtaining OCT images and ophthalmic technicians obtaining visual fields) will be masked to the allocated treatment. Patients will not be informed before, during, and after the laser treatment about which technology of laser was used for their treatment.

Similarly, the investigators obtaining outcome measures will only have access to the CRF booklet (but not to the notes of the patients) which will contain no information with regards to the type of laser the patient had been allocated or received.

**8.4.6 Participant Retention and Follow-up**

Local study groups, supported by each local PI, will assure that participation in this pragmatic trial will not represent a burden to participants and assure that retention during the 2 year period of the study will be achieved.

Patients will be followed, as per routine standard clinical care, at 4 month intervals (baseline, and at months 4, 8, 12, 16, 20 and 24) for a total of 7 visits.

In order to ensure adequate follow-up of participants, participants will be reminded by telephone, text or call the week prior to the study visit. This will be carried out by either research nurses or by administrative staff at each of the participating centres.
9. SCHEDULE OF ASSESSMENTS AND STUDY PROCEDURES

9.1 Schedule of Assessments and Procedures

All patients must be evaluated during the study according to the schedule of assessments and data will be collected at each of the following time-points as outlined below:

Table 2: Schedule of Assessments and Procedures

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Baseline*</th>
<th>4*</th>
<th>8*</th>
<th>12*</th>
<th>16*</th>
<th>20*</th>
<th>24*</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
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<tr>
<td>Humphrey 10-2 visual field in study eye</td>
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<td>✓</td>
<td>✓</td>
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<tr>
<td>Adverse Events</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* If Glycosylated Hemoglobin Type A1C (HbA1c) has been tested in the past three months and its value is available, it can be recorded in the CRF. If no previous HBA1c (within the previous three months from baseline) a blood sample should be drawn for the purpose of measuring levels of HBA1c.

$ For retreatment details see section 9.7 Study Procedures.

# Visits will take place at baseline and at 4, 8, 12, 16, 20 and 24 months. Visits taking place at 4, 8, 12, 16, 20, 24 months may take place within ±14 days of the due date.

^

Please note the laser treatment can only take place after the baseline assessments have been completed and post randomisation. Laser treatment must take place within 14 days of the date of randomisation; **ideally randomisation should be done on the day of laser treatment.**

9.2 Clinical Outcomes: Measures of Visual Function

9.2.1 Visual Acuity

The primary clinical outcome will be BCdVA in the study eye. BCdVA will be measured in both eyes using the ETDRS visual acuity charts at 4 meters at baseline and at months 4, 8, 12, 16, 20 and 24. BCdVA will be obtained following refraction [as specified in the pertinent Guideline within the DIAMONDS Trial Manual] at baseline, 12 months and 24 months by optometrists masked to the allocated treatment. In all other visits, BCdVA could be obtained by optometrists, research nurses or technicians.
Binocular BCdVA will be obtained also to give indication of the person’s vision in real life, using both eyes. Binocular BCdVA will be obtained also by masked optometrists using the ETDRS visual acuity charts at 4 meters at baseline, at months 12 and 24.

A refraction protocol (as set in the Guideline within the DIAMONDS Trial Manual) will be followed by the DIAMONDS optometrists to obtain BCdVA in the study and fellow eye as well as binocular BCdVA, at baseline and 12 and 24 month study visits. The ETDRS visual acuity score will be recorded for the study and fellow eye in the appropriate CRF at each of the study visits. Similarly, the ETDRS visual acuity score obtained binocularly, will also recorded in the CRF.

9.2.2 Visual Fields

10-2 Humphrey visual field testing will be obtained in the study eye, or in both eyes (if both eyes are included in the study) by a visual field technician masked to the allocated treatment at baseline and at months 12 and 24.

An Esterman binocular visual field (to determine patient’s ability to fulfil driving standards) will also be obtained by a visual field technician masked to the allocated treatment at baseline and at months 12 and 24.

