EMERALD

Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesseLs in Diabetic retinopathy (EMERALD)

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PROTOCOL AUTHORISATION

Protocol Title	Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesseLs in Diabetic retinopathy
Protocol Acronym (if applicable)	EMERALD
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A review of the protocol has been completed and is understood and approved by the following:

		DD / MM / YYYY
Chief Investigator Name	Signature	Date

		DD / MM / YYYY
Statistician	Signature	Date

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LIST OF ABBREVIATIONS

Acronym	Full Wording
AE	Adverse Event
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
BHSCT	Belfast Health and Social Care Trust
CI	Chief Investigator
CI	Confidence Interval
CARF	Central Angiographic Resource Facility
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DM	Diabetes Mellitus
DMO	Diabetic Macular Oedema
DMP	Data Management Plan
DR	Diabetic Retinopathy
EQ-5D 5L	European Quality of Life 5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment
HES	Hospital Eye Services
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
NEI VFQ	National Eye Institute Visual Functioning Questionnaire
NHS	National Health Service
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute of Health Research
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PI	Principal Investigator
PRP	Pan Retinal Photocoagulation
PIS	Patient Information Sheet
QUALY	Quality-adjusted Life Year
QUB	The Queen's University Belfast
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Data Verification
SD-OCT	Spectral Domain Optical Coherence Tomography
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VEGF	Vascular Endothelial Growth Factor

1 STUDY SUMMARY

Protocol title	Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesseLs in Diabetic retinopathy (EMERALD)
Health condition(s) or problem(s) studied	Diabetic macular oedema (DMO) and proliferative diabetic retinopathy (PDR)
Study Design	Prospective, case-referent cross-sectional diagnostic study.
Study Aim and Objectives	**Aim** The aim of this study is to determine the diagnostic performance and cost-effectiveness of a new form of surveillance (ophthalmic grader pathway) for people with stable DMO and/or PDR, using the current standard of care as the reference standard. **Objective** The specific objectives of this study are to evaluate the new surveillance pathway in terms of: 1. Quantify and compare the diagnostic accuracy (in terms of sensitivity, specificity, overall agreement, positive and negative likelihood ratios) of the new pathway of surveillance (ophthalmic grader pathway) using the current standard of care pathway as the reference standard. This will be done separately for DMO and PDR. 2. Acceptability of the new surveillance pathway. 3. Proportion of patients requiring subsequent full clinical assessment by an ophthalmologist under the new pathway. 4. Proportion of patients unable to undergo imaging tests, with images of inadequate quality and indeterminate findings under the new pathway. 5. Relative cost-effectiveness of the new surveillance pathway.
Study Intervention	Multimodal retinal imaging with subsequent review of the images by trained ophthalmic graders (new pathway) will be compared with current standard of care (ophthalmologist examining patients in clinic with imaging tests used in current practice).
Primary Outcome	The primary outcome measure is: • Sensitivity of the new pathway (ophthalmic grader pathway) in detecting active DMO/PDR, using the standard care pathway as the reference standard.

Secondary Outcomes	There are a number of secondary outcomes which will be measured and include: • Specificity, concordance (agreement) between the new pathway (ophthalmic grader pathway) and the standard care pathway, positive and negative likelihood ratios • Cost-effectiveness • Acceptability • Proportion of patients requiring subsequent full clinical assessment • Proportion of patients unable to undergo imaging, with inadequate quality images or indeterminate findings.
Key Inclusion and Exclusion Criteria	**Inclusion Criteria** Adults (18 years of age or older) with type 1 or 2 diabetes with previously successfully treated DMO and/or PDR in one or both eyes and in whom, at the time of enrolment in the study, DMO and/or PDR may be active or inactive. Patients can only be recruited once to the EMERALD study. Active DMO will be defined as a central subfield retinal thickness (CRT) of $\geq$ 300 microns and/or presence of intraretinal/subretinal fluid on spectral domain OCT. 1. Inactive DMO will be defined as no intraretinal/subretinal fluid. 2. Active PDR will be defined by the presence of sub-hyaloid/vitreous haemorrhage and/or active new vessels (new vessels with lack of fibrosis on them) 3. Inactive PDR will be defined by the lack of preretinal/vitreous haemorrhage and lack of active new vessels. **Exclusion Criteria** 1. Unable to provide informed consent. 2. Patients who do not read, speak or understand English.
Countries of Recruitment	United Kingdom
Study Setting	Specialist Hospital Eye Services (HES) in the UK
Target Sample Size	416 patients
Study Duration	30 months

2 STUDY TEAM

Chief Investigator	**Noemi Lois** Professor of Ophthalmology The Wellcome-Wolfson Institute for Experimental Medicine, Queens University Belfast, 97 Lisburn Road, BT9 7BL
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For full details of co-applicants and co-investigators please request by email from: EMERALD@nictu.hscni.net

3 BACKGROUND AND RATIONALE

Diabetic Retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM) and a leading cause of visual loss among individuals of working age (1,2). Patients with DR may lose sight as a result of the development of diabetic macular oedema (DMO) and/or proliferative diabetic retinopathy (PDR), the major complications of DR. In the former, fluid accumulates in the central part of the retina, the macula, which is responsible for detailed central vision. In the latter, abnormal new blood vessels ("new vessels") grow on the optic nerve head or on the surface of the retina and towards the inside of the eye (the vitreous cavity) leading to sight loss from haemorrhaging or/and traction on the retina with subsequent retinal detachment. Due to the increasing numbers of people with DM, principally the type 2 form of disease as a result of the increased overweight and obesity of the population, it is expected that the burden of DR will continue to rise. Indeed, it has been estimated that the worldwide prevalence of DR will increase from 126.6 million in 2010 to 191 million by 2030 (3).

