DIAMONDS

Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser

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STATISTICAL ANALYSIS PLAN

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This document and all preceding versions will be stored in the Trial Master File for this trial

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ABBREVIATIONS

Abbreviation / Acronym	Full Wording
AE	Adverse Event
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AR	Adverse Reaction
BCdVA	Best Corrected Distance Visual Acuity
BHSCT	Belfast Health and Social Care Trust
CI	Confidence Interval
CARF	Central Angiographic Resource Facility
CRF	Case Report Form
CSR	Clinical Study Report
CST	Central Retinal Subfield Thickness
DM	Diabetes Mellitus
DMEC	Data Monitoring and Ethics Committee
DMO	Diabetic Macular Oedema
DMP	Data Management Plan
DR	Diabetic Retinopathy
DSML	Diode Subthreshold Micropulse Laser
EQ-5D-5L	European Quality of Life – 5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Glycosylated Hemoglobin Type A1C
HTA	Health Technology Assessment
HES	Hospital Eye Services
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IQR	Interquartile Range
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to treat
MD	Mean Deviation
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire - 25
ND: YAG	Neodymium-doped Yttrium Aluminium Garnet
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute of Health Research
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy

Abbreviation / Acronym	Full Wording
PI	Principal Investigator
PIS	Patient Information Sheet
PP	Per Protocol
PRP	Panretinal Photocoagulation
REC	Research Ethics Committee
RPE	Retinal Pigment Epithelium
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee
uk	Unknown

1. BACKGROUND AND DESIGN

DIAMONDS is a pragmatic, multicentre, allocation-concealed, randomised, equivalence double-masked clinical trial. The aim of the trial is 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 (CST) of < 400 microns for whom laser treatment is currently recommended by NICE.

1.1 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.

1.2 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).

1.3 Study Intervention:

Patients will be randomised to one of two groups:

Intervention: Diode 577 nm subthreshold micropulse laser (DSML)

Comparator: Standard threshold laser (e.g. argon, frequency-doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser)

1.4 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

1.5 **Exclusion Criteria:**

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

1) The macular oedema is due to causes other than DMO 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 $\geq$ 400 microns.
4) The eye has active proliferative diabetic retinopathy (PDR) requiring treatment.
5) The eye has received intravitreal Anti- Vascular Endothelical Growth Factor (Anti-VEGF) therapy within the previous 2 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 6 weeks.
9) The eye has received panretinal photocoagulation (PRP) within the previous 3 months.
10) The patient is 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.

2. OUTCOME MEASURES

2.1 Primary outcome measure

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

2.2 Secondary outcome measures

- Mean change in binocular 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.
- Change in the proportion (%) of people meeting driving standards from baseline to month 24.
- Mean change in European Quality of Life – 5 Dimensions (EQ-5D 5L), National Eye Institute Visual Functioning Questionnaire – 25 (NEI VFQ25) and VisQoL scores from baseline to month 24.
- Incremental cost per quality-adjusted life year (QALY) gained.
- Side effects.
- Number of laser treatments needed.
- Use of additional treatments (other than laser).

Full details of the background to the trial and its design are in the trial protocol.

3. DATA

3.1 CRF Forms and variables

Full details of the data to be collected and the timing of data collection are in the trial protocol.

A copy of the CRFs and questionnaires are in the Trial Master File (TMF).

3.2 Management of datasets

At the time of analysis:

The Data Manager in collaboration with the Study Statistician will extract data from MACRO following procedures as detailed in the SOP DM09 Database Closure/Lock and the corresponding study Data Management Plan (DMP).

3.3 Data completion schedule

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

Table 3.1: Schedule of Assessments and Procedures

		Post randomisation (months)						
	Baseline[#]	4[#]	8[#]	12[#]	16[#]	20[#]	24[#]	
Informed Consent	✓							
Medical History	✓	✓	✓	✓	✓	✓	✓	
Blood Test - HbA1c[*]	✓							
Best Corrected Distance Visual Acuity (BCdVA) in study eye and fellow eye	✓	✓	✓	✓	✓	✓	✓	
Binocular distance vision	✓			✓			✓	
Humphrey 10-2 visual field in study eye	✓			✓			✓	
Esterman binocular visual field	✓			✓			✓	
SD-OCT	✓	✓	✓	✓	✓	✓	✓	
NEI VFQ-25	✓			✓			✓	
EQ-5D-5L	✓			✓			✓	
VisQol	✓			✓			✓	
Randomisation	✓							
Diode subthreshold micropulse laser / standard laser[#$]	✓^							
Adverse Events	✓	✓	✓	✓	✓	✓	✓	

[*] 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 and 24 months may take place within ± 14 days of the due date.

^ Laser treatment can only take place after the baseline assessments have been completed and the patient has been randomised. Ideally, randomisation should be done on the day of laser treatment but laser treatment must take place within 14 days after the date of randomisation.