Visual fields eligible for analysis will have to achieve pre-defined reliability criteria (false positives <15%). If the visual fields are not reliable they should be repeated. The MD value for the 10-2 Humphrey visual fields and the number of points seen/missed for the Esterman binocular visual fields will be recorded in the CRF, among other parameters.

9.3 Clinical Outcomes: Anatomical Measures

9.3.1 Retinal Status

Central retinal subfield thickness, as determined by using spectral domain optical coherence tomography (SD-OCT) in the study eye, will be obtained at baseline and at months 4, 8, 12, 16, 20 and 24. SD-OCT will be obtained by technicians, photographers or nurses masked to the allocated treatment, as per standard practice in each of the participating centres. The measure of the mean central retinal thickness obtained in the central 1 mm (i.e. central subfield thickness) will be recorded in the CRF and used for the analysis.

In addition, the total macular volume in the study eye, as determined by SD-OCT will be also recorded in the CRF. The presence or absence of intraretinal or subretinal fluid will be determined in a masked fashion at the 24 months follow-up visit by masked readers at the Central Angiographic Resource Facility (CARF) at Queens University, Belfast. Images sent to CARF will be anonymised; a specific patient identifier for the purpose of DIAMONDS will be used.

The same SD-OCT machine should be used to obtain the above measurement for each patient at baseline and at each of the follow-up visits.

9.4 Patient Reported Outcomes

NEI VFQ-25, a vision specific patient reported quality of life tool; the VisQol questionnaire, which is shorter than VFQ-25 but has not been validated (as of March 2016), and the generic health status measure EQ-5D-5L to generate utility data, will be used. All three questionnaires will be self-completed by patients at baseline and at months 12 and 24. The baseline questionnaires should be completed prior to the first session of laser treatment (DSML or standard laser). At the month 12 and month 24 visits, patients should complete the questionnaire during the study visit. If this is not possible, the questionnaires will be given to
patients along with a self-stamped envelope and once completed, the patient should return it by post to the NICTU. As stated above, patients will be masked to the allocated laser treatment they had received.

9.5 Adverse Events

9.5.1 Assessment of safety

The safety of the treatment will be assessed at each visit by noting any complications during or after laser treatment, including self-reported visual disturbances, > 10 letter score ETDRS visual acuity loss, and > 15 letter score ETDRS visual acuity loss. Patients will be asked about reduced colour vision, presence of paracentral scotomas and/or distortion ("waviness" of straight lines). Although Serious Adverse Events (SAE) related to the study procedures are unlikely to occur, a record will be kept of all SAEs. The NICTU will be responsible for informing the Sponsor and the Research Ethics Committee about any SAEs all study sites about any SAEs. The DMEC will provide information on all SAEs on a routine basis.

9.5.2 Analysis of safety data

Adverse events (AEs, SAEs) will be listed and summarised by treatment. Incidents will be listed and summarised by treatment.

9.5.3 Definition of Adverse Events

As the current study is not investigating medical products, adverse event reporting will follow the Health Research Authority guidelines on safety reporting in non CTIMP studies. The PI or designee will make an assessment of seriousness as per the definitions below:

An adverse event (AE) is defined as any untoward medical occurrence in a participant in a research study, including occurrences which are not necessarily caused by or related to the study.

A serious adverse event (SAE) is defined as an untoward occurrence that:
   a) results in death;
   b) is life-threatening;
   c) requires hospitalisation or prolongation of existing hospitalisation;
   d) results in persistent or significant disability or incapacity;
   e) consists of a congenital anomaly or birth defect; or
   f) is otherwise considered medically significant by the investigator.

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

9.5.4 Anticipated adverse events due to laser treatment

Below is a list of potential or anticipated Adverse Events:

- Foveal burn
- Central/paracentral scotomas
- Epiretinal membrane formation
- Choroidal neovascularisation
- Self-reported reduced colour vision
- Self-reported metamorphopsia
9.5.5 Eliciting Adverse Event Information

The PI or designee will record all directly observed AEs and all AEs spontaneously reported by the participant that are not related to underlying medical conditions. In addition, the participant will be asked about AEs at all visits following laser treatment.