The prevalence of DMO in England was estimated to be 7% of the total diabetic population in 2010 (4). A very similar estimate of the prevalence of DMO was found in a recently conducted individual participant data meta-analysis which included 22,896 individuals from 35 studies conducted in Asia, Australia, Europe, and US, which provided an overall age-standardised prevalence of DMO of 6.8% (5). Based on this published prevalence of DMO and considering the prevalence of DM in the UK (6) it can be conservatively estimated that there are 220,000 people in the UK affected by DMO. In the UK, patients with DMO are treated with focal or grid macular laser [when the central retinal thickness, measured by means of optical coherence tomography (OCT), is less than 400 microns], which is delivered in a single session, or with injections into the eye of antivascular endothelial growth factor (anti-VEGF) drugs, currently in the National Health Service (NHS) ranibizumab (Lucentis) and aflibercept (Eylea) [when the central retinal thickness measured by OCT is 400 microns or more] (6-9). Intraocular steroids are also available for those patients that do not respond to the above therapies and are pseudophakic (i.e. have had their cataracts removed) (6-9). Once treated, long-term follow-up is required, to determine whether DMO recurs. Typically patients are followed every three to four months following laser treatment for DMO or monthly initially and then every 1-3 months thereafter following treatment with anti-VEGFs (ranibizumab or aflibercept). Follow-up continues for the rest of the patient's life.

The estimated prevalence of PDR in the individual participant data meta-analysis referred to above (5) was 6.96%. Based on this and considering the prevalence of DM in the UK, 212,000 people in the UK may have PDR. Patients with PDR are treated with panretinal laser photocoagulation (PRP), which is delivered most often in two to three sessions. Once treatment is completed, patients are followed at 4-6 month intervals for their lifetime to determine whether reactivation occurs, as new vessels in PDR could come back. Indeed, a recent study showed that a high proportion of patients with diabetic retinopathy followed in Hospital Eye Services (HES) have treated and inactive PDR (10).

Currently in the NHS ophthalmologists with expertise in retinal diseases assess patients during follow up visits. At each visit, patients with DMO are evaluated with a visual acuity test, most often undertaken by a nurse; optical coherence tomography (OCT), obtained by a photographer and interpreted by the ophthalmologist, and slit-lamp biomicroscopy,

undertaken by an ophthalmologist. The ophthalmologist determines whether DMO is present based on the information obtained from all these tests. Optical coherence tomography is a non-invasive, user-friendly and safe imaging technique that obtains scans of the back of the eye. Optical coherence tomography allows measurement of the central retinal thickness (which is often increased when DMO is present) and visualising fluid in the retina which is the hallmark of DMO). Optical coherence tomography has been extensively used in clinical trials and clinical practice to determine the presence of DMO, select treatment, and monitor the response to treatment (11-17).

In the follow-up of patients with PDR ophthalmologists typically examine the patient by slit-lamp biomicroscopy. Photographs are not routinely obtained to determine whether active PDR is present and to monitor these patients. Standard cameras are not able to image the whole retina with a single picture; thus, several sequential images are needed to comprehensively capture the appearance of the centre, superior and inferior parts of the retina. In recent years new “wide-angle” imaging has become available, allowing imaging of greater extensions of the retina with a single image. This technology may be preferable for patients and may reduce the time required to obtain images of the whole retina.

3.1 Rationale for the Study

Given the high number of people with DMO and PDR, the need for patients to be seen at short follow-up intervals, the need for frequent treatments and the requirement for long-term follow-up, there is a very large workload in Hospital Eye Services related to DMO/PDR which is making it difficult for the NHS to cope with the demand, in particular, due to shortage of ophthalmologists. This is only expected to get worse given the increasing prevalence of DM. Identifying new ways of increasing the NHS capacity and efficiency without compromising the quality of care would greatly benefit the NHS.

The purpose of this study is to determine whether successfully treated patients with DMO and PDR could be followed up without a face-to-face examination by an ophthalmologist. EMERALD will evaluate a new care pathway which will include multimodal retinal imaging and separate image assessment by trained ophthalmic graders. This new pathway will be compared to the current standard care pathway: for DMO: ophthalmologist evaluating patients in clinic by slit-lamp biomicroscopy and with access to OCT images; for PDR ophthalmologists evaluating patients in clinic by slit-lamp biomicroscopy. EMERALD will compare how accurate the new pathway is at determining which patients have active or inactive disease. The costs and acceptability of current and new models of care will also be compared.

4 STUDY AIM AND OBJECTIVES

4.1 Research Hypothesis

The hypothesis is that the new form of surveillance for people with stable DMO and/or PDR will be as sensitive as the current standard of care but at a lower cost.

4.2 Study Aim

EMERALD aims to determine the diagnostic performance and cost-effectiveness of a new form of surveillance for people with stable DMO and/or PDR, using the current standard of care as the reference standard.

4.3 Study Objectives

The specific objectives of this study are to evaluate the new surveillance pathway to:

1. Quantify and compare the diagnostic accuracy (in terms of sensitivity, specificity, overall agreement, positive and negative likelihood ratios) of the new pathway of surveillance (ophthalmic grader pathway) using the current standard of care pathway as the reference standard. This will be done separately for DMO and PDR.
2. Assess acceptability of the new surveillance pathway.
3. Determine the proportion of patients requiring subsequent full clinical assessment by an ophthalmologist under the new pathway.
4. Determine the proportion of patients unable to undergo imaging tests, with images of inadequate quality and indeterminate findings under the new pathway.
5. Establish relative cost-effectiveness of the new surveillance pathway.

5 OUTCOME MEASURES

5.1 Primary Outcome

The primary outcome measure is:

- Sensitivity of the new pathway (ophthalmic grader pathway) in detecting active DMO/PDR, using the standard care pathway as the reference standard.

5.2 Secondary Outcomes

There are a number of secondary outcomes which will be measured and include:

- Specificity, concordance (agreement) between new pathway (ophthalmic grader pathway) and the standard care pathway, positive and negative likelihood ratios
- Cost-effectiveness
- Acceptability
- Proportion of patients requiring subsequent full clinical assessment
- Proportions of patients unable to undergo imaging, with inadequate quality images or indeterminate findings.

6 STUDY DESIGN

6.1 Study Design

EMERALD is a prospective, cross-sectional diagnostic study of patients with diabetic retinopathy and DMO or PDR (or both) who had been previously successfully treated and who, at the time of enrolment in the study, may have active or inactive disease (both are required to evaluate the diagnostic performance of the new pathway).

