The clinical efficacy and safety of light-masks at preventing dark adaptation in the treatment of early diabetic macular oedema (CLEOPATRA)

A Multicentre Phase III Randomised Controlled Single-Masked Clinical trial

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

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1. Study Synopsis

TITLE OF CLINICAL TRIAL:	A multicentre phase III randomised controlled single-masked clinical trial to test the clinical efficacy and safety of light- masks at preventing dark adaptation in the treatment of non-centre involving diabetic macular oedema (DMO)
Protocol Short Title/ Acronym:	CLEOPATRA
Medical Condition Or Disease Under Investigation:	Non-centre involving diabetic macular oedema
Purpose Of Clinical Trial:	To evaluate whether prevention of dark adaptation using light masks is safe and will prevent the progression of non-centre-involving diabetic macular oedema
Primary Objective:	To explore whether wearing light-masks during sleep at night reduces, relative to the dummy masks, the maximal zone thickness in the study eye as measured by OCT in patients with non-centre involving DMO at 24 months.
Secondary Objective(s):	I. To explore whether wearing light-masks during sleep at night reduces, relative to the dummy masks, the maximal zone thickness in the study eye as measured by OCT in patients with non-centre involving DMO at 12 months. II. To explore whether the effect of light-masks, relative to dummy masks, is safe and can prevent the progression of non-central DMO by assessing the following at 12 and 24 months: 1. Change in retinal thickness of each of the 9 ETDRS zones (specifically in parafoveal zones 2-5 and perifoveal zones 6-9) and macular volume. 2. Change in morphological characteristics of macular thickening on OCT 3. Change in visual acuity 4. Progression to clinically significant centre-involving macular oedema (defined as 300µm) within 24 months 5. Time to occurrence of clinically significant centre-involving macular oedema (300µm) 6. Proportion of participants requiring macular laser treatment or anti-VEGF treatment 7. Progression of retinopathy as assessed by the independent reading centre as changes in severity of ETDRS scale and assessing microaneurysm turnover using computerised software 8. Safety data on the device will be collected and all adverse events and serious adverse events will be reported. Sleep disturbance due to wearing the light-masks and the dummy masks will be assessed using validated questionnaires. 9. Compliance rate of using the light masks
Objectives of the mechanistic evaluation	The mechanistic evaluation will be assessed at 12 months to explore: 1. the regional changes induced by supplemental oxygen on multifocal ERG and scotopic micro perimetry as a function of retinal location. 2. whether in regions of anatomical change and in those of adjacent regions without apparent change, supplemental oxygen affects tests of function to a different extent

	3. whether outer (microperimetry) or inner retinal (multifocal ERG) functional loss is more closely associated with structural changes. 4. whether use of light-masks affects retinal hypoxia in regions of anatomical disturbance, and whether a distinction can be made regarding inner and outer retinal functional changes. 5. whether the long term changes induced by light-masks are similar to changes induced by oxygen supplementation.
Trial Design:	Single-masked, randomised controlled trial in at least 10 centres in the UK with primary and secondary outcomes assessed at 24 months post randomisation and a mechanistic evaluation at 12 months.
Endpoints:	*Primary endpoint* Primary efficacy measure is the difference between arms in the change from baseline in absolute thickness at the zone of maximum thickness as determined by OCT at 24 months *Secondary endpoints* I. The difference between arms in the change from baseline in retinal thickness at the baseline zone of maximum thickness as determined by OCT at 12 months. II. Secondary efficacy parameters at 12 and 24 months will be the difference between arms in the: 1. Change in retinal thickness in each of the 9 ETDRS zones (parafoveal zones 2-5 and perifoveal zones 6-9) and macular volume. 2. Change in morphological characteristics of macular thickening on OCT. 3. Mean change in visual acuity. 4. Progression to centre-involving macular oedema. 5. Time to occurrence of centre-involving macular oedema. 6. Proportion requiring macular laser treatment/ antiVEGF treatment. 7. Proportion of participants that show progression of retinopathy as measured by ETDRS severity levels and microaneurysm turnover. 8. Compliance rate of the light masks over 24 months. *Safety outcome measures* 1. Difference between arms in the measures of sleep disturbance in terms of daytime sleepiness and insomnia. 2. Difference between arms in ocular and systemic adverse events and serious adverse events. *Mechanistic outcome measures at 12 months* 1. Change in P1 and N1 amplitudes and peak time in multifocal ERG after supplemental oxygen 2. Change in retinal sensitivity in scotopic microperimetry after supplemental oxygen. 3. To determine differences in change in P1 amplitudes

	and peak time in multifocal ERG after light-masks and dummy masks at 12 months. 4. To determine differences in change in retinal sensitivity in scotopic microperimetry after light-masks and dummy masks at 12 months. 5. To correlate the changes induced by light-masks and oxygen supplementation on retinal sensitivity using oximetry
Sample Size:	300 adult patients with non-central diabetic macular oedema
Summary of Eligibility Criteria:	*Inclusion criteria* 1. Subjects of either sex aged 18 years or over 2. Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present: a. Current regular use of insulin for the treatment of diabetes b. Current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes c. Documented diabetes by ADA and/or WHO criteria 3. Best corrected visual acuity in the study eye better than 55 ETDRS letters (Snellen VA 6/24). 4. On clinical exam, retinal thickening due to early DMO not involving the central 1000μm of the macula characterised by presence of microaneurysm, exudates or oedema and OCT evidence of increased retinal thickness in at least 1 non-central ETDRS zone of ≥320μm. 5. Previous macular laser, intravitreal steroids or antiVEGF treatment is permitted provided the last treatment was done at least 4 months before date of recruitment. 6. Media clarity, pupillary dilation and subject cooperation sufficient for adequate fundus photographs. 7. Ability to return for study visits 8. Ability to give informed consent throughout the duration of the study *Exclusion criteria* I. The following exclusions apply to the study eye only (i.e. they may be present for the non-study eye): 1. Clinical evidence of centre involving macular oedema (central subfield on OCT>300μm). 2. Macular oedema is considered to be due to a cause other than DMO. 3. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-

	Gass syndrome, etc). 4. History of treatment for DMO at any time in the past 4 months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs, or any other treatment) in the study eye 5. History of panretinal scatter photocoagulation in the study eye. 6. Active proliferative diabetic retinopathy in the study eye. 7. A condition that, in the opinion of the investigator, would preclude participation in the study. 8. Corneal scarring, vitreous opacities, severe asteroid hyalosis that would inhibit proper visualisation, inability to be positioned in front of the OCT device, inability to understand the requirements of the imaging, and nystagmus. II. Patients with active insomnia or any other relevant sleep disturbances.
Intervention:	Post randomisation participants will wear either a light-mask or a dummy mask at night during sleep for 24 months. The Light mask is a device designed to deliver a precise photo-therapy to a user's retina through closed eyelids. The light mask comes in two parts, a fabric mask and a light emitting unit, or "Pod". The Pod contains two Organic Light Emitting Diodes (OLEDs), which will be located over the eyes of the patient when the light mask is being worn. The light output is designed to be safe and optimised to limit the disturbance to the patient's sleep whilst delivering the required therapeutic dose. The OLEDs are powered by two 3V (CR2450) batteries which eliminate the need for an external power source or recharging. At the end of the mask lifetime a replacement light mask is required. In the masks are also capacitive sensors that can sense when the masks are being worn. This data is logged and stored in the mask's on board memory and can be downloaded after the mask has been returned, using "contactless" RFID technology for data analysis.
Maximum Duration Of Treatment Of A Subject:	24 months
Version And Date Of Final Protocol:	Version 1.0, 01-12-2012
Version And Date Of Protocol Amendments:	Version 2.0, 14-02-2013 Version 3.0, 01-08-2013 Version 4.0, 01-11-2013 Version 5.0, 07-02-2014 Version 5.0, 21-02-2014 Version 5.1, 27-02-2014 Version 6.0, 11-08-2014