3.4 **Data verification**

Study specific data validation checks will be implemented. The process of data validation ensuring the accuracy and quality of the data will be carried out according to SOP DM04 Data Validation and Discrepancy Management and QM02 Quality Control Procedures – Data Management.

3.5 **Data coding**

The codings for the variables will be as specified on the CRF.

4. DEFINITION OF TERMS

Term	Definition
Per Protocol (PP) Population	All participants who are eligible, randomised and completed the allocated treatment.
Intention to Treat (ITT) Population	All participants who are randomised, regardless of what treatment (if any) they received (analysed in their allocated group).
Non-inferiority margin	Maximal difference of 5 ETDRS letters between groups. This margin was chosen because a ≤ 5 ETDRS letter difference would not be considered clinically relevant or meaningful to patients.
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 eyes will be included in the study and both will receive the same type of laser treatment (i.e. if a patient is randomised to receive DSML, both their eyes will receive this type of laser). If the fellow eye is not eligible for the study, baseline data, information on whether participants develop DMO or PDR during the period of the study in the fellow eye and information on treatments administered to the fellow eye during the period of the study will be collected in the appropriate CRF at months 12 and 24 to determine any possible effects of these events on, for example, binocular vision, fulfilling driving standards and/or visual related quality of life, among others.
Rescue Criteria	Rescue treatment (with steroids or anti-VEGFs, as appropriate) will be allowed in both treatment groups of the study, if the CST increases to ≥ 400 microns at any point during the follow-up or if a loss of > 10 ETDRS letters from the baseline value occurs related to DMO. Rescue treatments will be recorded (type and date) in the CRF.
High Risk Participants	Exploratory analyses will be conducted to investigate whether particular patients (e.g. based on HbA1c or cataract surgery) are at higher risk of poor outcomes.
Treatment Naive	Participants who have not received anti-VEGFs and have not received any macular laser (i.e. the answers are "No" for both the following questions on the CRF: Has the patient had previous laser treatment for DMO? and Has the patient had previous Anti-VEGF treatment for PDR?).

5. SAMPLE SIZE CALCULATIONS

The study is powered to demonstrate non-inferiority of DSML with respect to the primary outcome (BCdVA in the study eye at month 24). The study will have sufficient statistical power to determine superiority of one laser over the other. Furthermore, the study will 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[1] and a permitted maximum difference of 0.1 logMAR (5 ETDRS letters) between groups, the trial would require 113 patients per treatment group at 90% power and 0.05 level of significance. Allowing for a 15% dropout rate (which is similar to that observed in other randomised trials on DMO with outcomes determined at month 24[2,3]), 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 difference of ≤ 5 ETDRS letter would not be considered clinically relevant or meaningful to patients.[4,5]

The proposed sample size of 133 per group (which allows for 15% drop out) will be sufficient to detect a mean difference between lasers of 37.7 microns in central retinal thickness (based on a SD of 86.8[6]) and 6.55 in NEI-VFQ (based on a SD of 15.1[7]), which are important secondary outcomes for this study. Such differences in central retinal thickness and NEI-VFQ scores are clinically relevant.[8,9]

[1] Lavinsky D, Cardillo JA, Melo LA Jr, et al. Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema. Invest Ophthalmol Vis Sci. 2011;52:4314–23.
[2] Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119:789–801.
[3] Gillies MC, Sutter FK, Simpson JM, et al. Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology. 2006;113:1533–8.
[4] National Institute for Healthcare Excellence. www.nice.org.uk/guidance/ta274. Accessed 26 January 2021.
[5] National Institute for Healthcare Excellence. www.nice.org.uk/guidance/ta346. Accessed 26 January 2021.
[6] Vujosevic S, Bottega E, Casciano M, et al. Microperimetry and fundus autofluorescence in diabetic macular edema: subthreshold micropulse diode laser versus modified early treatment diabetic retinopathy study laser photocoagulation. Retina. 2010;30:908–16.
[7] Tranos PG, Topouzis F, Stangos NT, et al. Effect of laser photocoagulation treatment for diabetic macular oedema on patient's vision-related quality of life. Curr Eye Res. 2004;29:41–9.
[8] Fiore T, Androudi S, Iaccheri B, et al. Repeatability and reproducibility of retinal thickness measurements in diabetic patients with spectral domain optical coherence tomography. Curr Eye Res. 2013;38:674–9.
[9] Lloyd AJ, Loftus J, Turner M, et al. Psychometric validation of the visual function questionnaire-25 in patients with diabetic macular edema. Health Qual Life Outcomes. 2013;11:10–21.

6. RANDOMISATION AND MASKING

6.1 Randomisation

When consent has been obtained from a patient meeting the eligibility criteria, they will be recruited to the study.