Specifically, EMERALD will have a case-referent cross-sectional diagnostic study design with both sampling (selection) of patients and data collection carried out prospectively (18). This approach provides both a cost-efficient study design while also having a low risk of bias in terms of diagnostic accuracy (19)

6.2 Study Setting

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

6.3 Study Schematic Diagram

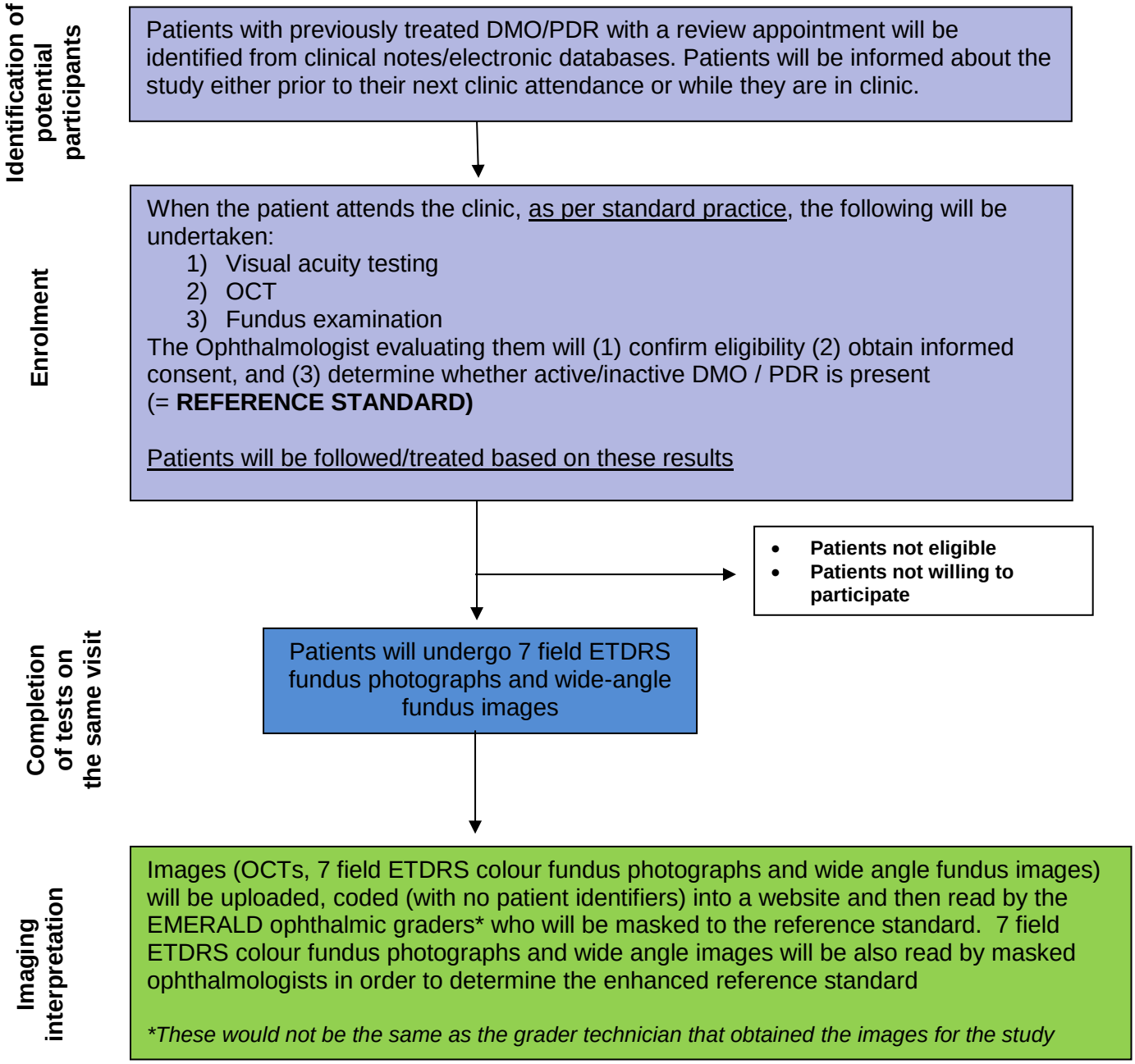

Figure 1: Study Flowchart

6.4 End of Study

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

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

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

7 PATIENT ELIGIBILITY

7.1 Eligibility Criteria

Patients will be screened for eligibility based on the inclusion and exclusion criteria outlined below. Eligibility will be confirmed by an ophthalmologist and documented on the eligibility checklist form.

7.2 Inclusion Criteria:

1. Adults (18 years of age or older) with type 1 or 2 diabetes with previously successfully treated DMO and/or PDR in one or both eyes and in whom, at the time of enrolment in the study, DMO and/or PDR may be active or inactive. Patients can only be recruited once to the EMERALD study.

Active DMO will be defined as a central subfield retinal thickness (CRT) of $\geq$ 300 microns and/or presence of intraretinal/subretinal fluid on spectral domain OCT.

Inactive DMO will be defined as no intraretinal/subretinal fluid.

Active PDR will be defined by the presence of sub-hyaloid/vitreous haemorrhage and/or active new vessels (new vessels with lack of fibrosis on them)

Inactive PDR will be defined by the lack of preretinal/vitreous haemorrhage and lack of active new vessels.

7.3 Exclusion Criteria

1. Unable to provide informed consent

2. Patients who do not read, speak or understand English.

7.4 Co-enrolment Guidelines

Patients enrolled in observational studies are potential candidates for EMERALD. Whether or not patients enrolled in EMERALD are also involved in other observational studies is at the Principal Investigator's (PI) discretion and should be considered when the burden on patients is not expected to be onerous. Co-enrolment with other studies should be documented in the Case Report Form (CRF) and discussed with the study CI prior to recruitment.