2. Glossary of Abbreviations

ADA	American Diabetes Association
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
ASR	Annual Safety Report
BCVA	Best Corrected Visual Acuity
CA	Competent Authority
CACE	Complier Average Causal Effects
CE	Communauté Européenne
CI	Chief Investigator
CRF	Case Report Form
CST	Central sub-field thickness
CTU	Clinical Trials Unit
DMEC	Data Monitoring Ethics Committee
DMO	Diabetic macular oedema
DR	Diabetic Retinopathy
EC	European Commission
ERG	Electroretinogram/Electoretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EUCTD	European Clinical Trials Directive
GAfREC	Governance Arrangements for NHS Research Ethics
GCP	Good Clinical Practice
GP	General Practitioner
HbA1C	Glycosylated Haemoglobin
ICF	Informed Consent Form
IOP	Intraocular pressure
ISF	Investigator Site File

ISRCTN	International Standard Random Clinical Trials Number
LDEP	Low density polyethylene
MEH	Moorfields Eye Hospital
mfERG	Multifocal ERG
MRC	Medical Research Council
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
OCT	Optical Coherence Tomography
OLED	Organic Light Emitting Diode
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
RCT	Randomised Control Trial
REC	Research Ethics Committee
RFID	Radio-frequency identification
ROS	Reactive Oxygen Species
SADE	Serious Adverse Device Effect
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SOP	Standard Operating Procedure
SPRAE	Serious Procedure Related Adverse Event
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
USADE	Unexpected Serous Adverse Device Effect
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

3. Contents

4. Background & Rationale

4.1 Background

4.1.1 Background information

Over 3 million people in the United Kingdom (UK) have diabetes. 150,000 people develop diabetes each year. Diabetic retinopathy is the most common complication of diabetes. The most common cause of sight threatening retinopathy is diabetic macular oedema (DMO). This condition is characterised by leakage of fluid from compromised blood vessels in the central retina and 240,000 (8%) people with diabetes in the UK have clinically significant DMO. Clinically significant oedema may be central or non-central oedema. Non-central oedema does not usually affect visual acuity. When it affects the central 1mm of the macula, it causes visual impairment. Over 30% of eyes with centre involving macular oedema lose 3 or more lines of vision by five years. Approximately, 100,000 people with DMO have visual impairment. It is the most common cause of registrable blindness in the working age-group in the UK. A Diabetic Retinopathy Screening Service annually photographs 3M people with diabetes at a cost of £65M to ensure early diagnosis of these sight- threatening complications.

Patients with early, non-sight threatening DMO are referred into Hospital Eye Service to be monitored more closely for progression to centre-involving DMO. These patients are monitored 4-6 monthly in eye clinics for disease progression to the centre using slit-lamp biomicroscopy and optical coherence tomography (OCT). OCT provides information on the changes in the retinal thickness and morphology of the retina due to DMO. Approximately 30% of these patients progress to centre involving macular oedema by 12 months.

Treatment is available only when the DMO becomes clinically significant or shows progression to the centre. Laser treatment is the standard of care when the DMO becomes clinically significant. Although laser treatment reduces the risk of moderate visual loss by 50% at this stage, it is not effective in restoring visual acuity and has significant side effects that impact on the quality of life of these people. Newer treatment options of injections of inhibitors of Vascular Endothelial Growth Factor (VEGF) are also available only for the more advanced form of centre-involving DMO. These anti-VEGF injections are now also being used for age-related macular degeneration and other retinal vascular diseases such as retinal vein occlusions to regularly inhibit the continued production of VEGF. These treatments are costly and cause significant burden to patient, their caregivers and the healthcare system.

There are no treatment options for non-clinically significant DMO except optimal control of diabetes and hypertension. Laser photocoagulation may be performed for non-central clinically significant macular oedema but these cases are often only observed in clinics. The Phase 3 clinical trial in patients with early DMO was the ruboxistaurin trial that did not meet its end-point (1). Ruboxistaurin is a protein kinase inhibitor and can indirectly block VEGF drive. The natural history of the disease is to progress from non-central to centre-involving DMO. Therefore, there is a substantial unmet need for both treatment and prevention of progression of non-centre involving DMO.

4.1.2 Existing research

The exact pathogenesis of diabetic retinopathy and DMO is uncertain. There is an enormous wealth of evidence that in diabetes, both in man and in animal models, there is an overproduction of Reactive Oxygen Species (ROS) - single and triplet oxygen radicals, hydrogen peroxide, and related radicals that include nitrogen and even sulphur - that are collectively referred to as Oxidative Stress, and these are instrumental in causing the retinal vascular damage seen in diabetes. ROS are produced by increased activity in mitochondria, as they utilize oxygen and glucose to produce energy (2-4). The chain of evidence is not complete: for example, retinal endothelial cells cultured in high glucose- to mimic diabetes- do not suffer from oxidative stress (5), and the retinal rods, which have the highest metabolic rate of all cells, do not suffer from oxidative stress (6).

This study focuses on a slightly different line of reasoning. The vascular changes of diabetic retinopathy only occur in the retina, not in the brain, and therefore there is a specific retinal factor causing diabetic retinopathy (7). The retina and brain are embryologically the same tissue, and the great difference in susceptibility of their capillaries to damage is surprising. The obvious difference between the two tissues is the presence of photoreceptors in the retina. 95% of these are rods that are used in night vision only. How could the presence of rods initiate the vasculopathy that characterises diabetic retinopathy? Rods use more oxygen than any other cell in the body (8). This is required to support the extreme sensitivity to light which develops during dark-adaptation. As a result, the oxygen tension in the mitochondrial region of the rods in darkness falls to zero (9). The exact mechanism is that in darkness the rod outer segment membrane becomes extremely permeable to ions and water, which enter the cell and are pumped out in the inner segment (10). The resulting "dark current" is large and requires all the oxygen available in the normal eye. If retinal circulation is compromised in any way, the hypoxia present in the outer retina increases and spreads into the inner part: this is what occurs in diabetic animals (11).

Hypoxia is the main stimulus for the increase in VEGF levels in patients with diabetic retinopathy and many other retinal diseases such as age–related macular degeneration. VEGF causes the changes in capillaries seen in DR. (12, 13). New treatments of DMO focus on inhibiting VEGF drive (14-18). There are many correlations between the increase or decrease in VEGF and the changes in the degree of diabetic retinopathy. Other supporting evidence of the role of hypoxia driven VEGF in the pathogenesis of diabetic retinopathy is that sleep apnoea increases the severity of diabetic retinopathy (19) and that VEGF polymorphisms are associated with the severity of diabetic retinopathy (20). Other examples have also been reviewed (21).

4.2 Rationale

We hypothesised that increased glucose is associated in various ways with a decrease in oxygen supply to the retina, and an increase in oxygen demand. This leads to increased hypoxia, and an overproduction of VEGF (21), which damages the circulation, and in doing so will further decrease retinal oxygen supply in a vicious circle (22). Only at such a stage will all the other mechanisms that contribute to retinal vascular damage operate and contribute to the various clinical features of diabetic retinopathy. A prediction was made from this hypothesis, that if dark-adaptation was prevented, the rod dark current would never become maximal and diabetic retinopathy would be alleviated by decreasing the oxygen demand (23).

Since man only dark adapts at night during sleep, sleeping in an illuminated environment should prevent or reverse the condition. In clinical trials it is important to treat every patient identically, so we have made 'light-masks' containing light emitting diodes to illuminate the closed eyelids during sleep. Sufficient light is transmitted by the lids to reduce the dark current. The quantity of light can be measured, and uncertainties as to whether the bedroom lighting is sufficient, or if the subject sleeps on one side, with his head under the blankets, are eliminated. There are obvious advantages for such devices as a therapy. Different sleeping positions affect the amounts of light exposure time. The light-masks ensure uniform illumination of weak light to which the eyes adapts quickly due to the Troxler effect. However it is important that the masks are comfortable to wear and do not disturb sleep.

The relationship of these OCT changes on morphology and thickness to hypoxia has not been determined. Similarly, the relation of the visual function to hypoxia is also unclear. This is the subject of the mechanistic investigation.

4.2.1 Main study on clinical efficacy and safety

There is no treatment for early DMO, causing a significant healthcare burden. The short trials referred to above show proof of concept that prevention of dark adaptation by using light-masks may be safe and effective in reducing the retinal thickness in non-central DMO. So, we need to investigate this further by conducting a robust multicentre randomised controlled trial comparing the efficacy and safety of light-masks relative to dummy masks in treating and preventing the progression of early DMO. This trial will be done in

collaboration with an accredited Clinical Trials Unit (CTU), to conform with the Consort 2010 statement, including those relating to research governance, independent data analysis and disclosure of all data.

