DIAMONDS

Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser

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HEALTH ECONOMICS ANALYSIS PLAN

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Northern Ireland Clinical Trials Unit
1st Floor Elliott Dynes
The Royal Hospitals
Grosvenor Rd
Belfast
BT12 6BA
Tel: +44 (0)28 9063 5794
Fax: +44 (0)28 9063 3328
Email: info@nictu.hscni.net

Contacts
Noemi Lois: Chief Investigator
Hema Mistry: Study Health Economist
Norman Waugh: Health Technology Assessment

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

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1. Abbreviations

AUC	Area-Under-the-Curve
CST	Central retinal subfield thickness
CEAC	Cost-Effectiveness Acceptability Curve
DIAMONDS	Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser
DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
DSML	Diode Subthreshold Micropulse Laser
ETDRS	Early Treatment Diabetic Retinopathy Study
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels
FFA	Fundus Fluorescein Angiogram
HEAP	Health Economics Analysis Plan
ICER	Incremental Cost-Effectiveness Ratio
ITT	Intention-To-Treat
MAR	Missing At Random
MNAR	Missing Not At Random
MI	Multiple Imputation
NEI	National Eye Institute
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NMB	Net Monetary Benefit
PSS	Personal Social Services
QALYs	Quality-Adjusted Life Years
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
VisQoL	Vision and Quality of Life
VFQ-25	Visual Function-25

2. Administrative information

This document describes the planned analysis of economic data within the Diabetic Macular Oedema and Diode Subthreshold Micropulse Laser (DIAMONDS) trial. The purpose of the Health Economics Analysis Plan (HEAP) is to outline an explicit framework of methods that will be used to analyse the health economic data in a robust manner and should be read in conjunction with the DIAMONDS trial Protocol and the DIAMONDS trial Statistical Analysis Plan (SAP), which provide further detail.

3. Introduction

Diabetic macular oedema (DMO) is the most common cause of irreversible blindness among people with diabetes mellitus and diabetic retinopathy (DR). DMO represents accumulation of fluid in the macula, the area responsible for central detailed vision. Laser has been the treatment of choice for people with DMO since its beneficial effects were demonstrated by the Early Treatment Diabetic Retinopathy Study (ETDRS).(1) In a recent technology appraisal, National Institute for 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 cost-effective in this patient group.(2) However, conventional laser treatment has potentially 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.

4. Trial design

DIAMONDS is a pragmatic, multicentre, allocation concealed, prospective, randomised, non-inferiority double-masked trial. Participants have type 1 or 2 diabetes mellitus and diabetic retinopathy with centre involving DMO, as determined by using spectral domain optical coherence tomography (SD-OCT) with the following characteristics in one or both eyes:

1) Central retinal subfield thickness of ≥300 but <400 microns as determined by SD-OCT
   OR
2) Central retinal subfield thickness of <300 microns provided that intraretinal or subretinal fluid is present in the central subfield (central 1 mm)

   AND

1) Visual acuity of > 24 ETDRS letters (Snellen equivalent > 20/320)
2) Over 18 years of age.

The aim of the DIAMONDS 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 DMO with a central retinal subfield thickness of (CST) of <400 microns for which laser treatment is currently recommended by NICE.

The primary objective of the trial 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. Secondary objectives of the trial 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 arms.

5. Health Economics Objective

The objective is to conduct a short-term (baseline to 2-years follow-up) within trial analysis comparing the cost-effectiveness of DSML with standard laser using resource use and quality-of-life data. The within-trial economic analysis will be conducted under the intention-to-treat (ITT) principle, presenting resource use, cost and quality-of-life findings by trial arm. This requires that study participants are analysed according to their treatment assignment regardless of actual treatment received. Attention will be paid to levels of completeness of data, identifying issues and potential remedies.