8 PATIENT SCREENING, CONSENT AND RECRUITMENT

8.1 Screening Procedure

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

8.2 Informed Consent

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

Informed Consent Forms (ICF) approved by the REC will be provided by the NICTU. The PI or designee is responsible for ensuring that informed consent for trial participation is given by each patient prior to any trial procedure being performed. This requires that the ICF be signed and personally dated by the patient prior to any trial procedures being undertaken. If no consent is given, a patient cannot be recruited into the trial. Two copies of the ICF must be signed and personally dated by the patient and the individual taking consent. A copy of the signed ICF will be filed in the patient's medical records, whilst the originals will be retained by the patient and by the PI in the Investigator Site File (ISF).

Patients will be consented to take part in the EMERALD study. Additionally, a group of patients will be also consented to take part in the Focus Group Discussions (see Focus Groups section below).

8.3 Withdrawal of Consent

As the study involves no extra visits for the patients, with the exception of the participation by some in the focus group meetings (see below), and only two additional imaging modalities and questionnaires, it is not envisaged that patients will withdraw consent. If they were to withdraw consent once the images had been obtained and/or questionnaires been completed, then the images/questionnaires will not be used for the study. Withdrawal of consent will be recorded on the Case Report Form (CRF).

8.4 Recruitment

EMERALD aims to recruit a maximum of 416 patients with previously successfully treated and stabilised DMO and/or PDR in one or both eyes at the time of enrolment into the study.

- 104 in whom DMO is active
- 104 in whom DMO is inactive
  Total = 208 patients with DMO
- 104 in whom PDR is active
- 104 in whom PDR is inactive
  Total = 208 patients with PDR

8.4.1 Patient Recruitment

Potential patients will be identified through patient databases at each of the participating centres or through other sources (e.g. treatment books) or while in the clinic. The potential patients will then be approached either before they come for their routine clinical appointment, by phone or via an invitation letter, or at the time they are in clinic for a routine review appointment (see study flow chart above). It is possible that a small proportion of patients may come to casualty with active disease; in this case, patients may be identified there and arranged to be seen thereafter in clinic. These patients may be approached either at their casualty visit or when coming to the clinic for evaluation and/or treatment.

When approached by phone, the potential patients will be informed about the study before they come to their hospital appointment; if willingness to participate is demonstrated, a patient information leaflet will be sent to them prior to the clinical appointment. Then, at their clinical appointment and if agreeable to participate, informed consent will be obtained and the patient will be recruited in the study while in clinic. If they are approached by letter, a letter of invitation to participate in the study and a patient information leaflet will be provided to the potential patient prior to their clinical appointment. Then, as above, when the patient comes to their clinical appointment, if willing to participate, they will be consented and enrolled in the study. Under the above circumstances, potential patients will have a minimum of 24 hours to decide whether or not they wish to participate in the study.

Potential patients may be also identified and approached at the time they come to the clinic (for their routine appointment or in casualty). In this case, information about the study will be given there and then, including a patient information leaflet. Under these circumstances, patients will be asked whether they wish to have time to think about their participation in the study once information has been provided to them and once they have had time to ask questions about it. As from the patients perspective, EMERALD involves only the undertaking of two sets of additional images (7 field ETDRS and wide angle fundus images) to what is routinely undertaken in clinical practice, and filling in some questionnaires it is envisaged that patients will be able to determine, while in clinic, whether or not they wish to participate in the study and, if willing to be recruited on the same day, following informed consent, they will be recruited into the study.

Patients will be informed at the time they are in clinic about the possibility of participating in focus group discussions (see below). If willing to take part, informed consent will also be obtained for their participation in these focus groups.

The recruitment progress will be monitored by the Trial Management Group (TMG) and the EMERALD Trial Steering Committee (TSC).

8.4.2 Pilot Study

An internal pilot study to assess feasibility will be undertaken, which will run during the first months of the study and within the study. Recruitment feasibility milestones will be as follows.

- If recruitment rates achieve 75-100% recruitment during the pilot study, the study will progress
- If recruitment rates achieve 50-75% recruitment, the study will progress following review of screening logs and the protocol, if required, and after barriers to achieving adequate recruitment are addressed
- If recruitment rates achieve 25-50% of the required number, the trial will be progressed only after screening logs and the protocol are reviewed and following approval by

National Institute of Health Research (NIHR) Health Technology Assessment (HTA), additional sites will be opened
- If recruitment rates achieve <25%, it is not expected that the trial will progress. The decision to stop the trial will be a decision to be made by the TSC and the NIHR HTA

9 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

9.1 Evaluation of the New Clinical Pathway

In EMERALD a new clinical care pathway, the ophthalmic grader pathway, will be evaluated:

Ophthalmic Grader Pathway

Surveillance of patients with stable DMO and/or PDR by evaluation of their images by a trained ophthalmic grader. Images will include:

Spectral Domain Optical Coherence Tomography (SD-OCT)
AND
Early Treatment Diabetic Retinopathy Study (ETDRS) 7 field fundus photographs
AND
Wide angle fundus images

Figure 2: Graders Pathway Summary

If this new pathway were to be used in clinical practice, patients would undergo multimodal retinal imaging with subsequent review by trained ophthalmic graders. If active disease were to be detected or if the ophthalmic graders were uncertain, the patient would be referred to an ophthalmologist for assessment. If the patient were to be stable (i.e. inactive DMO/PDR) the patient would remain under this model of surveillance with a pre-determined interval.

For the purpose of the EMERALD study, all patients will undergo the standard care pathway, which is: 1) for DMO: ophthalmologist evaluating patients in clinic by slit-lamp biomicroscopy and with access to SD-OCT images which are routinely obtained; 2) for PDR: ophthalmologists evaluating patients in clinic by slit-lamp biomicroscopy (see Study Flowchart – section 6.3). Additional images will be obtained including 7-field ETDRS fundus photographs and wide-angle fundus images. These latter images and the SD-OCT will be then made accessible to and read by the trained ophthalmic graders and this would represent the ophthalmic grader pathway.