4.2.2 Sub-study on mechanistic evaluation

There are only very small observational studies that suggest that hypoxia determines diabetic retinopathy. In the mechanistic evaluation, we will explore the concept of hypoxia as a contributing factor in early DMO. We will study the effect of inhalation of oxygen and light-masks on the retinal morphology and visual function. We will conduct the tests in 30 participants to establish whether local regions of retinal oedema correspond to areas of hypoxia, and whether functional defects of outer and inner retinal layers are associated with corresponding anatomical changes. As these tests are time-consuming, we have taken participant burden into account and limited the study to 30 participants who will be agreeable to longer tests.

4.3 Study population

The study will evaluate the efficacy and safety of light-masks in treating and preventing the progression of non-centre involving DMO. 300 patients with non-centre involving DMO will be randomised 1:1 to light-masks and dummy masks (with no light) for 24 months. While diabetic eye disease may affect both eyes of a single subject in a similar way, this is not always the case. **In subjects where only one eye meets the inclusion criteria:** the fellow eye (non-study eye) will be monitored during the course of the study by the trial investigators and will receive macular laser therapy or ranibizumab therapy in accordance with the NHS standard of care. **In subjects where both eyes meet the inclusion criteria:** the eye with the worse visual acuity will be included in the study and become the study eye. The fellow eye (non-study eye) will be treated in accordance with macular laser or ranibizumab therapy as part of the NHS standard of care, and will continue to be monitored by the study investigators throughout the study and receive further treatment if required in accordance with the standard guidelines for treating diabetic eye disease.

4.4 Risk and benefits

In terms of benefits to participants, the light-masks may result in a significant and meaningful effect by reducing the early non-central DMO and by decreasing the rate of progression of DMO to the centre. If efficacy is shown, it would have significant impact on the understanding of the pathogenesis of DMO and provide a non-invasive prevention and treatment option for the most common cause of visual impairment in the working age-group.

The risks of wearing the masks are small as the masks have been CE certified as a class 2a medical device and the manufacture meets ISO 13485 standards. Light, per se, is not an issue: the damaging effects of light on the retina are well known and what we propose is approximately 6 orders of magnitude less than for threshold toxicity and 2 orders below that which causes a 1% change in the melatonin cycle that drives circadian rhythms. There remains a small risk that the masks might not be comfortable to use and this might disturb sleep. For this reason, we propose to test for sleep disturbance and daytime drowsiness by the use of validated sleep questionnaires. Compliance with the light-masks may be an issue but all site personnel will stress optimal compliance with all patients and each masks is equipped with a capacitive sensor and memory chip capable of sensing when the mask is being worn and storing the data. This data will be downloaded and analysed providing an accurate measure of compliance in this trial. To prevent contamination of the fabric mask from prolonged use, the patients will be periodically provided with a new fabric mask throughout the trial at intervals of no greater then every three months. We have never witnessed any side effects of light toxicity on the retina at this dose. Thus, we believe that this approach will be safe. However, all adverse events will be reported.

In summary, the benefits to society are that if this method of treatment works, it opens the way to a much simpler, more effective, way of preventing diabetic retinopathy and DMO and other retinal vascular diseases such as age related macular degeneration in which overproduction of VEGF is causal.

5. Trial Objectives and Design

5.1 Trial Objectives

To explore whether wearing light masks during sleep at night is a practical and effective method of decreasing or slowing the progression of early DMO.

5.1.1 Primary objectives

To explore whether wearing light-masks during sleep at night reduces, relative to the dummy masks, the maximal zone thickness as measured by OCT in the study eye of patients with non-centre involving DMO at 24 months.

5.1.2.Secondary objectives

I. To explore whether wearing light-masks during sleep at night reduces, relative to the dummy masks, the baseline maximal zone thickness as measured by OCT in the study eye of patients with non-centre involving DMO at 12 months.

II. The secondary objectives of this study are to explore whether the effect of light-masks, relative to dummy masks, is safe and can prevent the progression of non-centre involving DMO by assessing the following at 12 and 24 months:

1. Change in retinal thickness of each of the 9 ETDRS zones (specifically within the parafoveal zones 2-5 and within the parafoveal and perifoveal zones 6-9) and macular volume.
2. Change in morphological characteristics of macular thickening on OCT.
3. Change in visual acuity
4. Progression to clinically significant centre-involving macular oedema (defined as CST of 300µm on OCT).
5. Time to occurrence of clinically significant centre-involving macular oedema (defined as 300µm on OCT).
6. Proportion of participants requiring macular laser treatment or anti-VEGF treatment..
7. Progression of retinopathy as assessed by the Independent Reading Centre as changes in severity of ETDRS scale and assessing microaneurysm turnover using computerised software.
8. Safety data on the device will be collected and all adverse events and serious adverse events will be reported. Sleep disturbance due to wearing the light-masks and the dummy masks will be assessed using validated questionnaires.
9. Compliance rate of using the lightmasks

5.1.3 Mechanistic evaluation objectives

1. To explore the changes induced by supplemental oxygen on multifocal ERG and scotopic microperimetry as a function of retinal location at 12 months.
2. To explore whether in regions of anatomical change and in those of adjacent regions without apparent change, supplemental oxygen affects tests of function to a different extent at 12 months.
3. To explore whether outer (microperimetry) or inner retinal (multifocal ERG) functional loss is more

closely associated with structural changes at 12 months.

4. To explore whether use of light-masks affects retinal hypoxia in regions of anatomical disturbance, and whether a distinction can be made regarding inner and outer retinal functional changes at 12 months.
5. To explore whether the long term changes induced by light-masks are similar to changes induced by oxygen supplementation at 12 months.

5.2 Trial End-points

5.2.1 Primary endpoints

Primary outcome measure is the change from baseline in absolute thickness of the zone of maximum thickness in the study eye as determined by OCT at 24 months.

5.2.2 Secondary endpoints

I. A secondary outcome is the change from baseline in retinal thickness of the baseline zone of maximum thickness in the study eye as determined by OCT at 12 months.

II. Endpoints at 12 and 24 months:

1. Change in retinal thickness in the 9 ETDRS zones (specifically within parafoveal zones 2-5, and within parafoveal and perifoveal zones 6-9) and macular volume.
2. Change in morphological characteristics of macular thickening on OCT
3. Change in visual acuity.
4. Proportion of patients that progress to significant centre-involving macular oedema (defined as CST of 300um on OCT).
5. Time to occurrence of significant centre-involving macular oedema (CST of 300um on OCT).
6. Proportion requiring macular laser or antiVEGF treatment.
7. Proportion of patients that show progression of retinopathy as assessed by the Independent Reading Centre as changes in severity of ETDRS scale and assessing microaneurysm turnover using computerised software.
8. Safety and tolerability:
    a. Changes in daytime sleepiness as measured by Epworth Sleepiness Scale score,
    b. Changes in insomnia score measured using Pittsburgh Insomnia Rating Scale (PIRS 20),
    c. Tabulation and comparison of all adverse events and serious adverse events in each arm.
9. Compliance rate of the lightmasks.

5.2.3 Outcome measures in mechanistic evaluation at 12 months

1. Change in P1 and N1 amplitudes and peak time in multifocal ERG after supplemental oxygen
2. Change in retinal sensitivity in scotopic microperimetry after supplemental oxygen.
3. To determine differences in change in P1and N1 amplitudes and peak time in multifocal ERG after light-masks and dummy masks.
4. To determine differences in change in retinal sensitivity in scotopic microperimetry after light-masks and dummy masks.
5. To correlate the changes induced by light-masks and oxygen supplementation on retinal sensitivity using oximetry.

5.3 Trial Design

This is a phase III randomised controlled single-masked clinical trial that will evaluate the efficacy and safety of light-masks in treating and preventing the progression of non-centre involving DMO. 300 patients with non-centre involving DMO in at least one eye will be randomised 1:1 to light-masks and dummy masks (with no light) to be used during sleep at night for a period of 24 months. This basic study design and the associated clinical measurements are well-established, having been successfully used in numerous previous clinical trials of DMO. These include retinal thickness measurements using OCT at various time points, visual acuity, retinal colour photographs, questionnaires to assess sleep disturbance, adverse events and measures of compliance. Participants recruited to the mechanistic evaluation will have additional oximetry, multifocal ERG and microperimetry.