6. Analysis

In accordance with this HEAP, a prospective economic evaluation of the DIAMONDS trial will be conducted from a National Health Service (NHS) and personal social services (PSS) perspective for the base-case analysis. Costs and resource use will be collected for both arms for the 24-month trial duration. Quality of life will be estimated from the EQ-5D-5L responses and combined with relevant tariffs to produce quality-adjusted life years (QALYs). As follow-up continues for 2 years, second year costs and benefits will be discounted at 3.5% in accordance with the NICE reference case.(3) Results will be expressed primarily as cost per QALY gained. The findings of this economic evaluation will be reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement for the reporting of health economic evaluations.(4)

6.1 Outcomes

The primary outcome of the within-trial economic evaluation will be the quality-adjusted life year as recommended in the NICE reference case.(3) This will allow an incremental cost-effectiveness ratio for DSML compared with standard laser to be generated in the form of incremental cost per QALY gained. The QALY is a measure that combines quantity and quality of life lived into a single metric, with one QALY notionally equating to one year of full health. QALY estimates are generated from combining length (survival) and health-related quality of life data from participants for the period covering the trial time horizon using area-under-the-curve (AUC) approach using a linear extraploation.(5) Since AUC estimates are predicted to correlate with baseline scores (and thus potential baseline imbalances), AUC estimates will be adjusted for baseline scores within regression analyses. Health-related quality of life will be converted into health-state utilities indexed at 0 and 1, where 0 represents death and 1 represents full health. Patients who die during the study are subsequently scored zero at later scheduled follow-up visits for both cost and quality of life scores and are included as observed data.

To generate QALYs, patients will be asked to complete the EQ-5D-5L questionnaire(6): which consists of the descriptive system and the visual analogue scale. The descriptive system includes five questions addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with each dimension assessed at five levels: from no to extreme problems. The EQ-5D-5L responses

can be converted into health utilities using a recently published value set for England.(7) However, since publication of the EQ-5D-5L value set, NICE has released a position statement advising against the use of the new tariff until the outcome of ongoing research exploring the impact of adopting the EQ-5D-5L valuation set in the NICE reference case becomes available.(8) The position statement further recommends that during this interim period, EQ-5D-5L responses should be mapped or cross-walked onto the EQ-5D-3L using the Hout et al algorithm.(9)

We will also estimate quality of life using two diseases specific measures: National Eye Institute Visual Function-25 (NEI VFQ-25) and Vision and Quality of Life (VisQoL).(10-12) VFQ-25 is a vision specific patient reported quality of life tool. This validated questionnaire has been used widely to evaluate visual outcomes in patients with eye diseases including diabetic retinopathy. In addition to eliciting information about general health and vision, it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision. We believe this provides a comprehensive evaluation of vision related quality of life. In addition, we will include the recently developed VisQol questionnaire which is shorter than VFQ-25 but has not yet been widely validated.

We will compare the results of VFQ-25 and VisQoL with EQ-5D-5L. All three questionnaires will be completed at baseline, and at 12 and 24 months when the patient visits the clinic. Questionnaires will be self-administered by participants and research nurses or administrative staff will be on hand if there are any queries. For example, patients will either 1) complete the questionnaires alone, 2) complete them with the help of staff in the research clinic or 3) have the research nurse/staff reading the questions to them and then depending on what the patient stated write their answers (for those people that may have find it hard to read and tick themselves). In order to ensure adequate attendance of participants to follow-up visits, participants will be reminded by telephone, text or call the week prior to the study visit.

6.2 Resource use and cost

Resource use assessments will be captured on trial CRFs at scheduled clinic visits and contacts over the 24-month follow-up period. On-site monitoring visits during the trial will ensure the accuracy of entries in the CRF. The primary analysis will concentrate on direct intervention and healthcare/PSS costs. Resource use data will explore the costs of delivering laser treatment and to find the key cost drivers. This will mainly consist of the different laser treatments (including how long it takes), staff time, equipment required, overheads, and consumables, alongside any laser retreatments, the use of imaging technologies (Fundus Fluorescein Angiogram (FFA), Spectral domain optical coherence tomography (SD-OCTs) scans) to guide laser treatment, number of outpatients visits, any admissions, other tests or investigations, and medication usage including any rescue treatments. Some costs of laser treatment are available from recent NICE appraisals but consideration will be given to the cost of different machines (if applicable, some machines can do both standard laser and pattern laser), the time used to deliver the treatment and number of treatments required as well as any difference in the need for rescue therapy.