9.2 Selection of Ophthalmic Graders and Training

Currently in ophthalmic clinical practice ophthalmic photographers/imaging technicians (working at a band 6-7 level which often equates to > 5 years 'experience) obtain images and interpret them routinely, but make no decisions with regards to the care of patients. In ophthalmic services, there are also ophthalmic graders that have been trained to interpret findings on fundus images for the purpose of undertaking diabetic retinopathy screening.

For EMERALD the ophthalmic graders at each participating site will be selected as follows. First, local PIs would provide names of individuals they believe have experience obtaining

and/or grading images of patients with DMO and PDR; these individuals would be also confirming their interest and willingness to participate in EMERALD. It is possible that some of these ophthalmic graders selected for EMERALD will be already involved in the grading of images for Diabetic Eye Screening Programmes.

Graders identified by the PIs, as explained above, will be asked to fill out questionnaires detailing their experience imaging and/or grading DMO and PDR as well as their experience recognising features of DMO and PDR and whether they feel confident that they could identify DMO on SD-OCT images and new vessels on fundus images. Graders stating that they do not have experience imaging/grading DMO and PDR and/or those stating that they could not recognise features of DMO/PDR will not be invited to take part in EMERALD as graders.

In addition to the above, formal training will be provided to all EMERALD ophthalmic graders prior to the initiation of the study, as described in the EMERALD Study Manual. The training will be given during a training meeting in which the imaging features of active/inactive DMO/PDR will be reviewed and discussed and where extensive clinical examples will be presented.

Furthermore, to ensure that graders selected will be in a position to undertake the task of grading the images, all potential graders will be required to take a test involving reading images of OCT, wide angle fundus images and 7 fields ETDRS fundus images, just in the same way they will be asked to do for EMERALD. Only those graders who reach a pre-set percentage standard (minimum of 80% of correct answers to detect presence of DMO or active PDR, when present) will be invited to act as graders for the EMERALD study. Graders will be allowed to undergo further training and take the test a second time but if the minimum of correct answers (80% to detect presence of DMO or active PDR, when present) is not reached they will not be invited to be part of EMERALD as graders.

A web-based teaching module on DMO/PDR will be prepared so that EMERALD ophthalmic graders can access it to consolidate their knowledge. Clear guidelines on when patients would need to be referred for an assessment by an ophthalmologist will be also given.

9.3 Schedule of Assessments

All patients must be evaluated during the study according to the Schedule of Assessments:

Step 1
Written patient informed consent is obtained to participate in the EMERALD study (and for a group of patients consent will be also obtained to participate in the Focus Group Discussions, see below).

Step 2
The patients' information obtained during the standard care pathway will be recorded in the CRF including details on:

- Medical and ophthalmic history
- Visual Acuity*
- Whether there was active or inactive DMO **/ PDR
- Details on the presence/absence of active/inactive new vessels in the disc
- Details on the presence/absence of active/inactive new vessels elsewhere in the retina
- Details on the presence/absence of pre-retinal haemorrhage
- Details on the presence/absence of vitreous haemorrhage
- Information on the proposed plan for the patient (review/treatment)

**Visual acuity will be obtained following routine clinical practice at each of the participating centres.*
*** In all patients an SD-OCT is routinely undertaking to determine whether there is DMO present*

Step 3
Once the information obtained in the standard care pathway is completed, the patients will undergo the following imaging tests:

- ETDRS 7 field fundus photography**
- Wide angle fundus images**

And will fill-in the following questionnaires:

- EQ-5D 5L, NEI VFQ-25, VisQoL questionnaires

***7-field ETDRS and Wide-angle fundus images will be obtained following the SOP set in the EMERALD Study Manual.*

Step 4
Most patients will then continue their routine care as their participation would have ended.

A selection of patients will also take part in Focus Group Discussions; Consent for focus group participation will be sought from these patients at the clinical visit and they will then be contacted at a later date with details of a meeting.

Step 5
Fundus photographs, including 7 field ETDRS, wide angle images, and OCT scans will be anonymised and transferred to Queens' University Belfast (QUB) reading centre where they will be uploaded in an electronic website developed for the study. The reading centre will then create folders and make these anonymised images accessible to the EMERALD ophthalmic graders (and ophthalmologists determining the "enhanced reference standard" for PDR, see below).

Step 6
Images will be read by the trained ophthalmic graders, masked to findings and clinical decisions made during the standard clinical care pathway (reference standard) (and by the ophthalmologists determining the "enhanced reference standard" for PDR, see below).

Ophthalmic graders reading the images will not evaluate images of patients from their own institution to assure masking (see below). Once the images are read, the ophthalmic graders will determine:

- whether there is active DMO / PDR
- inactive DMO / PDR
- whether they are unsure as to whether or not DMO/PDR is active or inactive
- whether patient could continue review in the ophthalmic grader pathway
- whether the patient requires a full clinical assessment by an ophthalmologist and the reasons why:
    - Presence of active DMO/PDR
    - Unsure
    - Poor quality images (for instance due to media opacities)
    - Presence of other disease (for instance, if age-related macular degeneration, in addition to diabetic retinopathy is noted).

The Graders will record this information in the appropriate CRF.

To avoid potential bias, images (7 field ETDRS and wide angle fundus images as well as OCTs) will be read by the ophthalmic graders independently of one another and, as stated above, masked to the reference standard (see Section 9.5 'Masking').

9.4 Enhanced Reference Standard

The reference standard for PDR will be an ophthalmologist evaluating patients in clinic by slit-lamp biomicroscopy (i.e., standard care) and this will be used for the primary goal of the study (see statistical analysis section, below). The reference standard for PDR, however, could potentially be improved. There is a possibility that new vessels (indicative of PDR) may not always be seen by the ophthalmologist evaluating the patient by the slit-lamp biomicroscopy but could be detected in a fundus photograph. In order to determine the impact of this potential event EMERALD will also evaluate an alternative "enhanced" reference standard. This "enhanced" reference standard will consist of the ophthalmologist assessment (examination by slit-lamp biomicroscopy) supplemented by the evaluation of the fundus images (7 field ETDRS and wide angle fundus images) done by an ophthalmologist. This reading by the ophthalmologist of the fundus images will be done only after the slit-lamp biomicroscopy examination has taken place and the reference standard has been set, to assure it will not affect or influence the reference standard. If either, the slit-lamp biomicroscopy, the 7 field ETDRS fundus images or the wide angle fundus images detect active PDR, the patient will be considered to have "active" PDR under this "enhanced" reference standard. This information will be recorded in the appropriate CRF. This PDR status based upon the enhanced reference standard will be used in a sensitivity analysis of the new pathway's diagnostic accuracy (see statistical analysis section, below).