5.4 Summary of assessments and Trial Flowchart

Table 1: Summary of assessments

	Screening/ Baseline+	Week 1^	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24 End of Trial	
Study Week/month	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Withdrawal**
Informed Consent	x								
Eligibility form	x								
Medical History	x								
Concomitant medications	x		x	x	x	x	x	x	x
Ocular examination	x		x	x	x	x	x	x	x
HbA1c and BP	x				x			x	x
Pittsburgh Insomnia Rating Score and Epworth Sleepiness Scale[26,27]	x	x			x			x	x
BCVA (Refraction at screening, 12 and 24 months ®)	X ®		x	x	X ®	x	x	X ®	X ®
VA to be repeated with new refraction**	x								
OCT –macular thickness protocol	x		x	x	x	x	x	x	x
Repeat OCT- macular thickness protocol					x			x	x
Retinal colour photographs: 3fields*	x				x			x	x
Mask Compliance		x	x	x	x	x	x	x	x
Adverse Events Form		x	x	x	x	x	x	x	x
#Randomisation form	x								
Withdrawal Form									x
Assessor outcome guess								x	x
Additional tests for Mechanistic evaluation (n=30)									
Microperimetry	x				x				
Multifocal ERG	x				x				
Oximetry	x				x				

* Colour photographs and OCT should also be done before commencing on first laser or anti-VEGF therapy. These tests may be repeated at investigator's discretion during the period of the study.

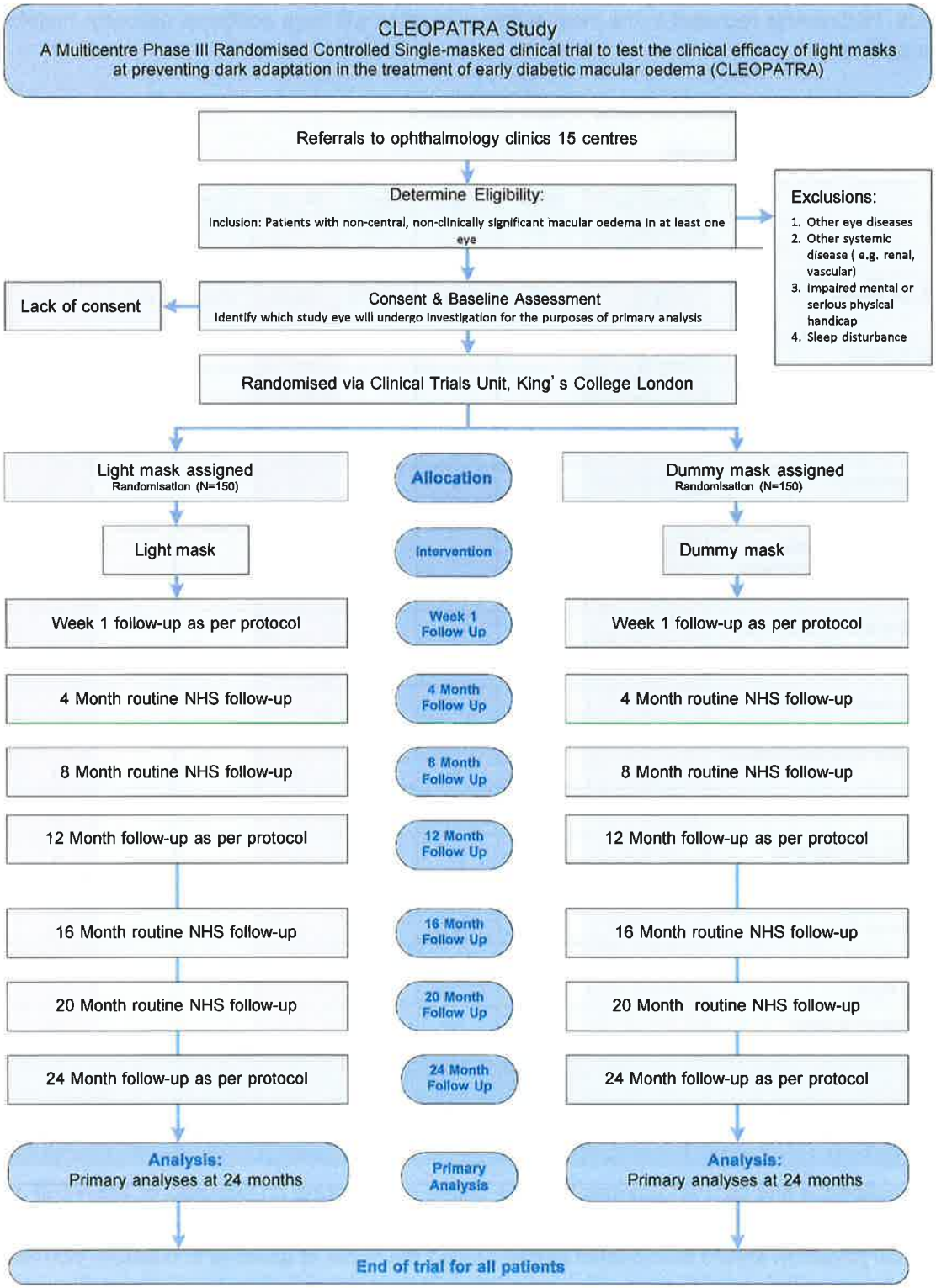
** VA with new refraction should be repeated before dilating the pupils at baseline to measure inter-test variability.

[+]Baseline tests that include mechanistic tests may be done over 8 days.

[#] Last procedure before patient is issued with a mask.

^ Week one visit can be either in person at the recruiting site or via the telephone. If on the telephone, Pittsburg Insomnia Rating Score and Epworth Sleepiness Scale will need to be provided to the patient at screening to be completed at home and returned to the recruiting site in a prepaid envelope.

5.5 Trial Flow Diagram



6. Trial Intervention

6.1 Description of the light and dummy masks

The light mask is manufactured by PolyPhotonix Medical Ltd. The light mask is a device designed to deliver a precise photo-therapy to a user's retina through closed eyelids. The light mask comes in two parts, a fabric mask and a light emitting unit, or "Pod". When worn, the Pod is inserted into the fabric mask and placed over the patients eyes and attached using an adjustable Velcro strap. The Pod contains two Organic Light Emitting Diodes (OLEDs), which will be located over the eyes of the patent when the light mask is being worn.

The fabric mask is made of nylon, polyurethane and polyester. These materials are non-toxic and are commonly used in a wide variety of skin-contacting apparel. The Pod is made from medical grade LDPE which has been tested and passed the relevant physiochemical and in vivo biological reactivity tests required for the U.S.P.<88> Class VI requirements. The Pod and fabric mask have been designed to be thin and flexible and contoured to compliment the face and improve comfort for the wearer.

The OLEDs are powered by two 3V (CR2450) batteries which power the device without the need for an external power source or recharging. At the end of the mask's lifetime a replacement light mask is required. A new fabric mask will be provided with each mask to minimise contamination resulting from continued use.

The mask is time, date and touch sensitive. The mask will only "work" between pre-determined operational windows – typically 8pm to 8am during the lifetime of the light mask. Within these times the mask can be activated by a light touch. If worn within three minutes of activation, sensors on the Pod will keep the mask illuminated for the night's therapy. The times for which the mask is worn will be logged for compliance analysis.

The light mask has CE certification and its design and manufacture meet the standards of ISO13485.

Supplier of the light masks and dummy masks:
Polyphotonix Medical Ltd. Petec Netpark Sedgfield TS21 3FG

6.1.1 Previous studies

The design must permit the mask to be worn by people with different head shapes and deliver rod excitation efficiently. The spectral output is important and should be matched as closely as possible to the response spectrum of the rod cells. This has been tested in 2 clinical trials. The first was a proof of concept study, in which 12 patients slept in a mask containing a chemoluminescent source which exposed one eye only to light. The trial lasted 3 months. All found the masks comfortable and the method of treatment acceptable. There were no reports of adverse effects. Measurements of colour contrast sensitivity and examination of standard fundus photographs showed that in the 10 for whom complete records were available, colour vision improved and the area of retina covered by microaneurysms and small dot haemorrhages decreased. These results were significant (p=0.01) even though the trial was very short and the numbers treated were so few (24).