Ideally, on the day of the laser procedure, participants will be randomised 1:1 to receive DSML or standard laser using an automated randomisation system, which used a minimisation algorithm to ensure balanced allocation of patients across treatment groups for the following important prognostic factors: centre, distance BCdVA at presentation [≥ 69 ETDRS letters (Snellen equivalent ≥ 20/40; Logarithm of the Minimum Angle of Resolution (logMAR) ≥ 0.3); 24–68 ETDRS letters (Snellen equivalent ≤ 2 0/50; logMAR 0.4–1.2)], and previous use of anti-VEGFs or macular laser in the study eye. The local ophthalmologist will be the person interacting with the automated randomisation system to generate the random allocation sequence. 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 and laser treatment must take place within 14 days after the date of randomisation.

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.

6.2 Masking of Treatment Allocation

This randomised trial is designed to be pragmatic so that its results would be applicable immediately in a NHS setting. For this reason, ophthalmologists undertaking laser treatments for DMO at each participating centre will also deliver the treatment for the trial. Although ophthalmologists delivering the treatment cannot 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, or after the laser treatment about which technology of laser was used for them.

Similarly, the investigators obtaining outcome measures will only have access to the CRF booklet (but not to the notes of the patients) and the CRF will contain no information on the type of laser the patient was allocated or received.

7. ANALYSIS PRINCIPLES

As this will be a non-inferiority trial, the primary statistical analysis will be per protocol (PP), but an intention-to treat (ITT) analysis will also be undertaken. ITT is recommended for superiority trials but, for non-inferiority or equivalence trials, a PP analysis is preferred because ITT increases the risk of a type I error for such trials. The main analyses will be those that were pre-specified in the protocol but some additional analyses will also be done (see section 8.5).

The difference between the 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 this non-inferiority margin. If the 95% confidence interval of the treatment difference lies wholly within 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 treatment groups using an analysis of covariance model adjusted for baseline BCdVA score, baseline central retinal thickness and minimisation factors/covariates: centre, distance BCdVA at baseline [≥ 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, and previous use of macular laser in the study eye. Change in BCdVA from baseline to month 24 will also be adjusted for occurrence of cataract surgery 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, unless adjustment for multiple testing is needed. The **principal analysis** will be based on available case data with no imputation of missing values.

Sensitivity analyses will be undertaken to assess the impact of missing data, by imputing extreme values (lowest and highest) and last observation carried forward; the impact of including patients who are not treatment naïve (i.e. excluding those who have had previous laser treatment for DMO in the study eye or previous anti-VEGF treatment for PDR in the study eye); the impact of including patients who have cataract surgery in the study eye; and the impact of using month 24 data that are collected outside ± 14 days of the due date.

Side effects of laser treatment and use of additional treatments (e.g. steroids or anti-VEGF) 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.

The number of AE, ARs, SAE, SARs, SUSARs and number (%) of patients experiencing these events will be reported. The chi-square test (or Fisher's exact test if appropriate) and proportion test will be used to check whether incidences of adverse events differ between the treatment groups. Relative risk and 95% CI will be reported.

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

7.1 Subgroup Analyses

The primary outcome will be analysed according to pre-specified subgroups for which there is an existing clinical rationale: centre, distance BCdVA at baseline [≥ 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-VEGFs and macular laser in the study eye; by including the corresponding interaction term in the regression model and 99% confidence intervals.

Analyses will be done to identify whether any groups of participants (e.g. related to their HbA1c or the use of cataract surgery) are at high risk of poor outcomes, and, if so, these groups will be analysed in **exploratory subgroup analyses**.

7.2 Missing Data

The principal analysis will be based on available case data with no imputation of missing values. Sensitivity analyses will be undertaken to assess the impact of missing data, by imputing extreme values (lowest and highest) and last observation carried forward.

Partial dates will be managed as follows:

- If both day and month are missing, the partial date will be recorded as uk/uk/YYYY in the text field and the study date field will be recorded as 01/06/YYYY.
- If day is missing, the partial date will be recorded as uk/MM/YYYY in the text field and the study date field will be recorded as 01/MM/YYYY.