9.5.6 Recording and Reporting of Adverse Events

All AEs not related to the patients underlying medical conditions will be assessed for seriousness, expectedness and relatedness by the PI or designee and, recorded in the CRF. AEs will be recorded in the participant’s medical notes.

9.5.7 Serious Adverse Event Reporting

If the event is judged to be serious based on the definition above, this should be reported to the NICTU using the SAE report form. All SAEs should be reported to the NICTU within 24 hours of becoming aware of the event.

The NICTU will notify the CI, Sponsor and Ethics committee within the required timelines. An SAE occurring to a research participant will be reported to the main REC where in the opinion of the CI the event was:

a) Related- that is, it resulted from administration of any of the research procedures, and
b) Unexpected- that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to REC within 15 days of the CI becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website available at: http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/. The CI will include a report on the safety of participants in the annual progress report.

9.5.8 Follow-up of Adverse Events

The AE reporting period for the trial begins upon enrolment of a participant into the trial and ends at month 24. All AEs assessed by the PI or designee as being related and unexpected will be followed until they are resolved or are clearly determined to be due to a participant’s stable or chronic condition or intercurrent illness(es). The CRF should be updated with the date and time of resolution or confirmation that the event is due to the participant’s illness as soon as this information becomes available.

9.5.9 Urgent Safety Measures

The PI or designee may take appropriate urgent safety measures in order to protect participants from any immediate hazards to their health or safety. The main REC will be notified by telephone immediately and in writing within three working days (by the CI or sponsor). The written notification should set out the reasons for the urgent safety measures and the plan for further action.

9.6 Systemic Parameters

The type of diabetes (type 1 or 2), the duration of the diabetes since the time of diagnosis, self-reported history of kidney disease and smoking status (current smoker, past smoker, non-smoker) will be recorded in the appropriate CRF. History of systemic high blood
pressure will be recorded in the CRF. In addition, height and weight, systemic blood pressure will be obtained at baseline and recorded in the CRF under medical history.

If HbA1c has been tested in the past three months and its value is available, this will be recorded in the CRF. If there is no HBA1c result (within the previous three months from baseline), a blood sample should be drawn, and HBA1c should be measured and recorded in the CRF.

9.7 Study Procedures

9.7.1 Treatment Strategy and Retreatments

Information on Study Eye, eye to be treated (right eye (RE), left eye (LE)), laser type and laser parameters used and time spent on applying the treatment, including the time invested in planning the laser (i.e. determining which areas are to be treated) and the time invested in applying the treatment (i.e. from sitting the patient in the slit-lamp prior to initiation of the laser treatment until the patient leaves the slit-lamp following completion of the laser treatment) will be recorded in the CRF. Information on retreatment details and on the use of other rescue treatments (e.g. anti-VEGFs, steroids) will also be recorded in the CRF.

Retreatments with laser can and should be undertaken, if necessary. All retreatments should be performed using the same laser as the baseline treatment, as determined by randomisation. Details of retreatments should be documented in the CRF accordingly.

Rescue treatment (with anti-VEGFs / steroids, as appropriate) will be allowed in both treatment groups of the study, if the CST increases to 400 microns or over at any point during the follow-up or if a loss of 10 or more ETDRS letters occurs related to diabetic macular oedema. Rescue treatments will be recorded (type and date) in the CRF.