A second study was carried out by the chief investigator of this grant at King's College Hospital using electronic sources of light - blue-green light emitting diodes (LEDs) to illuminate one eye. The electrical power of the system was < 3 mW. 40 patients were recruited and follow-up visits were at 3 and 6 months. All patients had early DMO. A total of 34 out of 40 patients completed the study. Twenty-eight study eyes showed intraretinal cysts compared with nine in the fellow eyes. At 6 months, only 19 study eyes had cysts while cysts were seen in 20 fellow eyes. The zone of maximum thickness showed a reduction of retinal thickness by 12μm (95%CI 20 to −7, P=0.01). The secondary outcomes of change in visual acuity, achromatic contrast sensitivity, and microperimetric thresholds improved significantly in study eyes and deteriorated in fellow eyes (25).

6.2 Dosing Regimen

The patients will wear the light mask each night, receiving a maximum of 8 hours therapy per night. The optical output of the mask has been tuned to optimise scotopic intensity while minimising photopic intensity. The masks regulate the light output to a constant luminosity x, 60cd/m² ≤ x ≤ 100 cd/m², well below toxic levels of luminosity but of sufficient scotopic intensity to prevent dark adaption. Emission below 470nm is less than 3% of total output posing little or no risk of harm.

6.3 Regulatory status

CE certification as a class 2a medical device has been granted.

6.4 Subject Compliance.

Every mask is capable of recording precisely when and for how long it has been used thus providing a very accurate measure of compliance. Each mask will have a predetermined lifetime and will need returning and replacing when this time expires. On the return of each mask the compliance data can be downloaded and analysed. If patient compliance is deemed to be low (below 70% of the maximum therapeutic dose) the patient will receive phone reminders and/or counselling.

6.5 Concomitant therapy

All concomitant and current and past therapies in the last 12 months will be recorded at screening. Any change in concomitant medications will be recorded at each visit.

6.5.1 Laser photocoagulation

Laser photocoagulation is indicated for clinically significant macular oedema if:

1. The investigator decides that the oedema has deteriorated to require laser after considering the risks and benefits of laser therapy. Laser therapy should be arranged to be done at the same visit or deferred to the next visit. Laser treatment should be avoided between study visits unless a detrimental effect is anticipated if laser is deferred to the next visit. A colour photograph and OCT should be done before laser treatment at any visit.
2. Regardless of laser treatment, the participant will continue to wear the mask until end of study.

3. Repeat laser treatment may be done at any scheduled visit but the interval between two laser treatment sessions should be not less than 4 months apart.

6.5.2 Intravitreal anti-VEGF or steroid therapy

The first line of treatment of centre-involving DMO of more than 400µm is anti-VEGF therapy in participants and treatment may be offered as per current standard of care. Intravitreal steroids may also be given to these individuals as per investigator discretion but the masks should be worn until end of study.

6.5.3 Treatment of fellow eye

The fellow eye should be treated according to standard of care and this may include laser photocoagulation, intravitreal anti-VEGF therapy or steroids.

6.5.4 Pan-retinal photocoagulation in either eye

Pan-retinal photocoagulation to either eye is permitted if high-risk retinal or disc neovascularisation is observed in any visit. The patient should then be seen at two weekly intervals until sufficient pan retinal photocoagulation is applied. The participants will continue to use the masks until end of study.

6.5.5. Change in control of diabetes

Changes in medications related to diabetes will be recorded within concomitant medications. An extra HbA1c test should be done at the next scheduled visit.

6.5.6. Cataract surgery

Cataract surgery should be avolided during the period of the study and will be recorded as a protocol deviation if the surgery is deemed necessary and performed during the study period.

7. Selection and Withdrawal of Subjects

7.1 Inclusion Criteria

1. Subjects of either sex aged 18 years or over
2. Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present:
    a. Current regular use of insulin for the treatment of diabetes
    b. Current regular use of oral anti-hyperglycaemic agents for the treatment of diabetes
    c. Documented diabetes by ADA and/or WHO criteria
3. Best corrected visual acuity in the study eye better than 55 ETDRS letters (Snellen VA 6/24).
4. On clinical exam, retinal thickening due to early DMO not involving the central 1000µm of the macula characterised by presence of microaneurysm, exudates or oedema and OCT evidence of increased retinal thickness in at least 1 non-central ETDRS zone of ≥320µm.
5. Previous macular laser, intravitreal steroids or anti-VEGF treatment is permitted provided the last treatment was done at least 4 months before date of recruitment.

6. Media clarity, pupillary dilation and subject cooperation sufficient for adequate fundus photographs.
7. Ability to return for study visits
8. Ability to give informed consent throughout the duration of the study

7.2 Exclusion Criteria

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

1. Clinical evidence of centre involving macular oedema (central subfield on OCT>300µm).
2. Macular oedema is considered to be due to a cause other than DMO.
3. An ocular condition is present (other than diabetes) that, in the opinion of the investigator, might affect macular oedema or alter visual acuity during the course of the study (e.g. vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma, Irvine-Gass syndrome, etc).
4. History of treatment for DMO at any time in the past 4 months (such as focal/grid macular photocoagulation, intravitreal or peribulbar corticosteroids, anti-VEGF drugs, or any other treatment) in the study eye
5. History of pan-retinal scatter photocoagulation in the study eye.
6. Active proliferative diabetic retinopathy in the study eye.
7. A condition that, in the opinion of the investigator, would preclude participation in the study.
8. Corneal scarring, vitreous opacities, severe asteroid hyalosis that would inhibit proper visualisation, inability to be positioned in front of the OCT device, inability to understand the requirements of the imaging, and nystagmus.

II. Patients with active insomnia or any other relevant sleep disturbances.

7.3 Selection of Participants

Patients may be identified from Diabetic retinopathy screening programmes and medical retina clinics of the trial sites and its satellite clinics. In addition, patients may be referred by other medical retina Consultants from other hospitals to the Principal Investigators.

Recruitment Strategy

	Method of approach	Ways in which patients can respond, in order to request more info, or arrange screening, or decline	Where there is no patient response to the approach after 14 days, contact with
Approach through medical retina clinics at participating sites	In clinic with Patient Information Sheet (PIS), via invitation letter (if eligible patients noted in clinic registers or databases) or via study poster in waiting room or reception area	By phone	Reminder letter or telephone
Approach through named Patient Identification Centre (PIC)	In clinic with PIS, via invitation letter (if eligible patients noted in clinic registers or databases) or via study poster in waiting room or reception area	By phone to the PIC, with request to forward contact details to the trial site	Reminder letter sent by (PIC)
Approach through any UK diabetic retinopathy screening programme	Generally in clinic without PIS, via invitation letter (if eligible patients noted in clinic registers or databases) or via study poster in waiting room or reception area	Generally patients will directly confirm their interest to be contacted by one of the trial sites, so that the screener/grader can then forward contact details to the nearest trial centre.	N/A

Table legend. PIS=Patient Information Sheet; N/A= Not applicable; PIC=Patient identification centres

Note: patients or doctors contacting one centre will be made aware of the closest centre to the patient's home address.

7.3.1 Pre-screening of patients

In order to prevent patients from being subjected to unnecessary trial procedures, it is recommended that potential participants have an OCT done before trial screening procedures are done to ensure exclusion of eyes with centre-involving macular oedema defined as central sub-field >300 µm.

7.3. 2 Re-screening of patients

Patients excluded from any of the following criteria may be screened two times (a total of three screens) at least 1 month apart.

1. Does not meet inclusion criteria of non-central retinal thickness >320μm with morphological evidence of oedema, microaneurysms or exudates.
2. History of any laser treatment done 4 months previously or anti-VEGF therapy done for DMO more than 2 months previously that has evidence of resolving central macular oedema.

7.4 Randomisation Procedure

A patient identification number (PIN) will be generated by registering the patient on the MACRO eCRF system (InferMed Macro), after consent has been signed. This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study. Randomisation will be via a bespoke web based randomisation system hosted at the King's CTU.

