



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

Chief Investigator: Professor Noemi Lois
Northern Ireland Clinical Trials Unit (NICTU)

Study Design & Setting



- Prospective, case-referent cross-sectional diagnostic study
- Sponsor: Belfast Health & Social Care Trust
- Funder: National Institute for Health Research HTA Programme
- Target sample size of 416 patients
- 30 months duration

Study Sites



PI	Site
NORTHERN IRELAND	
Noemi Lois	Belfast Health and Social Care Trust
ENGLAND	
Clare Bailey	Bristol
Faruque Ghanchi	Bradford
Geeta Menon	Frimley Park
Peter Scanlon	Gloucestershire
Haralabos Eleftheriadis	Kings College
Konstantinos Balaskas	Manchester
Sobha Sivaprasad	Moorfields
Samia Fatum	Oxford
Nachi Acharya	Sheffield
David Steel	Sunderland
Ahmed Saad	South Tees
SCOTLAND	
Caroline Styles	Fife

Rationale



- High numbers of patients in the UK with DMO and PDR.
- Patients require long-term follow-up and frequent visits.
- Constant increase workload in Hospital Eye Services related to DMO/PDR, made worse by increasing number of people with diabetes.
- Shortage of ophthalmologists.



“Capacity” does not meet “demand”

Need to identify new avenues to increase the efficiency of the NHS without compromising quality of care.

Plan



- To determine whether patients previously successfully treated for DMO/PDR could be followed through a new care pathway that does not involve a face-to-face examination by an ophthalmologist.
- The new proposed care pathway includes multimodal retinal imaging and separate image assessment by trained ophthalmic graders.
- The 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.

Study Aim



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.

Outcome Measures



Primary Outcome Measures

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

Secondary Outcomes

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

Inclusion Criteria



Adults (18 years 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.

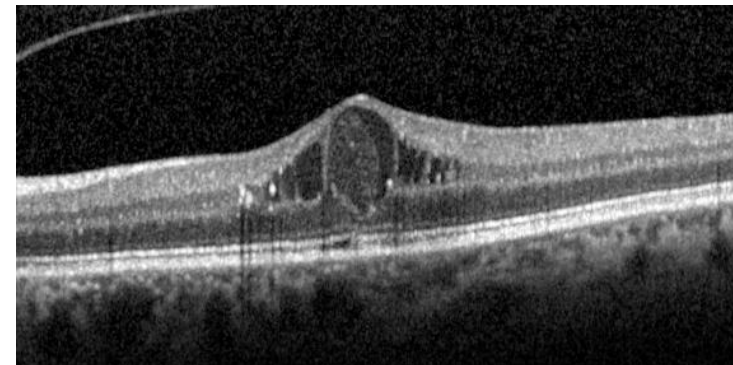
“Previously successfully treated” = in the past, had treatment and the disease became inactive not requiring any more treatment

Patient may enter the study with one eye or with both eyes


Inclusion Criteria



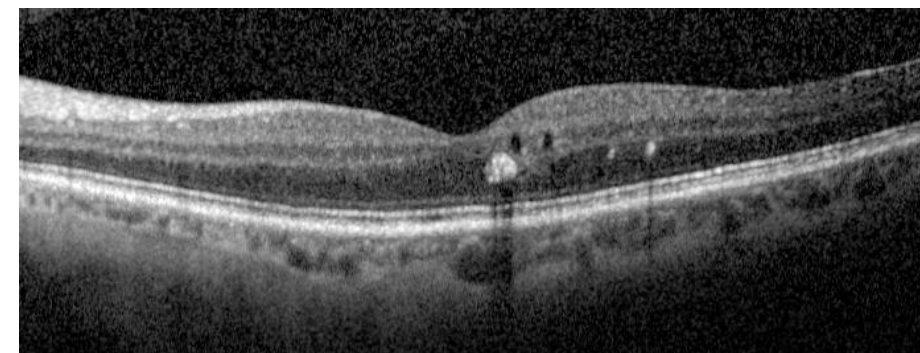
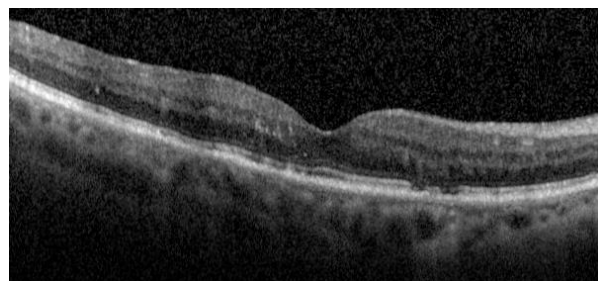
Active DMO is defined as a central subfield retinal thickness (CRT) of ≥ 300 microns due to DMO and/or presence of intraretinal/subretinal fluid due to DMO on spectral domain OCT.