9.7.2 Diode Subthreshold Micropulse Laser (DSML)

DSML is a relatively new laser technology aimed at minimising damage ("tissue-sparing") to choroid and retina but maintaining treatment efficacy by its selective effect on the retinal pigment epithelium (RPE). It is performed using laser that, instead of delivering a continuous-wave laser beam, as the standard laser, it provides very small, repetitive, low energy pulses of laser separated by a brief rest period. This rest period allows the tissue to cool down between laser pulses avoiding the increased tissue heat that would be produced by continuous laser and allowing the use of lower laser energy power to achieve an effect. The reduced heat produced in the tissue and the reduced energy power required for the treatment may reduce side effects. Specifically, the technology does not appear to cause retinal burns or scars associated with decreased retinal sensitivity in treated areas. Another potential advantage of this technology is that the treatment may be applied in a more "standardised" and reproducible manner. Laser spots can be placed throughout the entire macular area, obviating the need to identify areas of retinal thickening, leakage or ischaemia. This may subsequently reduce the variability in the results obtained that could arise from observer variability in the recognition of these fundus features and the variability of the laser application as a result. Accidental application of DSML treatment to the centre of the fovea would not be expected to have deleterious effects, as would be the case of conventional laser treatment.

9.7.3 Standard Laser

Green-yellow argon laser photocoagulation at threshold levels has been used for many years as the standard laser for the treatment of many retinal disorders including DMO. The ETDRS demonstrated the efficacy of laser in preventing visual loss in patients with DMO.
Although following the ETDRS studies argon green laser was used extensively over the years, other similar lasers are now in use in the NHS to do threshold laser to patients with DMO. Of these, one of the most frequently used type of lasers in the NHS to deliver standard laser treatment is the frequency-doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser, which is also applied at threshold levels. Conventional laser was found by NICE to be cost-effective for the treatment of patients with DMO with a central retinal thickness of < 400 microns [2]. Although infrequent, potential side effects of this treatment have been recognised, including burning of the retina at the site of the laser application, scar formation, decreased retinal sensitivity in treated areas, paracentral scotomas, enlargement of laser scars over time with potential visual loss, reduced colour vision, epiretinal membrane and subretinal fibrosis. If the centre of the retina (area responsible for the central sight) is accidentally treated, profound central visual loss can occur.

Standard laser is applied to areas of thickened retina, macular non-perfusion and leaking microaneurysms, in accordance with the Royal College of Ophthalmologist guidelines [13]. FFA and OCT are often used to identify areas of non-perfusion and leakage (FFA) and thickening (OCT) prior to treatment.

Details on the laser parameters to be used for micropulse and standard laser can be found in the Guideline for laser application within the DIAMONDS Trial Manual.

10. DATA COLLECTION & DATA MANAGEMENT

10.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the trial protocol and using quality control measures to establish and maintain high standards for data quality.

The Chief Investigators (CI) and NICTU will provide training to site staff on trial processes and procedures, including the completion of the CRF and data collection.

On-site monitoring visits during the trial will check the accuracy of entries on CRF’s against the source documents, the adherence to the protocol, procedures and GCP.

Quality control is implemented by the NICTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process, and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements [14].

Data quality control checks will be carried out by the Data Manager to ensure accuracy and data errors will be documented in Quality Control Reports with corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

10.2 Data Collection

To ensure accurate, complete and reliable data are collected, the NICTU will provide training to site staff through investigator meetings and site initiation visits.
All data for an individual patient will be collected by the PI or designee and recorded in source documents and the CRF for the study. Patient identification on the CRF will be through their unique trial identifier, allocated at the time of recruitment. Data will be collected and recorded on the CRF and questionnaires by the PI or designee from the time the patient is considered for entry into the trial through to their 24 months follow up.

CRFs and questionnaires are to be submitted to the NICTU as per the CRF Submission Schedule, along with a CRF Tracking Form.

10.3 Data Management

Trial data, including the CRF and questionnaires, will be entered onto a web-based Clinical Trial Database (MACRO) by NICTU personnel and processed electronically as per NICTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within an agreed time period. All queries will be responded to/resolved within the study database. Any amended information will then be entered in the study database.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel. All study documentation (including participant medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework.

Ophthalmic images will be anonymised and uploaded electronically by each local PI or designee at the CARF website. CARF is only accessible by a username/password combination unique to the site. Once uploaded, the images will be downloaded by CARF personnel and stored on secure servers housed by Queen’s University Belfast.