8. ANALYSIS DETAILS

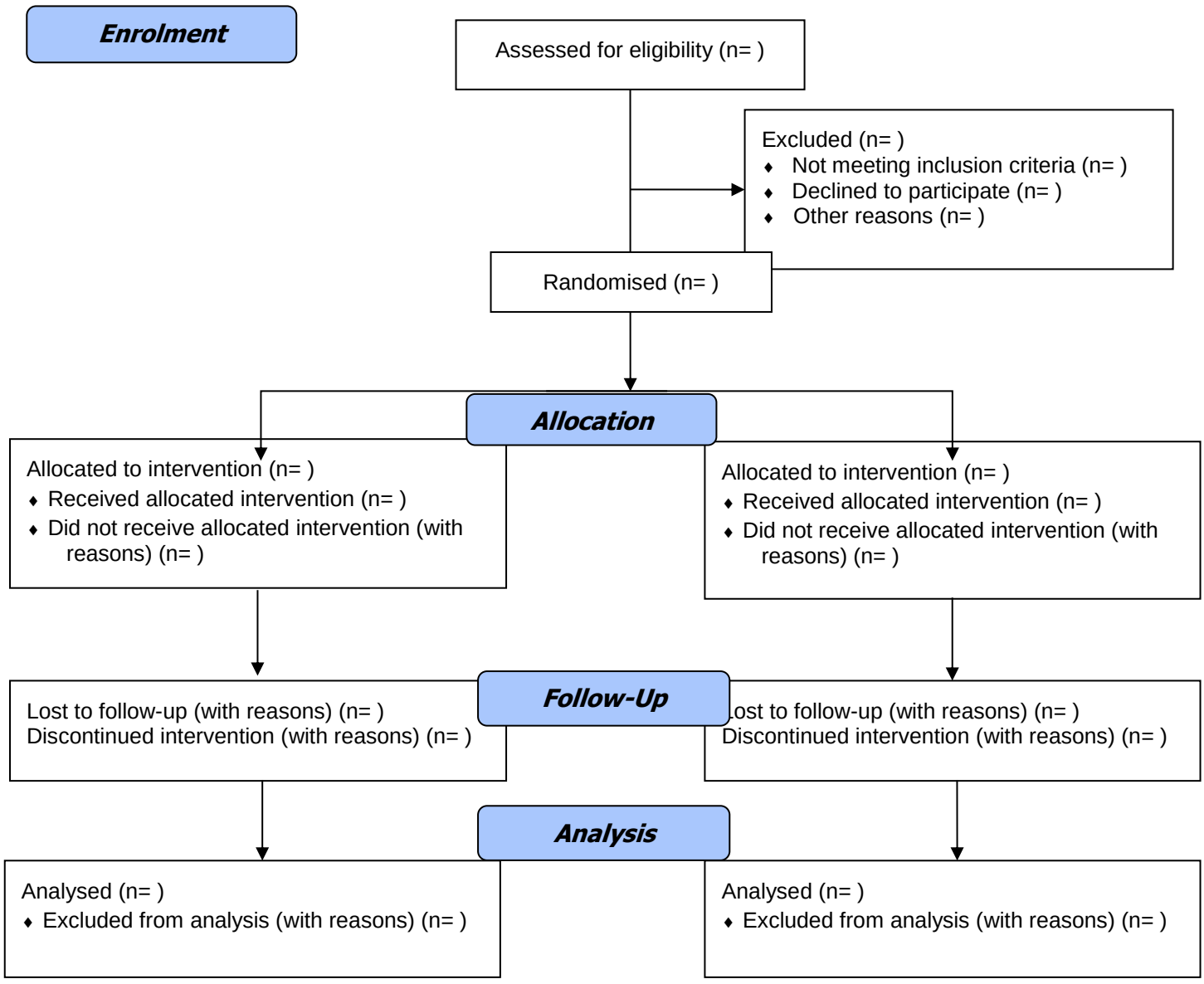
The results of the analyses will be reported following the principles of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and follow-up patterns

The DIAMONDS trial requires 266 participants to be recruited. We will present:

- Recruitment by site.
- Withdrawals by site.

8.2 CONSORT Flow Diagram



8.3 Baseline Characteristics

- Age (years): mean (SD) by treatment group
- Gender: number (%) by treatment group
- Ethnicity: number (%) by treatment group
- Type of Diabetes: number (%) by treatment group
- Duration of Diabetes (years): mean (SD) by treatment group
- Smoking Status: number (%) by treatment group
- Smoking Duration (years): mean (SD) by treatment group
- DMO Diagnosis: number (%) by treatment group
- Length of DMO diagnoses (years): mean (SD) by treatment group
- Previous laser treatment for DMO: number (%) by treatment group
- Number of previous DMO laser sessions: median [IQR] by treatment group
- Time since last DMO laser session (years): mean (SD) by treatment group
- Previous Anti-VEGF treatment for DMO: number (%) by treatment group
- Number of Anti-VEGF injections received: median [IQR] by treatment group
- Time since last Anti-VEGF injection (years): mean (SD) by treatment group
- PDR History: number (%) by treatment group
- Received PRP: number (%) by treatment group
- Length of time since last PRP (years): mean (SD) by treatment group
- Lens Status: number (%) by treatment group
- Colour Vision affected: number (%) by treatment group
- Vision Distorted: number (%) by treatment group
- Paracentral scotomas: number (%) by treatment group
- Weight (kg): mean (SD) by treatment group
- Height (cm): mean (SD) by treatment group
- BMI (kg/m^2): mean (SD) by treatment group
- BMI (kg/m^2): number (%) in BMI categories by treatment group
- HbA1c (mmol/mol and %): mean (SD) by treatment group
- BCdVA Assessment-Visual Acuity Score: mean (SD) by treatment group
- BCdVA Assessment-Visual Acuity Score: number in stratification categories (%) by treatment group
- Central Retinal Subfield Thickness: mean (SD) by treatment group
- Study Eye selection: number (%) by treatment group
- Patient meets UK driving standards: number (%) by treatment group
- Patient is treatment naïve: number (%) by treatment group