9.5 Masking

The ophthalmic grader interpreting patients' images will be masked to the reference standard. To assure masking, ophthalmic graders will not be interpreting images from patients recruited at their own centre and will not have access to the reference standard. Furthermore, they will not know from which patients 7 field ETDRS fundus images, wide angle fundus images or OCTs come from and will not read 7 field ETDRS and wide angle fundus images of the same patient, to assure that their reading of one imaging technology will not influence their reading of the other.

Ophthalmologists doing the standard of care evaluation will also be masked to the findings/decisions made by the ophthalmic graders (who will be reviewing the images at a later date). Ophthalmologists reading the fundus photographs (7 field ETDRS and wide angle fundus images) for the purpose of evaluating the alternative "enhanced" reference standard will also be masked in the same manner as the ophthalmic graders (they will not assess images obtained in their own centres, to ensure they are masked to the result of the reference standard and not influenced by it and will not be aware of the ophthalmic graders assessment, which will not be made accessible to them).

Patients will also be masked to findings/decisions made by the ophthalmic graders (these will not be available at the time of the study's clinical visit). Patients will not be masked to the decisions made in the standard of care pathway as these will guide their care. However, this should not introduce any bias as the photographer/imaging technicians obtaining the images will be different from the ophthalmic graders interpreting the images (i.e. the ophthalmic graders evaluating the images for the proposed new care pathway will be from a different institution than that where the patients will be evaluated).

9.6 Focus Group Discussions: Assessment of Acceptability of the New Care Pathway

The acceptability of the new pathway (ophthalmic graders pathway) will be evaluated through the undertaking of a qualitative assessment through focus group discussions. Patients' views on the acceptability of the proposed new clinical care pathway are essential if this new pathway were to be incorporated into clinical practice in NHS Trusts. Focus group discussions are particularly useful to help identify issues that resonate with lay people and the public at large in matters of health care and have been widely used in health services research. Indeed, some advocates have argued that focus groups discussions reach the parts that other methods cannot reach (20). Their use in this study will enable us to acquire data on a full range of issues – some of which are unlikely to have been anticipated by professionals.

The aim of the focus group is to access as broad a range of views and opinions on a given topic as possible; it is not to assess the distribution of opinions in the population neither to identify only widely held opinions. All views count. With that end in mind the sample frame is designed to include consenting participants drawn from different areas of the UK and from different age-groups. Each group will contain 5-8 participants and will meet on a site as close to the relevant clinic as possible. The group discussions will last for at least 1 hour and will be facilitated by a trained researcher. Discussions will be audio-recorded and later transcribed for analysis. Focus group members will be recruited from the sample of 416 participants to be recruited for the main study.

Appropriate information (verbal and written in the form of a patient information sheet) about these focus group discussions will be given to participants while in clinic or prior to their attendance at the clinic (see above section 8.4.1). If patients agree to take part, informed consent will be obtained. Patients will be consented to participate in the EMERALD main study but also, specifically, to be part of the focus group discussions.

Patients enrolled in EMERALD will be approached consecutively to take part also in these focus group discussions. Patients consented to take part will be approached at a later date via letter/phone call to inform them about the date/location/time of the focus group meeting. Once all patients required for the focus group discussions (see below) have been identified, recruitment for this part of the study will cease.

EMERALD will also examine the acceptability of the new pathway to health professionals. For this purpose, a small number of focus groups (n=4) will be conducted involving photographer/imaging technicians/graders and ophthalmologists (in separate groups). All will be recruited from staff at participating study sites.

The data from the focus groups will be analysed by the use of simple content analysis strategies. The focus of the analysis will be on 'acceptability' of the new alternative pathway and factors that might facilitate or impede such acceptability (21)

9.7 Adverse Events (AEs)

9.7.1 Assessment of safety

It is not expected that adverse events will occur as a result of the procedures undertaken during the routine clinical visit neither related to the procedures performed for the purpose of the study (additional 7 field ETDRS and wide angle imaging and questionnaire assessment). However, if an AE or SAE occurs during the EMERALD study visit, related or not to the study procedures but unrelated to underlying medical conditions, these will be recorded in the appropriate CRF. The NICTU will be responsible for informing the Sponsor and the Research Ethics Committee (REC) and all study sites about any SAEs.

9.7.2 Analysis of safety data
Adverse events (AEs, SAEs) will be listed and summarised.

9.7.3 Definition of Adverse Events
As the current study is not investigating medicinal products, adverse events reporting will follow the Health Research Authority guidelines on safety reporting in non Clinical Trial Investigational Medicinal Product (CTIMP) studies. The PI or designee will make an assessment of seriousness of the incident as per the definitions below:

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

A **Serious Adverse Event (SAE)** is defined as an untoward occurrence that:

A) Results in death;
B) Is life-threatening;
C) Requires hospitalisation* or prolongation of existing hospitalisation;
D) Results in persistent or significant disability or incapacity;
E) Consists of a congenital anomaly or birth defect; or
F) Is otherwise considered medically significant by the investigator.

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

9.7.4 Anticipated adverse events related to OCT, ETDRS and Wide Angle Imaging.
There are no anticipated adverse events as imaging of the retina has no known side effects.

9.7.5 Eliciting Adverse Event Information
The PI or designee will record all directly observed AEs and SAEs as well as those spontaneously reported by the participant that are not related to any underlying medical conditions. Mild blurriness or visual disturbance occurring immediately following imaging will not be considered to be an AE and will not be reported.

9.7.6 Recording and Reporting Adverse Events
All AEs not related to the patients' underlying medical conditions will be assessed for seriousness, expectedness and relatedness to the study procedures by the PI or designee and recorded in the CRF. AEs will be recorded in the participant's medical notes.