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size

The study is powered to demonstrate non-inferiority of DSML with respect to the primary outcome (BCdVA in the study eye at 24 months). The study will have sufficient statistical power to determine superiority of one laser over the other. Furthermore, the study will also have sufficient statistical power to determine equivalence of the lasers.

Based on a mean (standard deviation(SD)) of 0.08 (0.23) log MAR for BCdVA change from baseline for the standard care laser [3] and a permitted maximum difference of 0.1 logMAR (5 ETDRS letters) between groups it is estimated that the trial will require 113 patients per arm at 90% power and 0.05 level of significance. Allowing for a possible 15% dropout rate, which is similar to that observed in other randomised trials on diabetic macular oedema with outcomes determined at 24 months [15, 16], a total of 266 patients will be required for the study.

A permitted maximal difference of 5 ETDRS letters between groups was chosen as the non-inferiority margin because a 5 ETDRS letter difference would not be considered clinically relevant or meaningful to patients (2).

The proposed sample size of 113 per group (which allows for 15% drop out) will be sufficient also to detect a mean difference between lasers of 37.7 microns in central retinal thickness (based on a SD of 86.8 as per [4] and 6.55 in NEI-VFQ based on a SD of 15.1 as per [17])
which are important secondary outcomes on this study. These differences in central retinal thickness and NEI-VFQ scores are both clinically relevant differences [18, 19].

11.2 Statistical Methods

As this will be a non-inferiority trial, the primary statistical analysis will be as per protocol, although an intention-to-treat (ITT) analysis will also be undertaken. ITT is recommended for superiority trials but, for non-inferiority or equivalence trials, a per protocol analysis is preferred [20] because ITT increases the type I error under these circumstances.

The difference between lasers for change in BCdVA (using 95% CI) from baseline to month 24 (primary endpoint) will be compared to the permitted maximum difference of 5 ETDRS letters (0.1 logMAR). The DSML laser can be deemed to be non-inferior to the standard laser if the lower limit of the 95% confidence interval of the treatment difference lies above the non-inferiority margin. If the 95% confidence interval of the treatment difference lies wholly within both the upper and lower margins of the permitted maximum difference (+/- 5 ETDRS letters), then the DSML laser can be deemed to be equivalent to the standard laser. Change in BCdVA from baseline to month 24 will be compared between the two laser groups using an analysis of covariance model adjusted for baseline BCdVA score, baseline central retinal thickness and minimisation factors/covariates: centre, distance BCdVA at presentation [≥ 69 ETDRS letters (Snellen equivalent of ≥ 20/40; logMAR ≥ 0.3); 24-68 ETDRS letters (Snellen equivalent ≤20/50; logMAR 0.4-1.2)]; previous use of anti-VEGF therapies in the study eye, previous use of macular laser in the study eye. The primary analysis will be based on data from the study eye only. When performing a secondary analysis on the subset of subjects with both eyes treated, study eye will be included as a random effect within the mixed model. Statistical diagnostic methods will be used to check for violations of the model assumptions and data transformations or non-parametric equivalents such as Mann-Whitney may be performed as appropriate.

Statistical significance will be based on two-sided tests, with P < 0.05 taken as the criterion for statistical significance. The principal analysis will be based upon available case data with no imputation of missing values. Sensitivity analyses which will assess the impact of missing data by imputing extreme values (lowest and highest) will also be undertaken. Additionally, the primary outcome will be analysed according to pre-specified subgroup [previous use of anti-VEGFs or macular laser in the study eye] by including the corresponding interaction term in the regression model using stricter criteria for statistical significance (2P ≤ 0.01). Side effects of the treatment and use of additional treatments (e.g. anti-VEGF, steroids) will be analysed using logistic regression models with adjustment for the minimisation covariates. Analyses of health related quality of life measures (EQ-5D-5L, NEI VFQ-25 and VisQol scores), secondary measures of visual function and anatomical outcomes [mean deviation (MD) of the 10-2 visual field test, central retinal thickness and macular volume] and number of treatments required will be undertaken using linear regression models adjusted for baseline BCdVA score and minimisation variables. Analysis of “driving ability” (meeting standards for driving) will be undertaken using a logistic regression model adjusted for baseline BCdVA and the minimisation variables.