Note: isolated or sparse small intraretinal cysts are not a criteria supporting active DMO if none of the criteria for active DMO defined above are met.

Inactive DMO (No DMO) 

Inactive DMO no intraretinal/subretinal fluid.



Exclusion Criteria



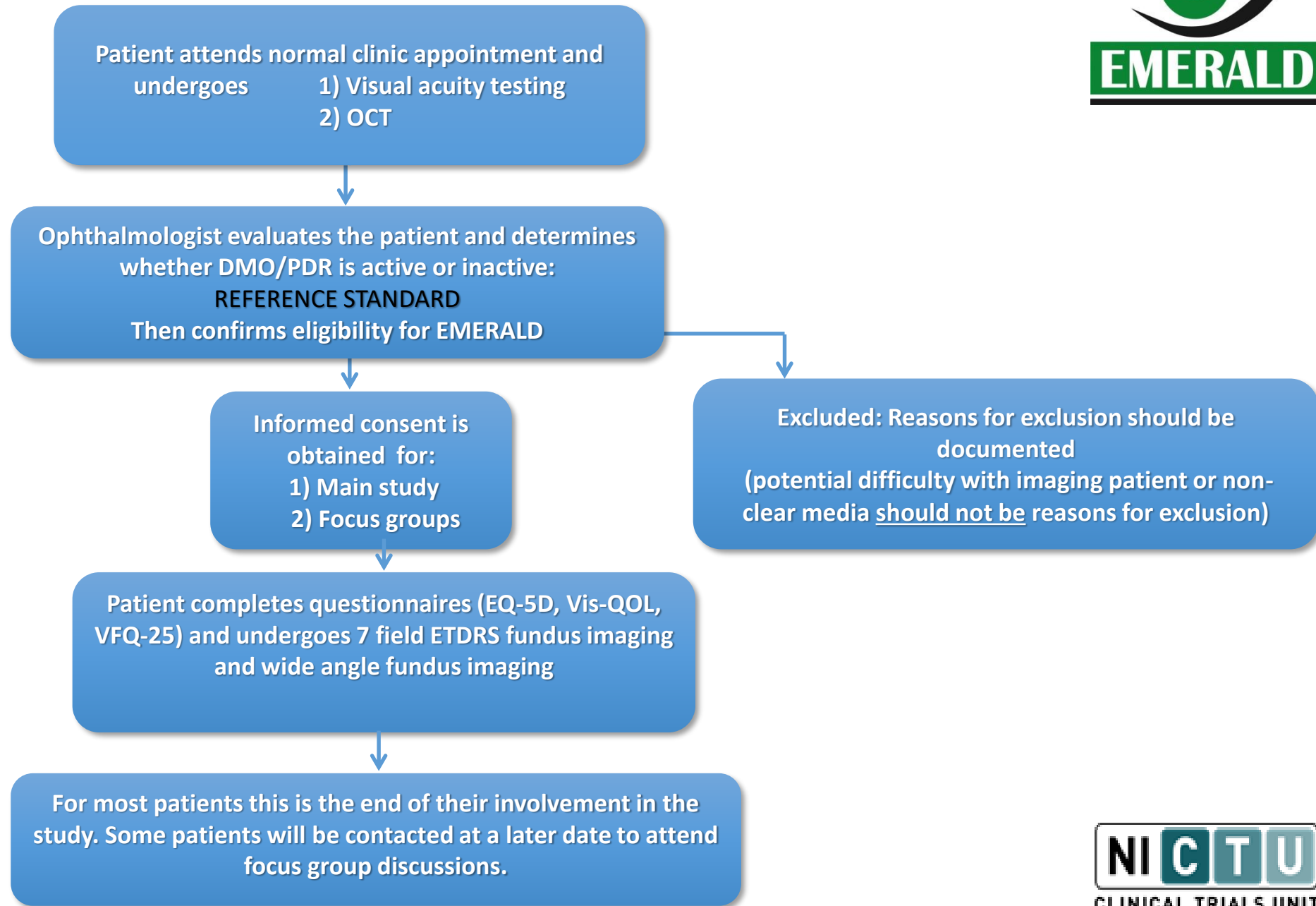
1. Unable to provide informed consent.
2. Unable to speak, read or understand English.