8.4 Trial treatment

- Treatment given: number (%) by treatment group
- Spot size, mean (SD) by treatment group
- Duration, mean (SD) by treatment group
- Laser power: number (%) by treatment group, in categories
- Number of spots: number (%) by treatment group, in categories
- Number of treatments: mean (SD) by treatment group
- Protocol violations: number (%) by treatment group

- Post randomisation withdrawals: number (%) by treatment group
- Did not receive allocated treatment (which includes those who received no treatment and those who received the treatment of other group): number (%) by treatment group
- Received treatment of other group: number (%) by treatment group

8.5 Trial Outcomes

Primary Outcome

- Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from ANCOVA adjusted for baseline BCdVA and minimisation variables. Non inferiority margin will be compared against 95% CI for both PP and ITT analyses.

Secondary Outcomes

- Mean change in binocular BCdVA from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Mean change in central subfield retinal thickness, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Change in the proportion (%) of people meeting driving standards from baseline to month 24: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for baseline BCdVA and minimisation variables.
- Number of participants experiencing side effects from baseline to month 24: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.
- Number of laser treatments used in study eye from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Number of participants with at least one additional treatment (other than laser) from baseline to month 24: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.

Additional Analyses (not specified in protocol)

- Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 12: mean (SD) by treatment group, difference in means with 95% CI, p-value from ANCOVA adjusted for baseline BCdVA and minimisation variables.
- Mean change in binocular BCdVA from baseline to month 12: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Mean change in central subfield retinal thickness, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 12: mean (SD) by

treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.

- Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field from baseline to month 12: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Change in the proportion (%) of people meeting driving standards from baseline to month 12: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for baseline BCdVA and minimisation variables.
- Number of participants experiencing side effects from baseline to month 12: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.
- Number of laser treatments used in study eye from baseline to month 12: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for baseline BCdVA and minimisation variables.
- Number of participants with at least one additional treatment (other than laser) from baseline to month 12: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.
- Number of steroid injections as additional treatments from baseline to month 12 and from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for minimisation variables.
- Number of participants with at least one steroid injection from baseline to month 12 and from baseline to month 24, n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.
- Number of anti-VEGF treatments as additional treatments from baseline to month 12 and from baseline to month 24: mean (SD) by treatment group, difference in means with 95% CI, p-value from linear regression adjusted for minimisation variables; and as number (%) in categories (≤4, 5 to 10, >10).
- Number of participants with at least one anti-VEGF treatment as additional treatment from baseline to month 12 and from baseline to month 24, n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for minimisation variables.
- Number of participants receiving rescue treatments from baseline to month 12 and from baseline to month 24: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for high risk participants and minimisation variables.
- Number of participants satisfying rescue criteria from baseline to month 12 and from baseline to month 24: n(%) by treatment group, odds ratio with 95% CI, p-value from logistic regression adjusted for baseline BCdVA and minimisation variables.

8.6 **Safety**

- Adverse Events (AEs): number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Adverse Reactions (ARs): number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.

- Unexpected Adverse Reactions: number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Serious Adverse Events (SAEs): number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Serious Adverse Reactions (SARs): number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Serious Unexpected Adverse Reactions (SUSARs): number (%) of events by treatment group and System Organ Class: number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Adverse Events (AEs): number (%) of events by treatment group and preferred term (eye disorders only): number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.
- Serious Adverse Events (SAEs): number (%) of events by treatment group and preferred term (eye disorders only): number (%) of participants by treatment group; risk ratio and 95% CI for the differences between groups.

9. ADDITIONAL INFORMATION

9.1 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC. The TSC oversees 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 participants.

The TSC will include an independent Chair, at least two independent clinicians or trialists, a patient representative and the chief investigator. Representatives of the Sponsor and 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 Data Monitoring and Ethics Committee (DMEC) (see below) meetings will be dependent on recruitment rates, TSC meetings will be arranged to coincide with these and will be convened to discuss issues and recommendations raised by the DMEC.

9.2 Data Monitoring and Ethics Committee (DMEC)

A DMEC will be appointed with responsibility for safeguarding the interests of trial participants. 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 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 of the DMEC 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 the DMEC to monitor the trial and guide overall progress.