Current unit costs in UK pounds sterling will be applied to each resource item to value total resource use in each arm of the trial using national sources such as the Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) annually, NHS reference costs and the British National Formulary.(13-15)

Each cost category will be calculated by multiplying the resource use measure with the respective unit cost estimate. For each cost category, descriptive statistics (mean, median, standard error and interquartile range) will be calculated. Total costs per patient from a healthcare/PSS perspective will be calculated.

6.3 Data quality and cleaning

All data relevant to the health economics analysis will be examined for data quality. All questionnaires will be checked for completeness on return to the trial office. Any questionable data will be queried with trial staff and inappropriate or unclear responses will be handled in accordance with pre-specified data entry guidance. Unresolved issues after referral to the data entry instructions will be discussed with the trial health economists and clarification sort from the clinical team if necessary. Agreed line of actions for addressing data quality issues will be documented in the data entry guidance documentation.

6.4 Analysis

6.4.1 Missing data

Follow-up of trial participants is problematic particularly over long periods and some incompleteness (missing) of data is anticipated. Any missing items present after the data cleaning stage will be addressed within the health economic analysis strategy as missing data. Descriptive analyses of missing data will be carried out (missing data patterns using graphical tools, association between missing data and baseline variables, association between missing data and outcomes). The results of the descriptive analysis will be discussed by the trial team to infer possible reasons for missing data and inform the assumption about the missing data mechanism. Consequently, the base-case analysis will use multiple imputation (MI), to account for missing data. The base-case analysis will present the imputed within trial incremental cost and QALYs gained, adjusted for trial baseline covariates. Supportive sensitivity analyses will include participants with complete data and explore the impact of imputation.

Multiple imputation will be conducted according to good practice guidance.(16) MI generates a series of datasets with each dataset replacing missing values with sampled values. For example, MI replaces each missing observation with a set of plausible imputed values, taken from the predictive distribution of the missing data given the observed data.(17) Such methods can handle data assumed missing at random (MAR) and can be modified to handle data assumed missing not at random (MNAR).(18) Appropriateness of the MAR assumption will be assessed by comparing the characteristics of patients with and without missing data at each follow-up time point. Imputated data will be generated separately by treatment group as recommended by Faria et al (18) using the predictive mean matching method which has the advantage of preserving non-linear relationships and correlations between variables within the data. Estimates obtained will be pooled to generate mean and variance estimates of costs and QALYs using Rubin's rule in order to capture within and between variances for imputed samples.(19)

6.4.2. Cost-effectiveness analysis

For the base-case analysis, bivariate regressions using seemingly unrelated regressions equations will be used to model incremental changes in costs and QALY. This method respects the correlation

of costs and outcomes within the data, and allows adjustment for a set of covariates, which can be explored and which improve precision.(20) The covariates to be included in the regressions will be those selected a priori for the adjusted statistical analysis, namely baseline characteristics. Baseline costs and EQ-5D-5L scores will be included within all models to allow for potential baseline imbalances, a practice that is now standard for trial-based economic evaluations.(21) Failure to account for such an imbalance will inevitably lead to biased cost-effectiveness estimates.

Joint distributions of costs and outcomes will be generated using the (non-parametric) bootstrap method, with replicates used to populate a cost-effectiveness plane. Bootstrapping jointly resamples costs and outcomes from the original data with replacement to create a new bootstrap sample from which a change in costs and QALYs are estimated. Using bias-corrected non-parametric bootstrapping, 5000 bootstraps will be taken per model evaluated. Mean estimates will be reported with 95% confidence intervals. Costs and benefits beyond the first year will be discounted at 3.5%.