Authorised site staff will be allocated a username and password for the randomization system. Once a patient is consented, all baseline data collected and eligibility confirmed, the staff member will log into the randomization system (www.ctu.co.uk) and click 'randomisation – advanced' and select CLEOPATRA MINIMISATION and enter the patients details using the unique PIN. The 'help' section of the system has video demonstrations to aid new staff in using the system. Once randomized, the system automatically generates confirmation emails to key staff, with or without treatment allocation information, depending on their role in the study.

7.5 Withdrawal of Subjects

Visit windows of +/-10 days should ensure visit attendance; non-attendance for study visits will prompt follow-up by telephone. However, a delayed visit should be entered in the database. An appointment is only defined as missed if the delayed visit is within 10 days of the next pre-defined trial visit date.

Participants have the right to withdraw from the study at any time for any reason, and without giving a reason. The investigator also has the right to withdraw patients from the study mask in the event of inter-current illness, adverse events, serious adverse events, suspected unexpected serious adverse reactions, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from intervention only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from study mask will be asked to confirm whether they are still willing to provide the following:

- study specific data at follow-up month 12 and 24
- end of study data as per month 24, at the point of withdrawal
- questionnaire data collected as per routine clinical practice at annual follow up visits
- if participants agree to any of the above, they will be asked to complete a confirmation of withdrawal form to document their decision.

7.6 Expected Duration of Trial.

The expected clinical participation will be 24 months, starting from the day that the first participant gives informed consent to the end of the trial at the final visit of the last participant after 24 months.

The study period of the mechanistic evaluation will be 12 months.

8. Trial Procedures

8.1 Informed consent

We will design patient information leaflets containing this information and consent forms with service user involvement. We will supply individuals with as much information as they require to make an informed decision about participation in the study. They will be given as long as they wish to make a decision about their involvement and will be informed that any decision will not affect any on-going or future treatment within each Trust. A copy of the informed consent will be given to a prospective participant for review. The investigator will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason. They will be assured that confidentiality will be maintained at all times.

All participants will be required to read, sign, and date a consent form before participating in the study. All information about participants will be collected during the course of the study and will not be derived from existing databases.

8.2 Optical coherence tomography (OCT)

The primary outcome is change in the zone of maximal retinal thickness on OCT. OCT is a well-established tool used as an assessment and monitoring tool for DMO. The OCT thickness map is divided into 9 zones with the central zone representing the centremost area of the retina (the fovea). The DMO trials to date have used this central zone as the outcome measure because the trials are on centre involving DMO. However, in non-central DMO the central zone is not affected and disease progresses to the centre over time. Therefore, we have used the baseline zone of maximal retinal thickness as a measure. We will also, as a secondary outcome, measure the thickness of parafoveal zones (zone 2-5) and perifoveal zones (zone 6-9) and macular volume to provide further evidence about changes in other zones at 24 months or at the point of withdrawal. If both parafoveal and perifoveal thickening is present, it is categorised as parafoveal (zone 2-5). The OCT macular thickness protocol will be done twice at 12 and 24 months to assess test-retest variability.

8.3 Visual acuity tests

The visual acuity tests are done using the validated ETDRS vision charts using standard operating procedures for trials in DMO. Refracted visual acuity will be done at baseline and at the point of withdrawal. At baseline, following recording of refracted BCVA, the patient may complete another assessment that do not require pupil dilation and then return to repeat visual acuity recording with the new refraction to ensure that we account for inter-test variability. Please note that refraction does not need to be repeated the second time. The optometrists and OCT technicians will be masked of the treatment arm. At baseline, the

optometrist should not have the recorded visual acuity from the first BCVA test when conducting the second test. The second test may also be done by another visual acuity assessor.

8.4 Retinal colour photographs

Retinal colour photographs will be done at baseline, 12 and 24 months or at the point of withdrawal to explore progression of diabetic retinopathy. The photographs will be read by masked graders at the Independent Reading Centre in Moorfields Eye Hospital.

8.5 Sleep and insomnia rating scales

We have additional tests to explore sleep disturbance in this study. We will be using the validated Pittsburgh Insomnia Score Index questionnaire to assess insomnia (26). Daytime sleepiness is measured by Epworth Sleepiness Scale, which is another validated self-administered questionnaire (27). Both questionnaires will be administered at baseline, week 1, 12 and 24 months or at the point of withdrawal.

8.6 Mechanistic tests

30 participants who are selected for the mechanistic evaluation will undergo further tests in the baseline visit. Oximetry, multifocal ERG and scotopic microperimetry will be done at baseline while breathing either air or oxygen through a face mask. The test will begin 10 seconds after the gas flows and continue for the length of the test. The tests will be repeated at 12 months. Half the patients will have used the light masks, and the other half would have used the dummy masks. The BP and IOP will also be measured in these visits. A within-visit flexibility of 14 days is allowed for these patients to complete all the tests in these visits.

8.7 Laboratory tests

Laboratory test for HbA1C for all participants will be done at the local labs at each site. HbA1C results from within 3 months of the visit date will be also accepted.

9. Assessment of Efficacy

9.1 Primary Efficacy Parameters

Primary efficacy measure is the difference between arms in the change from baseline in absolute thickness at the zone of maximum thickness as determined by OCT at 24 months.

9.2 Secondary Efficacy Parameters at 12 and 24 months

I. Difference between arms in the change from baseline in absolute thickness at the zone of maximum thickness as determined by OCT at 12 months.

II. Other measures include:

1. Difference between arms in the change in retinal thickness in the 9 ETDRS zones (parafoveal zones 2-5 and perifoveal zones 6-9) and macular volume.
2. Difference between arm in morphological characteristics of macular thickness
3. Difference between arms in the mean change in visual acuity.
4. Difference between arms in the proportion of centre-involving macular oedema within 24 months.
5. Difference between arms in the time to occurrence of centre-involving macular oedema.
6. Difference between arms in the proportion requiring macular laser or antiVEGF treatment.
7. Difference between arms in the proportion of participants that show progression of retinopathy as measured by the ETDRS severity levels and microaneurysm turnover.
8. Compliance rates in the light mask arm.

9.3 Assessment of Safety Parameters

1. Difference between arms in the measures of sleep disturbance in terms of daytime sleepiness and insomnia.
2. Difference between arms in ocular and systemic adverse events and serious adverse events.

9.4 Assessment of Mechanistic Parameters

1. Change in P1 and N1 amplitudes and peak time in multifocal ERG after supplemental oxygen
2. Change in retinal sensitivity in scotopic microperimetry after supplemental oxygen.
3. To determine differences in change in P1 and N1 amplitudes and peak time in multifocal ERG after light-masks and dummy masks at 12 months.
4. To determine differences in change in retinal sensitivity in scotopic microperimetry after light-masks and dummy masks at 12 months.
5. To correlate the changes induced by light-masks and oxygen supplementation on retinal sensitivity using oximetry.

10. Assessment of Safety

10.1 Specification, Timing and Recording of Safety Parameters.

All adverse events and side effects will be recorded in the electronic case report form (eCRF) throughout the study regardless of their severity or relation to study participation.

10.2 Procedures for Recording and Reporting Adverse Events

The masks are CE marked. The definitions below are for non-CE marked devices but may be useful to classify the adverse events in this study.

10.2.1 Adverse Event (AE):

Any untoward medical occurrence which does not necessarily have a causal relationship with the treatment. "Treatment" includes all investigational and non-investigational agents administered during the course of the study. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment.

10.2.2 Adverse Device Effect (ADE):

Any untoward or unintended responses to the Investigational Device - All AEs judged by either the reporting investigator or the sponsor as having a reasonable suspected causal relationship to the device (i.e. definitely, probably or possibly related) qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship.

10.2.3 Causality:

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. If any doubt about the causality exists, the investigator should inform the Chief Investigator. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA, main REC and other bodies will be informed of both points of view.

Relationship	**Description**
None	There is no evidence of any causal relationship to study treatment.
Remote	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.2.4 Serious Adverse event (SAE):

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing in patients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

10.2.5 Serious Adverse Device Effect (SADE):

An ADE that has resulted in any of the consequences characteristic of a SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune, is defined as SADE. Note: this definition includes incidents and near incidents.