10. SIGNATURES OF APPROVAL

Date: *11/03/2021*
Version: Final Version 1.0
This document has completed a final review and is understood and approved by the following:

Noemi Lois Chief Investigator	*Chief Investigator Signature*	Date DD/MM/YYYY
Clíona McDowell Head of Statistics, NICTU	*Head of Statistics Signature*	Date DD/MM/YYYY
Christina Campbell Study Statistician	*Study Statistician Signature*	Date DD/MM/YYYY

APPENDIX 1: EXAMPLE DRAFT SUMMARY TABLES

Table x.x.x. Baseline characteristics at trial entry

Baseline characteristics at trial entry		Treatment Group		Total
		Standard Laser	DSM Laser	
		n=<n>	n=<n>	n=<n>
Gender	Male	n (%)	n (%)	n (%)
	Female	n (%)	n (%)	n (%)
Age (years) (SD)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Ethnicity	White	n (%)	n (%)	n (%)
	Black (African)	n (%)	n (%)	n (%)
	Black (African American)	n (%)	n (%)	n (%)
	Hispanic	n (%)	n (%)	n (%)
	Asian	n (%)	n (%)	n (%)
	Middle East	n (%)	n (%)	n (%)
	Other	n (%)	n (%)	n (%)
Diabetes	Type 1	n (%)	n (%)	n (%)
	Duration of Type 1 (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Type 2	n (%)	n (%)	n (%)
	Duration of Type 2 (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Other	n (%)	n (%)	n (%)
	Duration of Other (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Smoking Status	Current smoker	n (%)	n (%)	n (%)
	Number of years smoked (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Past smoker	n (%)	n (%)	n (%)
	Number of years smoked (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Never smoked	n (%)	n (%)	n (%)
DMO Diagnosis	**Study Eye**			
	Present	n (%)	n (%)	n (%)
	Duration of diagnosis (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Absent	n (%)	n (%)	n (%)
	Non Study Eye			
	Present	n (%)	n (%)	n (%)
	Duration of diagnosis (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Absent	n (%)	n (%)	n (%)
Previous DMO Laser Treatment	**Study Eye**			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Number of previous DMO laser sessions* [IQR]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Length of time since last DMO laser session (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Non Study Eye			
	Yes	n (%)	n (%)	n (%)

Baseline characteristics at trial entry		Treatment Group		Total
		Standard Laser	DSM Laser	
		n=<n>	n=<n>	n=<n>
	No	n (%)	n (%)	n (%)
	Number of previous DMO laser sessions* [IQR]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Length of time since last DMO laser session (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Previous Anti-VEGF Treatments	**Study Eye**			
	Bevacizumab			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Ranibizumab			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Aflibercept			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Pegaptanib			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Non Study Eye			
	Bevacizumab			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Ranibizumab			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Aflibercept			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Pegaptanib			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Study Eye			
	Number of Anti-VEGF injections* [IQR]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Length of time since last Anti-VEGF injections (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Non Study Eye			
	Number of Anti-VEGF injections* [IQR]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]	xx.x [xx.x, xx.x]
	Length of time since last Anti-VEGF injections (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
History of PDR	**Study Eye**			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)

Baseline characteristics at trial entry		Treatment Group		Total
		Standard Laser	DSM Laser	
		n=<n>	n=<n>	n=<n>
	Non Study Eye			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
Previous PRP	**Study Eye**			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Time since last PRP session (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Non Study Eye			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Time since last PRP session (years) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Lens Status	**Study Eye**			
	Phakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Pseudophakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Aphakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Non Study Eye			
	Phakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Pseudophakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Aphakic			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
Self-reported colour Vision deficit	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	If yes, which eye			
	Study Eye Only	n (%)	n (%)	n (%)
	Non Study Eye Only	n (%)	n (%)	n (%)
	Both Eyes	n (%)	n (%)	n (%)
Self-reported distorsion	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	If yes, which eye			
	Study Eye Only	n (%)	n (%)	n (%)

Baseline characteristics at trial entry		Treatment Group		Total
		Standard Laser	DSM Laser	
		n=<n>	n=<n>	n=<n>
	Non Study Eye Only	n (%)	n (%)	n (%)
	Both Eyes	n (%)	n (%)	n (%)
Self-reported paracentral scotomas	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	If yes, which eye			
	Study Eye Only	n (%)	n (%)	n (%)
	Non Study Eye Only	n (%)	n (%)	n (%)
	Both Eyes	n (%)	n (%)	n (%)
Weight (kg) (SD)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Height (cm) (SD)		xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BMI (kg/m^2)	Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	BMI <18.5	n (%)	n (%)	n (%)
	BMI 18.5-24.9	n (%)	n (%)	n (%)
	BMI 25-29.9	n (%)	n (%)	n (%)
	BMI 30-39.9	n (%)	n (%)	n (%)
	BMI ≥40	n (%)	n (%)	n (%)
HbA1c	Mmol/mol (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	% (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
BCDVA (ETDRS)	Study Eye (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	≥ 69 ETDRS letters	n (%)	n (%)	n (%)
	24-68 ETDRS letters	n (%)	n (%)	n (%)
	Non Study Eye (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	≥ 69 ETDRS letters	n (%)	n (%)	n (%)
	24-68 ETDRS letters	n (%)	n (%)	n (%)
Mean Central Retinal Subfield thickness	Study Eye (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
	Non Study Eye (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Study Eye selection	One eye eligible	n (%)	n (%)	n (%)
	Both eyes eligible	n (%)	n (%)	n (%)
Patient meets UK driving standards	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
Treatment naive	**Study Eye**			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)
	Non Study Eye			
	Yes	n (%)	n (%)	n (%)
	No	n (%)	n (%)	n (%)