Co -Enrolment

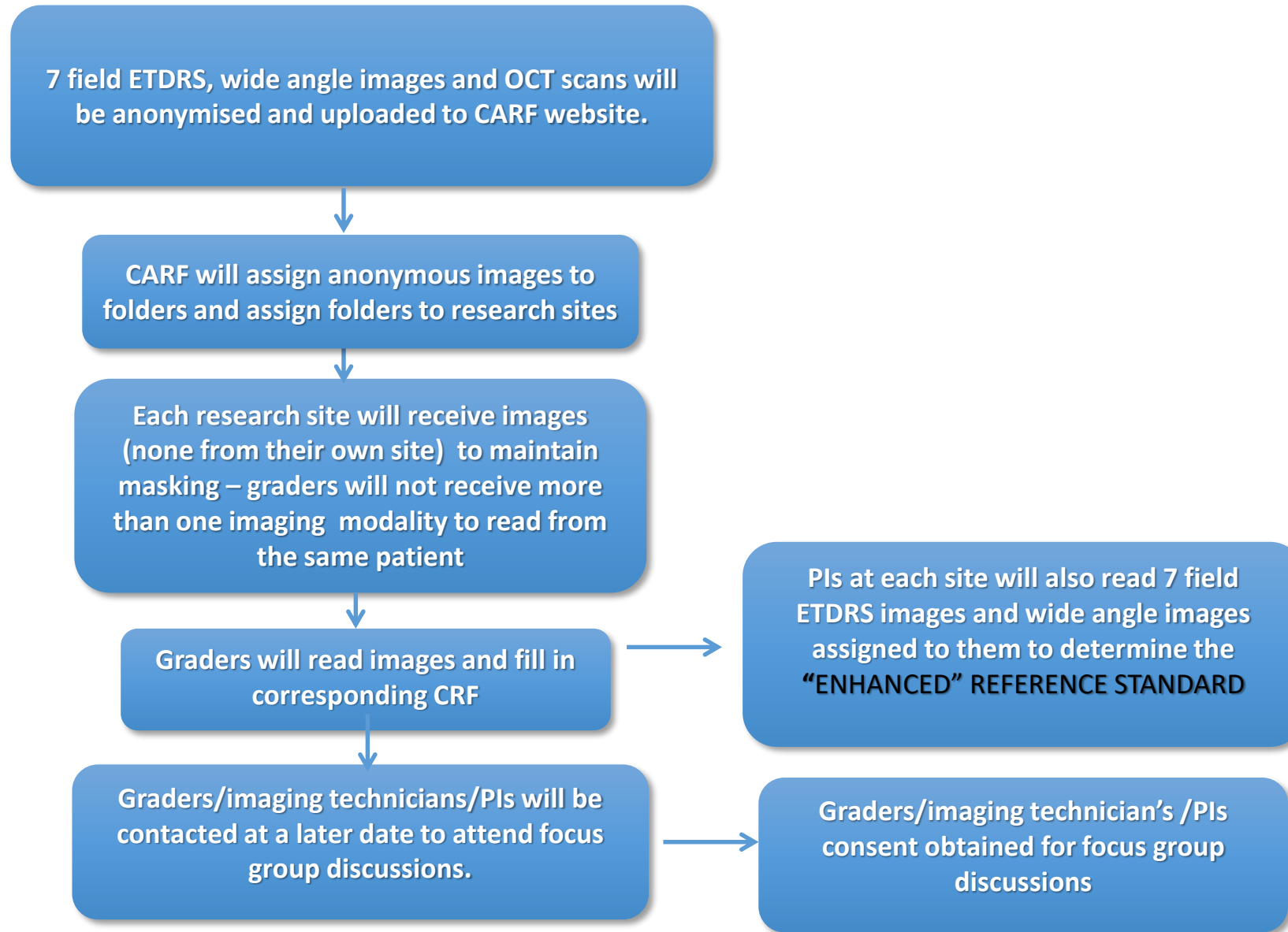


- Patients enrolled in observational studies are potential candidates for this trial.
- This is at the Principal Investigator's (PI) discretion and should be considered when the burden on participants is not expected to be onerous.
- Co-enrolment with other studies should be documented in the Case Report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