The incremental cost-effectiveness ratio (ICER) will be estimated as the difference between treatments in mean total costs divided by the difference in mean total QALYs. Results will be expressed as cost per QALY gained. Value-for-money is determined by comparing the ICER with a threshold value, typically the NICE threshold for British studies, of £20-30k per QALY.(3) This represents the willingness to pay for an additional QALY, and lower values than the threshold could be considered cost-effective for use in the NHS. Appropriate sensitivity analyses will be conducted to assess the robustness of the results. A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. The net monetary benefit (NMB) of changing treatment will be reported as a recalculation of the ICER at a range of thresholds of willingness to pay for an additional QALY. The NMB describes the resource gain (or loss) when investing in a new treatment when resources can be used elsewhere at (up to) the same threshold. NMB estimates will be used to generate cost-effectiveness acceptability curves (CEACs). The CEAC compares the likelihood that treatments are cost-effective as the willingness to pay threshold varies.(20)

Should costs and quality-of-life not converge within two-years, a Markov model based cost-utility analysis will extend beyond the trial analysis to estimate the longer-term cost-effectiveness, with costs and benefits discounted at 3.5%. The model will be informed by data from the trial and supplemented by estimates of effectiveness, quality of life and costs from published literature and expert opinion. All analyses and modelling will be undertaken using Microsoft Excel and Stata 15 SE.

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8. Example tables

Table 1 illustrates the presentation of completeness of data; Table 2 and 3 illustrates the presentation of quality-of-life, resource and cost data for complete cases and complete cases with imputed data for missing/withdrawals, respectively; Table 4 cost-effectiveness results.

Table 1: Completeness of data by follow-up visit

	DSML		Standard laser		Total	
	n	(%, N)	n	(%, N)	n	(%, N)
EQ-5D-5L utility scores						
Baseline						
12 months						
24 months						
VFQ-25 scores						
Baseline						
12 months						
24 months						
VisQoL scores						
Baseline						
12 months						
24 months						
Resource use[1]						
Outpatient visits						
FFA						
SD-OCTs						
Laser retreatments						
Other tests or investigations						
Other surgery i.e. cataract						
Rescue treatments						
Medications						
Complications related to laser treatment						

[1] Range shown, lowest to highest completion at measurement points

NB for outcomes we will look at composite scores as well as individual domains

Table 2 Quality of life, resource use and cost (complete cases)

	DSML		Standard laser		Mean difference	p-value	Bootstrap 95% CI
	mean	(SD)	mean	(SD)			
EQ-5D-5L utility scores							
Baseline							
12 months							
24 months							
VFQ-25 scores							
Baseline							
12 months							
24 months							
VisQoL scores							
Baseline							
12 months							
24 months							
Resource use frequency (all visits)							
Outpatient visits							
FFA							
SD-OCTs							
Laser retreatments							
Other tests or investigations							
Other surgery i.e. cataract							
Rescue treatments							
Medications							
Complications related to laser treatment							
Other							
Cost							
Outpatient visits							
FFA							
SD-OCTs							
Laser retreatments							
Other tests or investigations							
Other surgery i.e. cataract							
Rescue treatments							
Medications							
Complications related to laser treatment							
Total cost							

NB for outcomes we will look at composite scores as well as individual domains

Table 3 Quality of life, resource use and cost (with imputed data)

	DSML		Standard laser		Mean difference	p-value	Bootstrap 95% CI
	mean	(SD)	mean	(SD)			
EQ-5D-5L utility scores							
Baseline							
12 months							
24 months							
VFQ-25 scores							
Baseline							
12 months							
24 months							
VisQoL scores							
Baseline							
12 months							
24 months							
Resource use frequency (all visits)							
Outpatient visits							
FFA							
SD-OCTs							
Laser retreatments							
Other tests or investigations							
Other surgery i.e. cataract							
Rescue treatments							
Medications							
Complications related to laser treatment							
Other							
Cost							
Outpatient visits							
FFA							
SD-OCTs							
Laser retreatments							
Other tests or investigations							
Other surgery i.e. cataract							
Rescue treatments							
Medications							
Complications related to laser treatment							
Total cost							

NB for outcomes we will look at composite scores as well as individual domains

Table 4 Cost-effectiveness results

	Mean incremental costs, £ (95% CI)	Mean incremental QALYs (95% CI)	ICER	Probability of cost-effectiveness	Incremental net monetary benefit
Base case analysis					
Sensitivity analyses					
Unadjusted analysis					
Complete case analysis					