Mean (SD) presented for continuous data and n (%) presented for categorical data
*Median [IQR] presented

Table x.x.x. Treatment after Trial Entry (Study Eye)

Treatment after Trial Entry (Study Eye)		Treatment Group	
		Standard Laser	DSM Laser
		n=<n>	n=<n>
Treatment given	Yes	n (%)	n (%)
	No	n (%)	n (%)
Spot Size (microns) (SD)		xx.x (xx.x)	xx.x (xx.x)
Duration (ms) (SD)		xx.x (xx.x)	xx.x (xx.x)
Laser power (SD) **(Micropulse power for DSML)**		xx.x (xx.x)	xx.x (xx.x)
Number of spots (SD)		xx.x (xx.x)	xx.x (xx.x)
Number of treatments (SD)		xx.x (xx.x)	xx.x (xx.x)
Protocol Violations (as recorded on the Case Report Form)	Eligibility	n (%)	n (%)
	Visit out of schedule	n (%)	n (%)
	Data not collected according to the protocol	n (%)	n (%)
	Consent	n (%)	n (%)
	Randomisation	n (%)	n (%)
	Site personnel	n (%)	n (%)
	Missed visit	n (%)	n (%)
	Study intervention	n (%)	n (%)
	Other	n (%)	n (%)
Withdrawal of consent	Refused use of data already collected	n (%)	n (%)
	Refused permission for clinical data to be reviewed	n (%)	n (%)
Did not receive allocated treatment (which includes those who received no treatment and those who received the treatment of other group)		n (%)	n (%)
Received treatment of other group		n (%)	n (%)

Table x.x.x. Treatment after Trial Entry (Non-Study Eye)

Treatment after Trial Entry (Non-Study Eye)		Treatment Group	
		Standard Laser	DSM Laser
		n=<n>	n=<n>
Treatment given	**Yes**	n (%)	n (%)
	No	n (%)	n (%)
Spot Size (microns) (SD)		xx.x (xx.x)	xx.x (xx.x)
Duration (ms) (SD)		xx.x (xx.x)	xx.x (xx.x)
Laser power (SD) **(Micropulse power for DSML)**		xx.x (xx.x)	xx.x (xx.x)
Number of spots (SD)		xx.x (xx.x)	xx.x (xx.x)
Number of treatments (SD)		xx.x (xx.x)	xx.x (xx.x)

Table x.x.x Primary Outcome (Observed Values)

Primary Outcome; Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	p-value
Per protocol analysis (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Intention to treat analysis (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx

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. The DSML laser can be deemed to be superior to the standard laser if the lower limit of the 95% confidence interval of the treatment difference lies above the no difference value.

Table x.x.x Primary Outcome adjusted analyses

Primary Outcome	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	p-value
Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx

***ANCOVA adjusted for baseline BCdVA score, baseline central retinal thickness and minimisation factors/covariates: centre, distance BCdVA at baseline** [≥ 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**. Change in BCdVA from baseline to month 24 will also be adjusted for occurrence of cataract surgery in the study eye and sensitivity analyses (see below) will examine the impact of visits outside the scheduled time window.

Table x.x.x Primary Outcome secondary analysis

Primary Outcome	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	p-value
Mean change in best-corrected distance visual acuity (BCdVA) in both eyes* from baseline to month 24 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx

* study eye will be included as a random effect within the mixed model.

Table x.x.x Primary Outcome subgroup analyses

Primary Outcome; Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24		Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (99% CI)	Interaction Term
Centre	**Site 01 (SD)**	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
	Site 02 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 03 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 04 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 05 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 06 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 07 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 08 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 09 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 10 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 11 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 12 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 13 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 14 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
	Site 15 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	

Primary Outcome; Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24		Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (99% CI)	Interaction Term
	Site 16 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
Distance BCdVA at baseline	**≥ 69 ETDRS letters (Snellen equivalent of ≥ 20/40; logMAR ≥ 0.3) (SD)**	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
	24-68 ETDRS letters (Snellen equivalent ≤20/50; logMAR 0.4-1.2) (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
Previous use of anti-VEGF therapies in the study eye	**Yes**	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
	No	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
Previous use of macular laser treatment in the study eye	**Yes**	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
	No	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	
High risk (as identified in exploratory analyses of HbA1c)	**Yes**	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
	No	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	

Subgroup analyses are conducted using the PP approach.