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

The CI or the Sponsor must report the SAE to REC within 15 days of the CI becoming aware of the SAE. An SAE occurring to a research participant will be reported to the main REC where in the opinion of the CI the event was:

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

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

9.7.8 Follow-up of Adverse Events

The AE reporting period for the trial begins upon enrolment of a participant into the trial and ends once the visit is completed. All AEs assessed by the PI or designee as being related and unexpected will be followed until they are resolved or considered to be stable. The CRF should be updated with the date and time of resolution or confirmation that the event is stable or if found to be due to the participant's known underlying illness.

9.7.9 Urgent Safety Measures

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

9.7.10 Progress Reports

A progress report will be submitted by Sponsor, Sponsor's legal representative or CI (must always be signed by the CI) to the REC annually beginning 12 months after the favourable ethical opinion. The annual progress reports are available from the HRA website http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/

9.7.11 Declaration of the Conclusion or Early Termination of the Research.

The Sponsor or CI must submit the end of study declaration form: http://www.hra.nhs.uk/resources/during-and-after-your-study/end-of-study-notification-studies-other-than-clinical-trials-of-investigational-medicinal-products/ to the REC within 90 days of conclusion of the study or within 15 days of early termination of the study.

9.7.12 Summary of Final Report

The Sponsor or CI must submit the summary of final report to REC within one year of conclusion of the research.

10 DATA COLLECTION AND DATA MANAGEMENT

10.1 Data Quality

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

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

On-site monitoring visits during the trial will check the accuracy of entries in the CRF's against the source documents, the adherence to the protocol, procedures and GCP, as outlined in the trial monitoring plan.

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

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

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

10.2 Data Collection

To ensure accurate, complete and reliable data are collected, the NICTU will provide training to site staff through investigator meetings and site initiation visits.

All data for an individual patient will be collected by the PI or designee and recorded in source documents and the CRF for the study. Patient identification on the CRF will be through their unique trial identifier, allocated at the time of recruitment. Data will be collected and recorded on the CRF and questionnaires by the PI or designee.

Case report forms and questionnaires are to be submitted to the NICTU as per the CRF submission schedule.

In addition to the data specified in the sections above, the following information will be obtained and recorded in the appropriate CRF:

1) The time required for a patient to complete the standard of care visit [time at which the patient is registered at the reception desk, time at which the patient is called for visual acuity assessment, time at which the patient is called to obtain the OCT images, time the patient spent with the ophthalmologist, and time at which patient would be leaving the department once being assessed by the Ophthalmologist. This information will be obtained in a representative group of patients until saturation is reached.

2) The time required to obtain the 7-field ETDRS fundus photographs and the wide angle fundus images, separately. This information will be obtained in a representative group of patients until saturation is reached

3) The time required by the EMERALD ophthalmic grader to interpret each of the images (OCT scans, 7-field ETDRS fundus photographs and wide angle fundus images) and to determine whether there is active/inactive DMO/PDR and the outcome of the visit (further review by graders or referral to ophthalmologist), as stated above.

4) The time required for the ophthalmologist to read the 7 field ETDRS and wide angle fundus images to determine the “enhanced reference standard” for PDR.

5) Scores obtained in the health related quality of life questionnaire (EQ-5D-5L) and visual function questionnaires (NEI VFQ-25 and Vis-QoL) filled in by participants and collected at the study visit, which will provide utility data for different health states.

6) Resource use data will be collected to explore the costs of delivering the standard care pathway and the new proposed ophthalmic grader pathway and to find the key cost drivers. This will mainly consist of staff costs. Costs of 7-field ETDRS fundus photography will be compared with those of wide angle imaging.

10.3 Data Management

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

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

Ophthalmic images will be anonymised and uploaded electronically at a specifically designed EMERALD imaging website. This website will be established at the QUB reading centre (CARF) where images will then be made accessible in specific folders to the ophthalmic graders and ophthalmologists, as stated above, using a username/password.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

The sample size was determined upon the basis of setting a target of the number of reactivated (active) DMO and PDR patients which would enable sensitivity to be tested against a pre-specified target level of 80% (22). This level was considered the minimum acceptable level for the new pathway (ophthalmic grader pathway) to be clinically viable. A lower specificity is considered acceptable and a target of 65% for specificity was used to confirm sufficiency of the sample size for assessing specificity. However, it should be noted that the actual specificity level which would be acceptable in practice is uncertain as in reality this would be driven by cost-effectiveness and resource availability considerations which may make a substantially lower specificity still viable, because it would still result in saving of ophthalmologist time. In such a scenario this calculation may be conservative. To be able to detect if the sensitivity of the new pathway (photographer/imaging technician pathway) with 80% and 90% power (10% and 12% higher than the 80% minimal target set) would require 89 participants with each DMO/ PDR who have reactivated (active DMO/PDR), with 2-sided 5% significance level (23). 93 participants who have not reactivated (inactive DMO/PDR) would enable a specificity 15% (10%) higher than the 65% target to be detected with 90% power. A 95% confidence interval for photographer sensitivity and specificity would have a confidence interval (Wilson method) with a width of 10-20% depending on the observed level (24). Allowing for 10% missing/indeterminate results, 104 individuals who have re-activated and 104 who have not, are required (208 for each, DMO and PDR) which leads to a need for a maximum of 416 participants in the study overall; some participants may have both existing DMO and PDR thus contributing to both the DMO and the PDR targets.

11.2 Data Analysis

Outcomes for the DMO and PDR patients will be assessed in two separate analyses. Participants will be categorised as having active/inactive DMO and/or active/inactive PDR according to the diagnosis established at the standard care pathway on the person level (i.e. using data from both eyes where appropriate). This reflects the consequences of the clinical decision. The diagnostic performance of the new pathway will be quantified and compared with the standard care pathway. Reflecting how the new pathway would function in practice,

an “unsure” classification or an “active” classification will both require an examination by an ophthalmologist. Sensitivity analyses will include assessment of the impact of the “unsure” test classification and of the ophthalmic grader‘s grade upon the diagnostic performance.