10.2.6 Serious Procedure Related Adverse Event (SPRAE):

A SAE that occurs due to any procedure specific to the clinical investigation, including modification of the system, is defined as a SPRAE.

10.2. 7. Unexpected Serious Adverse Device Effect (USADE):

A SADE that is unexpected in nature is define as an Unexpected Serious Adverse Device Effect.

All adverse events and all serious adverse events will be recorded. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event recording/reporting should be directed to the Trial Manager in the first instance. The reporting procedures are as follows:

- Non-serious Adverse Events will be recorded on the study CRF. Severity of all AEs will be graded on a three-point scale of intensity (mild, moderate, severe):
    - **Mild**: Discomfort is noticed, but there is no disruption of normal daily activities.
    - **Moderate**: Discomfort is sufficient to reduce or affect normal daily activities
    - **Severe**: Discomfort is incapacitating, with inability to work or to perform normal daily activities.
- Relationship of an AE to treatment should be assessed by the investigator/delegate (must be a clinician) at site, Investigators will be responsible for managing all adverse reactions.
- Serious Adverse Event (SAE, including SADE): All SAEs, SADE, SPRAE & USADE shall be recorded and reported on the serious adverse event form to the Chief Investigator / delegate within 24 hours of learning of its occurrence. The initial report can be made by completing the serious adverse event form, and faxing to the King's CTU (**020 7848 5229**). A record of this notification (including date of notification) must be clearly documented to provide an audit trail. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up as soon as this becomes available.
- Relationship of the SAE to the treatment should be assessed by the investigator/delegate (must be a clinician). Treating clinicians will report SAE' s in both trial arms which will include the assessment of seriousness, and causality. Expectedness will be assessed by the CI once the report is faxed to KCTU.
- The Chief Investigator will report all USADEs to the relevant ethics committee within the required timeframe, with the support of the Kings CTU. The Sponsor and Polyphotonix (supplier of the masks) will also receive a copy.

- Onward reporting of all USADEs to the MHRA will be the responsibility of Polyphotonix.

The Chief Investigator will provide an annual report of all SAE (expected and unexpected) which will be distributed to the Sponsor, and the REC. The DMEC will be provided listings of all SAEs on an on-going basis.

10.3 Treatment Stopping Rules

The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring and Ethics Committee and/or Trial Steering Committee, Sponsor, or Research Ethics Committee concerned.

Following six months of recruitment, initial rates of recruitment will be used to project total recruitment to ensure sufficient participants to power the study. The Trial Steering Committee will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

11. Statistics

11.1 Sample Size

With 300 patients, we anticipate 240 to be followed up (20% dropout). This is sufficient to provide 90% power to detect a 15 μm in mean change of retinal thickness at the zone of maximal thickness between arms using a two sided analysis of covariance test, adjusting for baseline, at the 5% level of significance, assuming a standard deviation of 35.7 micrometres. The chosen detectable effect size (retinal thickness of 15μm) is both plausible, in terms of being consistent with a confidence interval estimate for this intervention in preceding research (Ruboxistaurin trial Protocol: B7A-MC-MBCU), and also minimally detectable in terms of being distinguishable from test-retest variation (25). Detectable effect sizes for secondary outcomes based on 240 followed up (for 90% power with 5% significance level) would be a between-arm difference in mean outcome of a size that is equivalent to 0.42 of a standard deviation.

We expect the DMEC would want to monitor study power and we would regularly provide information such as non-compliance, withdrawal, and variability of the primary outcome as increasing proportions of the participants pass each of the four-monthly measurement points. We will follow your recommendation and defer the monitoring of outcome variability within the six-monthly reports to the DMEC.

11.2 Randomisation

Randomisation will be via a bespoke web based randomisation system hosted at the King's CTU. Patients will be randomised at the level of the individual, using the method of minimisation incorporating a random element. The minimisation factors will be HbA1C (<7.999% (63.89 mmol/mol or below) or ≥ 8% (69.90 mmol/mol or above)), perifoveal verus parafoveal and study site. If both parafoveal and perifoveal co-exist, it will be categorised as parafoveal.

Patients may only be randomised into the study by an authorised member of staff at the study research site, as detailed on the Delegation Log. Patients may only be randomised into the study once.

11.3 Blinding

Control patients will be provided with identical dummy masks, with no active light. Primary outcome assessors (optometrists and OCT technicians) will remain masked to treatment allocation. The optometrists are the visual acuity examiners and OCT technicians do the OCT scans at all visits and both will be masked to the participant study arm. The visual acuity examiners will receive the participants into the visual acuity lanes with a visual acuity case report form, study number and detail of study eye and non-study eye to be refracted, but with no previous subject records or case report forms by which the subject treatment arm could be identified. Similarly, the OCT technicians will receive the subjects into the OCT room on a specific CRF that provides details of subject study number and eye to be examined. The subjects will be advised at enrolment that they must not discuss the study arm they are in with the OCT or Visual Acuity examiner. The retinal photographs will be graded by masked graders in the independent Reading Centre at Moorfields Eye Hospital. This will avoid performance and detection bias. We will describe the completeness of outcome data for each outcome, including reasons for attrition and exclusions from the analysis.

11.4 Analysis

The primary outcome will be analysed using a two-sided test from a linear mixed effects model for repeated measures across visits, which will enable a comparison between participants receiving light-masks (active arm) and dummy masks (control arm), with covariates for each follow-up visit of baseline, randomisation stratifiers and arm, and with a random participant effect at each visit with unstructured covariance matrix. The primary time point will be 24 months. The 20% allowance for dropout (trial withdrawal) is based on 18% early non-compliance observed in the pilot study and we would expect a reasonable proportion of non-compliers to provide primary timepoint and intermediate visit outcome information for thisanalysis.

We expect the DMEC would want to monitor study power and we would regularly provide information such as non-compliance, withdrawal, and variability of the primary outcome as increasing proportions of the participants pass each of the four-monthly measurement points.

The detailed statistical analysis plan will include an additional sensitivity analysis involving all randomised participants (Intention to Treat Strategy) examining the influence on the primary outcome analysis of opposing optimistic and pessimistic scenarios assumed for the intervention effect in those withdrawing in each arm.

We will adopt the CACE analysis to estimate efficacy in completers (under a missing at random assumption) as recommended and outlined by Dunn et al. (Estimating psychological treatment effects from a randomised controlled trial with both non- compliance and loss to follow-up. Br J Psychiatry. 2003;183:323-331).

Linear mixed effects models for repeated measures (as specified above for the primary outcome), Logistic regression, and stratified Cox regression will also be undertaken to analyse secondary and mechanistic outcomes of continuous, binary and time to occurrence type respectively. Differences will be considered significant at $P<0.05$. Differences between the groups will be estimated with 95% confidence intervals. Repeated measures analyses (linear mixed effects models) will be used to document trends over time.

Sub-group analysis will be conducted for baseline HbA1C strata (<8 or ≥ 8) and location of increased (≥320μm) baseline retinal thickness (in parafoveal zone 2-5, or in perifoveal zone 6-9 alone).

12. Trial Steering Committee

The key purpose of the TSC will be to ensure the overall integrity of the study by monitoring its progress; investigating any serious adverse events; and taking account of regular reports from the DMEC and Trial

Management group. Ultimate responsibility for any decision required on the trial's continuation will lie with the TSC. The Committee will consist of an independent Chair and at least 2 other members. The TSC membership will be approved by the Sponsor, and will reflect all relevant disciplines. TSC meetings will be attended by the Chief Investigator, Mr Philip Hykin as co-lead, KCTU Operational Director, Trial Statistician and Trial Manager (secretary to the TSC). A NIHR MR C EME representative and Moorfields Eye Hospital representative (Sponsor) will be invited.