Table x.x.x Primary Outcome Sensitivity Analyses

Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 24	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	P-value
Highest Value Imputed	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Lowest Value Imputed	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Last Observation Carried Forward	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
No previous laser treatment for DMO in study eye	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
No previous anti-VEGF treatment for DMO in study eye	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
No cataract surgery in the study eye	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Excluding participants with month 24 follow-up outside ± 14 days of the due date	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx

Table x.x.x Secondary Outcomes

	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	P-value
Mean change in binocular BCdVA from baseline to month 24* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Mean change in central subfield retinal thickness, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 24* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field from baseline to month 24* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Change in the percentage (%) of people meeting driving standards from baseline to month 24†	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients experiencing Side effects from baseline to month 24‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of laser treatments needed from baseline to month 24* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients with at least one additional treatment (other than laser) from baseline to month 24‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx

Mean (SD) presented for continuous outcomes and number (%) presented for categorical outcomes.

*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.

‡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.

Table x.x.x Additional Analyses

	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	P-value
Mean change in best-corrected distance visual acuity (BCdVA) in the study eye from baseline to month 12* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Mean change in binocular BCdVA from baseline to month 12* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Mean change in central subfield retinal thickness, as determined by spectral domain optical coherence tomography (OCT), from baseline to month 12* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Mean change in the mean deviation (MD) of the Humphrey 10-2 visual field from baseline to month 12* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Change in the percentage (%) of people meeting driving standards from baseline to month 12†	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients experiencing side effects from baseline to month 12‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of laser treatments needed from baseline to month 12* (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Number of participants receiving additional treatments from baseline to month 12 (other than laser)‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients with at least one steroid injection (as additional treatment) from baseline to month 12	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients with at least one steroid injection (as additional treatment) from baseline to month 24	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of steroid injections (as additional treatment) from baseline to month 12	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx

	Standard Laser n=<n> (%)	DSM Laser n=<n> (%)	Difference (95% CI)	P-value
Number of steroid injections (as additional treatment) from baseline to month 24	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients receiving at least one anti-VEGF treatment (as additional treatment) from baseline to month 12	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of patients receiving at least one anti-VEGF treatment (as additional treatment) from baseline to month 24	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of anti-VEGF treatments (as additional treatment) from baseline to month 12 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Number of anti-VEGF treatments (as additional treatment) from baseline to month 24 (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.xx (xx.x – xx.x)	0.xxx
Number of anti-VEGF treatments (as additional treatment) from baseline to month 12 [rows for ≤ 4, 5-10, >10]	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of anti-VEGF treatments (as additional treatment) from baseline to month 24 [rows for ≤ 4, 5-10, >10]	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of participants receiving rescue treatments at least once from baseline to month 12‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of participants receiving rescue treatments at least once from baseline to month 24‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of participants satisfying rescue criteria at least once from baseline to month 12‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx
Number of participants satisfying rescue criteria at least once from baseline to month 24‡	n (%)	n (%)	xx.xx (xx.x – xx.x)	0.xxx

Mean (SD) presented for continuous outcomes and number (%) presented for categorical outcomes.

*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.

‡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.

Table x.x.x. Safety by Treatment Group

-		Standard Laser n=<n> (%)		DSM Laser n=<n> (%)		Risk Ratio (for number of patients) (95% CI)	P-value
		Number of events	Number of patients	Number of events	Number of patients		
AEs, SAEs and SUSARs	Total SAEs	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Related to study treatment	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Related to study treatment and unexpected	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Total AEs	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Related to study treatment	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
SAEs	Cardiac Arrhythmia	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Cardiac General	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Gastrointestinal	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Etc…..	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
AEs	Cardiac Arrhythmia	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Cardiac General	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Gastrointestinal	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Etc…..	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
ARs	Cardiac Arrhythmia	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Cardiac General	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Gastrointestinal	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Etc…..	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
SARs	Cardiac Arrhythmia	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Cardiac General	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Gastrointestinal	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx

-		Standard Laser n=<n> (%)		DSM Laser n=<n> (%)		Risk Ratio (for number of patients) (95% CI)	P-value
		Number of events	Number of patients	Number of events	Number of patients		
	Etc…..	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx

Table x.x.x. Additional Safety by preferred term and treatment group (eye disorders only)

		Standard Laser n=<n> (%)		DSM Laser n=<n> (%)		Risk Ratio (for number of patients) (95% CI)	P-value
		Number of events	Number of patients	Number of events	Number of patients		
AEs	Foveal burn *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Central/paracentral scotomas *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Epiretinal membrane formation *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Choroidal neovascularisation *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Self-reported reduced colour vision *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Self-reported metamorphopsia *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Etc….	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
SAEs	Foveal burn *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Central/paracentral scotomas *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Epiretinal membrane formation *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Choroidal neovascularisation *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Self-reported reduced colour vision *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Self-reported metamorphopsia *	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx
	Etc….	n (%)	n (%)	n (%)	n (%)	x.xx (x.xx-x.xx)	0.xxx

*AEs that were actively pursued throughout the course of the trial.