Baseline characteristics, follow-up measurements and safety data will be described graphically and in tabular format using appropriate descriptive summary measures depending on the scale of measurement and distribution.

A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician prior to the final analysis.

11.3 Missing Data
The principal analysis will be based upon available case data with no imputation of missing values. Sensitivity analyses which will assess the impact of missing data by imputing extreme values (lowest and highest) will also be undertaken.

11.4 Health Economic Analysis

A Markov model based cost-utility analysis will extend beyond the trial analysis period to estimate the longer-term cost-effectiveness, with costs and benefits discounted at 3.5%. The model will be populated by data from the trial and supplemented by estimates of effectiveness, quality of life and costs from published literature and expert opinion. Results will be expressed as cost per QALY gained. Sensitivity analyses will be conducted to assess the robustness of the results. Probabilistic sensitivity analyses will be undertaken to explore uncertainty in model parameters and allow the presentation of cost-effectiveness acceptability curves.

11.5 Longer Term Patient Outcomes

After completion of the trial, funding will be sought for an evaluation of longer-term patient outcomes at 5 years. If available, these data will be incorporated into an updated economic model.

12 DATA MONITORING

12.1 Data Access

Prior to commencement of the study, the PI will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from patients for direct access to their data will also be obtained. Patients’ confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.2 Monitoring Arrangements

The NICTU will be responsible for trial monitoring. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor. On-site monitoring visits and central monitoring activities will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial close-out and will comply with the principles of GCP.

On-site monitoring visits during the trial will check the accuracy of entries on CRFs against the source documents, the adherence to the protocol, study procedures and GCP.

The PI or designee will ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification (SDV) will be documented in the monitoring plan.

13 TRIAL COMMITTEES

13.1 Trial Management Arrangements
The CI will have overall responsibility for the conduct of the study. The NICTU will undertake trial management including all clinical trial applications (Ethics and Research Governance), site initiation and training, monitoring, analysis and reporting. The Trial Co-ordinator will be responsible on a day to day basis for overseeing and co-ordinating the work of the multi-disciplinary trial team, and will be the main contact between the trial team and other parties involved. Before the trial starts, site training will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. The NICTU will assist and facilitate in the setting up and co-ordination of the trial committees including the TMG, TSC and DMEC.

13.2 Trial Management Group (TMG)

A TMG will be established and Chaired by the CI. The TMG will include representation from the NICTU and other investigators or collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician, health economist). This group will have responsibility for the day to day operational management of the trial. Regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the Trial Master File.

A TMG Charter will be drawn up to detail the terms of reference of the TMG, including roles and responsibilities of the members.

13.3 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC. The TSC is a group that act as the oversight body for the trial on behalf of the Sponsor and Funder. Throughout the trial, the TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial patients.

The TSC will include an independent Chair, at least two independent clinicians or trialists, a patient representative and the CI. Representatives of the Sponsor/Funder and the NICTU may attend TSC meetings as observers and at the discretion of the Chair. The TSC Charter will outline the terms of reference of the TSC including roles and responsibilities, membership, organisation of meetings, reporting, decision making and the relationship with the other trial committees.

As the frequency of DMEC meetings will be dependent on recruitment rates (see below), TSC meetings will be arranged to coincide with these and will be convened to discuss issues and recommendations raised by the DMEC.

13.4 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed with responsibility for safeguarding the interests of trial patients. The DMEC will monitor the main outcome measures including safety and efficacy and assist and advise the TSC to protect the validity and credibility of the trial.

The DMEC will include two clinicians and a statistician who are independent of the trial. The DMEC Charter will outline the terms of reference of the DMEC including roles and responsibilities, membership, organisation of meetings, reporting, decision making (including stopping rules if applicable) and the relationship with the other trial committees. In the light of interim data and other relevant evidence, the DMEC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated.