The impact of using wide angle imaging (OPTOS) instead of standard imaging (7 field ETDRS images) on the diagnostic performance of the new pathway will also be assessed under the principal analyses for PDR detection. In addition, for PDR, a sensitivity analysis will assess the diagnostic performance of the ophthalmic grader against the alternative “enhanced” reference standard (ophthalmologist slit-lamp biomicroscopy assessment supplemented by ophthalmologist evaluation of 7 field ETDRS / wide angle fundus images) to detect active PDR.

Sensitivity, specificity, positive and negative likelihood ratios will be calculated (with appropriate 95% confidence intervals (CIs) for the alternative strategy using the current standard of care pathway findings as the reference standard. Agreement (concordance) between the new pathway and current standard of care pathway will also be calculated (with 95% Wilson CI) (24). The difference in sensitivity and specificity between wide-angle and 7 field ETDRS fundus images assessed by the ophthalmic graders will be compared with corresponding 95% CIs produced using Newcombe’s method for paired data (25)

The proportion of patients requiring subsequent full clinical assessment or unable to undergo assessments, with inadequate quality images or indeterminate findings will be calculated for the alternative pathway with corresponding CIs. All analyses will be carried out using STATA 15 (26).

11.3 Cost Effectiveness Analysis

This analysis will need to take into account: 1) the sensitivity of the new pathway (ophthalmic grader pathway) for both DMO and PDR; 2) the specificity of the new pathway for DMO and PDR; 3) whether the new pathway detects any PDR missed by current standard of care and 4) the relative costs.

In the ophthalmic grader pathway, patients will be in one of four groups depending on the decisions made by these staff after reading of the images: 1) true negative – no treatment required and patients will return for follow-up at the usual interval; 2) true positive – referred for treatment as required; 3) false negative – patient who may come to harm by visual loss; 4) false positive – patient will be referred to the ophthalmologist but will not require treatment. These patients will not come to harm apart from possible anxiety and inconvenience, but will consume ophthalmologist time.

If the sensitivity and specificity of the new pathway were exactly the same as those of the standard care, there would be no QALY differences, though there might be some disutility from process changes, for example if one pathway caused more anxiety than the other. The key gain would be ophthalmologist time freed for other activities. The real benefits might be reduction in waiting times and earlier treatment of other patients leading to QALY gains for them. Such benefits would be difficult to estimate and the simplest measure would be ophthalmologist sessions or days released for other activities. However, we will identify ways in which time released would be used. An underlying assumption to be checked is that the cost of assessment by the ophthalmic graders is less than that of the ophthalmologist assessment. Both pathways would require nurse or optometrist time for checking visual acuity, as done in routine clinical practice. The costs of the image-based pathways will include both time for taking and reading the images, using both conventional and wide-angle cameras. If there was marginal loss in sensitivity from the new pathway the consequences could be visual loss before next visit was due, or detection at next visit (with or without visual loss occurring) followed by possibly later than optimal treatment. Both could have disutilities.

Note that assessment in clinical practice is repeated over time so lesions missed at one assessment might be picked up at the next. Given the cross-sectional design of EMERALD and the fact that all patients will undergo the standard care pathway, we will not be able to assess the disutility of any visual changes in patients recruited.

Modelling will use data from both this study (the EQ-5D 5L data for different states) and from published studies on progression, so analysis of the effect of a reduced sensitivity will include, for DMO and PDR separately: 1) The probability of progression before the next visit, 2) the probability that this would lead to irreversible visual loss and if so, how much; 3) if there was irreversible visual loss, the resulting disutility and hence the QALY loss.

Specificity would be the determining factor in savings in ophthalmologist time: the poorer the specificity the lower the savings. However even quite poor specificity (e.g. 50%) might be associated with useful savings in ophthalmologist time. In the PDR group, wide-angle fundus imaging will be compared both with standard care (reference standard: ophthalmologist evaluating patients by slit-lamp biomicroscopy) and with 7-field ETDRS fundus photographs to assess the cost-effectiveness of wide-angle imaging, which may require less time to take and to read the images. If there are differences amongst the assessment methods, a Markov model based cost-utility analysis will examine the cost-effectiveness of the potential surveillance pathways: standard care; ophthalmic grader's assessment of DMO based on OCT; ophthalmic grader's assessment of PDR using 7-field ETDRS fundus photographs; and ophthalmic grader's assessment of PDR using wide-angle fundus imaging. Costs and benefits will be discounted at 3.5%. NHS and personal social services perspective will be adopted. The model will be populated by cost, sensitivity and specificity data from the study and by estimates of progression, effectiveness of treatment (prompt and delayed), quality of life and future costs from published literature and expert opinion. Results will be expressed as cost per QALY gained. Appropriate sensitivity analyses will be conducted to assess the robustness of the results. Probabilistic sensitivity analyses will be undertaken to explore uncertainty in model parameters and to allow the presentation of cost-effectiveness acceptability curves.

12 METHODS: MONITORING

12.1 Data Monitoring and Data Access

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

12.2 Monitoring Arrangements

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

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

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

13 TRIAL COMMITTEES

13.1 Trial Management Arrangements

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

13.2 Trial Management Group (TMG)

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

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

13.3 Trial Steering Committee (TSC)

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

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

14 REGULATIONS, ETHICS AND GOVERNANCE

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

14.1 Sponsorship

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

14.2 Funding

Funding was obtained from the National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA). NETSCC ID: 15/42/08.

14.3 Indemnity

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

14.4 Contributorship

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

14.5 Competing Interests

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

14.6 Ethical Approvals

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

14.7 Good Clinical Practice

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

14.8 Protocol Compliance

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

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

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

(b) the scientific value of the trial

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

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

14.9 Protocol Amendments

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

14.10 Patient Confidentiality

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

14.11 Record Retention

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

15 DISSEMINATION/PUBLICATIONS

15.1 Study Publications

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

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

15.2 Authorship Policy

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

15.3 Trial Registration

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

15.4 Data Sharing Statement

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

15.5 Data Access

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

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