Trial Steering Committee (TSC):	
Chair:	Dr Gillian Hood - NE London Diabetes Research Network Manager Barts Health NHS Trust Queen Mary, University of London QM Innovation Centre, Room G2, 5 Walden Street London E1 2EF Tel 0207 882 8610 Fax 0207 882 7210 e-mail: Gillian.Hood@bartshealth.nhs.uk
Members:	Prof David Crabb – Professor of Statistics, City University London, London Prof Graham Hitman - Professor of Molecular Medicine and Diabetes, Barts and The London School of Medicine and Dentistry Mr. Alaistair Denniston, Ophthalmologist, Queen Elizabeth Hospital, Birmingham Rev Douglas Lewin- Lay Member Professor Ian Grierson BSc PhD FIBiol Cbiol FRCPath, Professor of Ophthalmology Royal Liverpool University Hospital, Liverpool and Vision and Science advisor to Polyphotonix (non-voting member)

Trial Management Group (TMG)	
Members:	Sobha Sivaprasad Philip Hykin Toby Prevost Caroline Murphy Joanna Kelly Trial Manager TBA

13. Data Monitoring and Ethic Committee

An independent data monitoring and ethics committee (DMEC) has been appointed. It will consist of two physicians not connected to the study and one independent statistician and will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints. The DMEC and trial statisticians will have access to unblinded study data. The committee will meet at least three times, at the start, middle and completion of the study.

Data Monitoring and Ethics Committee (DMEC)
Chairman of DMC

Sarah Walker - Senior Statistician, NIHR Oxford Biomedical Research Centre (OxBRC), Medical Research Council Clinical Trials Unit (MRC CTU), London
t: 020 7670 4726 f: 020 7670 4949 e: asw@ctu.mrc.ac.uk

Members

Mr Debandra Sahu, Consultant Ophthalmic Surgeon, Southampton General Hospital

Prof Jackie Sturt, Professor of Behavioural Medicine in Nursing, King's College London

14. Monitoring

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

Site monitoring will include:

- All original consent forms will be reviewed as part of the study site file. The presence of a copy in the patient hospital notes will be confirmed for 10% of participants
- All original consent forms will be compared against the study participant identification list
- All reported serious adverse events will be verified against treatment notes/medical records (source data verification)
- The presence of essential documents in the investigator site file and study files will be checked
- Source data verification of primary endpoint data and eligibility data for 10% of participants entered in the study

Central monitoring will include:

- All applications for study authorisations and submissions of progress/safety reports will be reviewed for accuracy and completeness, prior to submission
- All documentation essential for study initiation will be reviewed prior to site authorisation

All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

The study may be subject to inspection and audit by Moorfields Eye Hospital NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit study-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents. The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients" case sheets, blood test reports, OCT, colour retinal photographs reports, etc.).

15. Ethics & Regulatory Approvals

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

This protocol and related documents will be submitted for review to the National Research Ethics Service Committee London – Dulwich. Local approval will be sought before recruitment may commence at the site. The Study Coordination Centre will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Prior to any study procedures information sheets will be provided to all eligible subjects and written informed consent obtained. This study will not enrol subjects who cannot consent for themselves.

The Chief Investigator will submit a final report at conclusion of the trial to the Sponsor and the REC within the timelines defined in the Regulations.

General

The main ethical issues in relation to this study are the use of the light-masks. There are 3 visits that the participants need to undergo in excess of standard of care. Standard care of laser or anti-VEGF injections will be given to all those who require it. The precise risks and benefits of participating in the study will be outlined in patient information sheets, to be formulated with service user involvement.

Mechanistic evaluation

The patients that participate in the mechanistic tests have to undergo Oximetry, a non-invasive test and there are no known risks for multifocal ERG and microperimetry,

On-going treatment if the study is successful

Participants can be made aware of the results of the study if they wish. However, this will only be once all participants have completed the trial and the data has been analysed. If the study successfully establishes efficacy, the patients will be informed that these masks can be purchased but will not automatically be available in the NHS, though the treatment will be submitted for NICE approval.

16. Quality Assurance

The study will be managed through the King's Clinical Trials Unit (CTU). The Trial Management Group (TMG) will include: the Chief Investigator, Operational Director, Trial Manager, Data Management Strategic Lead and other members of the trial team when applicable.

Kings CTU will provide day-to-day support for the site and provide training through Investigator meetings, site initiation visit and routine monitoring visits.

The Principal Investigator will be responsible for the day-to-day study conduct at site.

Quality control will be maintained through adherence to CTU SOPs, Study SOPs, study protocol, the principles of GCP, research governance and clinical trial regulations.

17. Data Handling

The Chief Investigator will act as custodian for the trial data. Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. No identifiable patient data will leave the study site. The study will comply with the Data Protection Act, 1998. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access. Any breach of confidentiality will be minimised by adherence to the European Data Protection Act, with reassurance stated on the consent form to minimise any potential distress.

Data collection

Each participant will be assigned a sequential identification number via the InferMed MACRO web based data entry system. This number, rather than the participant's name, will be used to collect, store and report participant information.

18. Data Management

Data management will be consistent with MRC Guidelines for Good Clinical Practice in Clinical Trials and the Data Protection Act. Centre PIs will ensure that all personnel are familiar and comply with these guidelines. Data management procedures for the trial will be developed and overseen by King's CTU.

18.1 eCRF

All baseline and follow-up data will be entered on the online InferMed MACRO electronic data capture (EDC) system (http://www.infermed.com). This system is regulatory compliant (GCP and the EC Clinical Trial Directive). An eCRF using the MACRO EDC will be programmed by the CTU in collaboration with the Trial Manager, and Trial Statistician and hosted on a dedicated secure server within KCL. The eCRF system will have full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting. The CTU will provide training, essential documentation, and user support to the study centres, and on-site audit and monitoring. A detailed Standard Operating Procedure will cover data recording, online entry, checking, central backup and storage. A regularly updated coding manual will be developed to accompany the study database. Each research worker and centre PI will have a unique username and password provided by the CTU for the eCRF. The Trial Manager will provide usernames and passwords to any new researchers. Only those authorised by the Trial Manager will be able to use the system.

18.2 Data collection and recording

Baseline data will be collected and entered by researchers in each study site prior to randomization. Each participant will be assigned a unique trial ID number at the start of the assessment process. This number will be written on all clinical assessment forms, datasheets and databases used to record participant data. Trial data will be first entered on to paper source datasheets provided to each centre during the preparation

phase. We will endeavour to minimise the use of paper at all times. The datasheets will be immediately checked for completeness and accuracy. If data queries arise, these will be logged and followed up locally before data are entered online. A hard copy of a record sheet linking patient identity, contact details and trial ID number for all participants will be kept at each site. This will be placed securely in a locked filing cabinet separate from datasheets. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act and archived locally according to clinical trial GCP regulations and the host institutions additional procedures.

18.3 Quality assurance

The study incorporates a range of data management quality assurance functions. As the data are entered online, the Data Manager will log any queries generated and feed these back to the centre research workers in a timely manner. Maintaining a single point of contact between each centre and the CTU, the Trial Manager will conduct regular monitoring visits at each centre, checking 10% of entered data for consistency with the written data worksheet. Any necessary alterations to entered data will be indicated clearly with an audit trail from the original point of data entry, to ensure that any such amendments, and the reasons for them, can be inspected and tracked.

18.4 Database lock

After written recording, each research worker will transcribe data onto the eCRF within one working week of a participant assessment. After completion of all follow-ups and prompt entry of data, the Trial Manager will review the data and issue queries. The research worker must then answer these queries before the participants data is "frozen" within the database. After that time, changes will not be made to the database by the centres unless specifically requested by the Study Office in response to statistician data checks. At the end of the trial, the centre PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with a CD-ROM containing the eCRF data for their centre. This will be filed locally for any future regulatory or internal audit.

19. Publication Policy

The data will be the property of the Chief Investigator. Publication will be the responsibility of the Chief Investigator.

It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report.

Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results.

20. Insurance / Indemnity

NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the study for potential liability in respect of negligent harm arising from the conduct of the study. Moorfields Eye

Hospital NHS Foundation Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS. This is a non-commercial study and there are no arrangements for non-negligent compensation. MRC and NIHR Efficacy and Mechanism Evaluation Programme is funding the study.

21. Financial Aspects

MRC and NIHR Efficacy and Mechanism Evaluation Programme is funding the study.

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23. Signatures

Sobha

11-08-2014.

Chief Investigator, Miss Sobha Sivaprasad — Date

Print name

M Hassard

11.08.14.

Sponsor representative, Mrs Maria Hassard — Date

Print name M HASSARD.