An inaugural meeting will be held prior to recruitment commencing. Subsequent meetings will be scheduled at regular intervals.
The Trial Statistician will produce reports for the DMEC which may include recruitment, baseline data, adverse events, compliance and outcome data to enable them to monitor the trial and guide overall progress.

14. REGULATIONS, ETHICS AND GOVERNANCE

The trial will comply with the principles of GCP, the requirements and standards set out by the applicable regulatory requirements in the UK and the Research Governance Framework.

14.1 Sponsorship

The Belfast Health and Social Care Trust (BHSCT) will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor, CI and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

14.2 Funding

This study is funded by NIHR HTA. The funding reference number is 13/142/04.

14.3 Indemnity

The Parties agree that Queen’s shall be liable for its employees’ negligence in connection with research-related activities, and that the Trust shall be liable for the negligence of any employee of Queen’s who is jointly appointed by the Trust, and whose negligence relates to clinical activities.

14.4 Contributorship

The CI conceived the study. The CI and co-investigators initiated the study design and these researchers along with the trial statistician and trial manager from the NICTU contributed to the study design and development of the protocol. The trial statistician provided statistical advice and will oversee the primary statistical analysis. The CI is the grant holder and will oversee the management and conduct of the study.

14.5 Competing Interests

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

14.6 Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

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

14.8 Protocol Compliance

A protocol deviation is defined as an incident which deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.

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

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

The PI or designee is responsible for ensuring that serious breaches are reported directly to the NICTU within one working day of becoming aware of the breach.

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

14.9 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval or favourable opinion by the Research Ethics Committee (REC). Changes to the protocol may require ethics committee approval or favourable opinion prior to implementation. The NICTU in collaboration with the sponsor will submit all protocol modifications to the REC for review in accordance with the governing regulations.

14.10 Patient Confidentiality

In order to maintain confidentiality, all study reports and communication regarding the study will identify the patients by their assigned unique trial identifier only. Computers where information will be stored will be password protected. Patient confidentiality will be maintained at every stage and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.11 Record Retention

The PI will be provided with an ISF by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The TMF will be held by the NICTU within the BHSCT and the essential documents that make up the file will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the BHSCT Sponsor. Following confirmation from the Sponsor the NICTU will notify the PI when they are no longer required to maintain the files. If the PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the NICTU and Sponsor.

Images stored in CARF will be archived according to the applicable regulatory requirements at the request of the CI.
15. DISSEMINATION/PUBLICATIONS

15.1 Trial Publications

The final study report will be provided by the Trial Statistician. It is anticipated that the study findings will be published in national and international peer review journals and these articles will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health care professionals. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups.

A report containing the methodology and results of this randomised trial will be published as a Health Technology Assessment monograph, freely accessible via the NIHR HTA webpage. The Royal College of Ophthalmologist will be contacted once the study is completed to allow the trial’s findings to be incorporated in future Diabetic Retinopathy guidelines.

15.2 Authorship Policy

An author will be considered to be someone who has made a substantive intellectual contribution to the study and the relevant report. All investigators, Trial Statistician and relevant members of the Trial Management Group will potentially be co-authors. Collaborators will be acknowledged.

15.3 Trial Registration

The trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register and with clinicaltrials.gov.

15.4 Data Sharing Statement

Requests for data sharing will be reviewed on a case by case basis by the CI and TMG.

15.5 Data Access

Following the publication of the primary and secondary outcomes, there may be scope to conduct additional analyses on the data collected. In such instances, formal requests for data will need to be made in writing to the CI who will discuss this with the TMG. In the event of publications arising from such analyses, those responsible will need to provide the CI with a copy of any intended manuscript for approval prior to submission. Authorship will need to take the format of “[name] on behalf of the DIAMONDS Clinical Trial Group” or something similar, which will be agreed by the TMG.
REFERENCES