Study Flow Chart - Patients



Study Flow Chart – Grading



Enhanced Reference Standard



- Reference standard for PDR: Ophthalmologist evaluating patients in clinic by slit-lamp biomicroscopy (i.e., standard care) - Will be used for the main analysis.
- It is possible that new vessels may not be seen by the ophthalmologist evaluating the patient by the slit-lamp biomicroscopy but could be detected in a fundus photograph.
- To determine the impact of this potential event EMERALD will evaluate also an “enhanced” reference standard: Ophthalmologist assessment (examination by slit-lamp biomicroscopy) + evaluation of the fundus images (7 field ETDRS / wide angle fundus images) done by an ophthalmologist
- 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.
- PDR status based upon the enhanced reference standard will be used in a sensitivity analysis of the new pathway’s diagnostic accuracy.



OCT, ETDRS & Wide Angle Imaging and Grading Guideline

- Photographers and graders will be trained and must sign training log
- Training taking place at this investigator's meeting and can be supplemented on-line (EMERALD website)

Questionnaires



- 1) **NEI VFQ-25:** A vision specific patient reported quality of life tool containing 25 questions
- 2) **VisQol :** A vision specific patient reported quality of life tool containing 6 questions
- 3) **EQ-5D-5L:** A health related patient reported quality of life tool containing 5 questions to generate utility data

To be filled in by the patient at their appointment before (or after, if preferred) ETDRS 7 fields and Wide angle imaging.

Focus Groups - Assessment of the acceptability of the new care pathway

- Acceptability of the new pathway will be evaluated through the undertaking of a qualitative assessment through focus group discussions.
- If patients agree to take part, informed consent will be obtained at clinic visit.
- Patients will be contacted at a later date with a date and location of the focus group discussion meeting

IMPORTANT TO INFORM AND RECRUIT AS MANY PATIENTS ELIGIBLE FOR EMERALD AS POSSIBLE FOR THE FOCUS GROUP DISCUSSIONS TO ASSURE WE WILL REACH NUMBER OF PARTICIPANTS REQUIRED FOR THE FOCUS GROUPS



Focus Groups – Health Care Professionals

- EMERALD will also examine the acceptability of the new pathway to health professionals.
- A small number of focus groups (n=4) will be conducted involving photographer/imaging technicians/graders and ophthalmologists
- All will be recruited from staff at participating study sites.
- Informed consent required – To determine who can get informed consent from the PIs

Cost Effectiveness 2

Key diagnostic parameters

- Sensitivity – not missing disease that should be treated
- Specificity – avoiding false positives

Sensitivity takes priority

- Poor sensitivity could result in visual loss
- Poor specificity just means ophthalmologists see more patients
- But – a “poor” specificity may still result in significant savings in ophthalmologist time



Retinal Imaging

Steve Aldington

Retinal Research & Professional Development Manager

Gloucestershire Hospitals NHS Foundation Trust



Gloucestershire Retinal Research Group



Imaging / grading process overview



- We need three different types of images for all patients:
 - Spectralis OCT in one or both eyes depending on whether one or both eyes eligible:
Considered to be 'Standard Care'
 - Full-colour 7-field modified ETDRS non-stereo 35° to 40° in one or both eyes depending on whether one or both eyes eligible – study specific
 - Optos wide-angle 3-field in one or both eyes depending on whether one or both eyes eligible – study specific
- Images and scans to be captured only by staff authorised on the delegation log
- Images and scans uploaded to CARF Belfast for confirmation / anonymization
- CARF allocates each imaging modality for a patient to other clinical sites' reading lists
- Site grading staff will have one 'Reading List' assigned to them (OCT, 7F & 3F)
- Ophthalmologists will be grading 7F, 3F for the enhanced reference standard

7-field 'modified ETDRS'

We have provided two different field-layout diagrams:

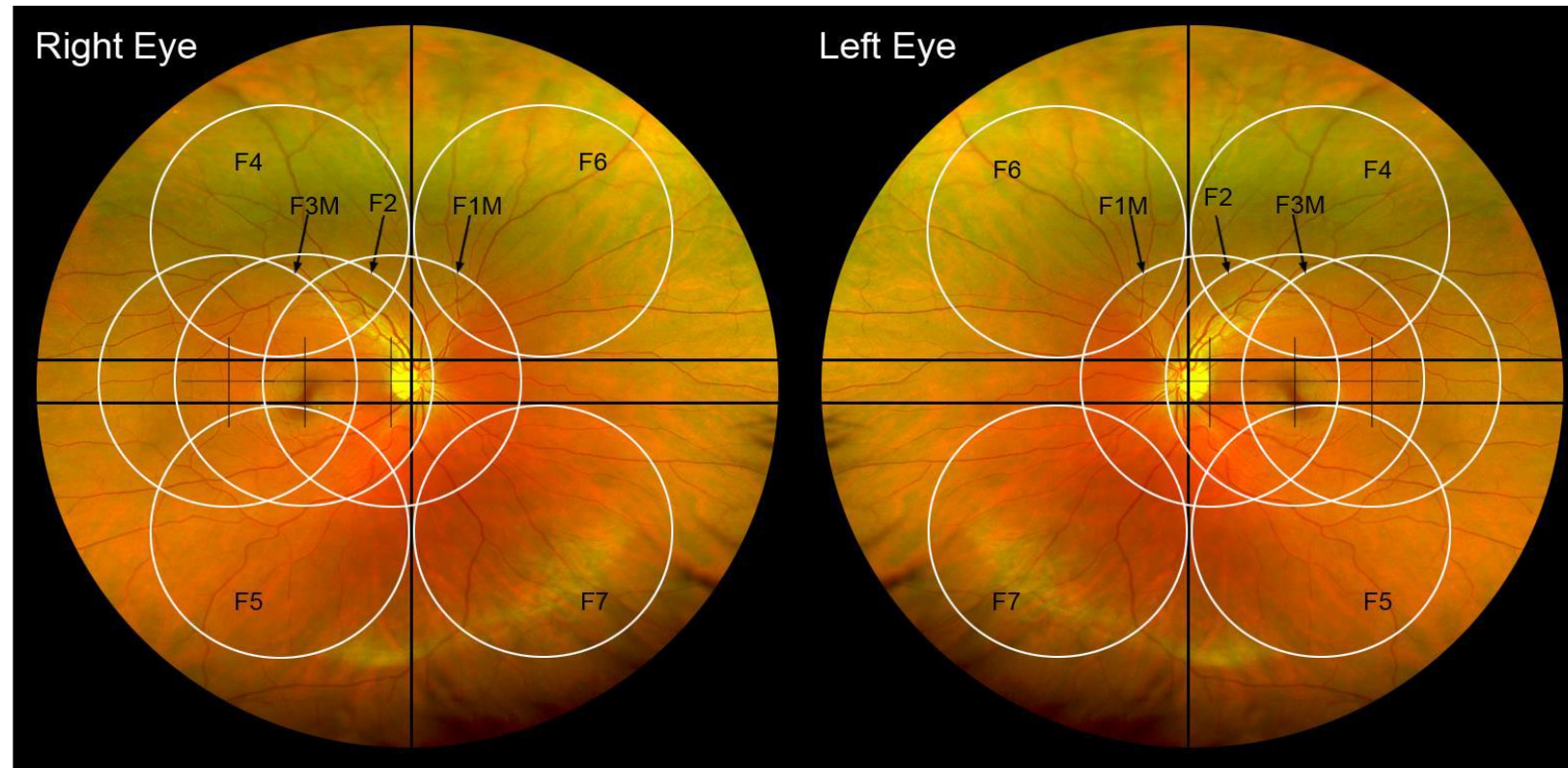
- On the 7F Grading form it shows for circular image Zeiss-type cameras
- In the 7F Imaging protocol it shows for cut-off images from Topcon-type cameras

Both versions are actually correct, to achieve about the same retinal coverage

To avoid any confusion, if you are using a camera producing:

- circular 35° or 40° images – position the optic disc OUTSIDE the field of view
- cut-off 35° or 40° images – position the optic disc just WITHIN the field of view

7-field 'modified ETDRS' – Zeiss etc.



These are the original circular image 'Modified ETDRS' positions.

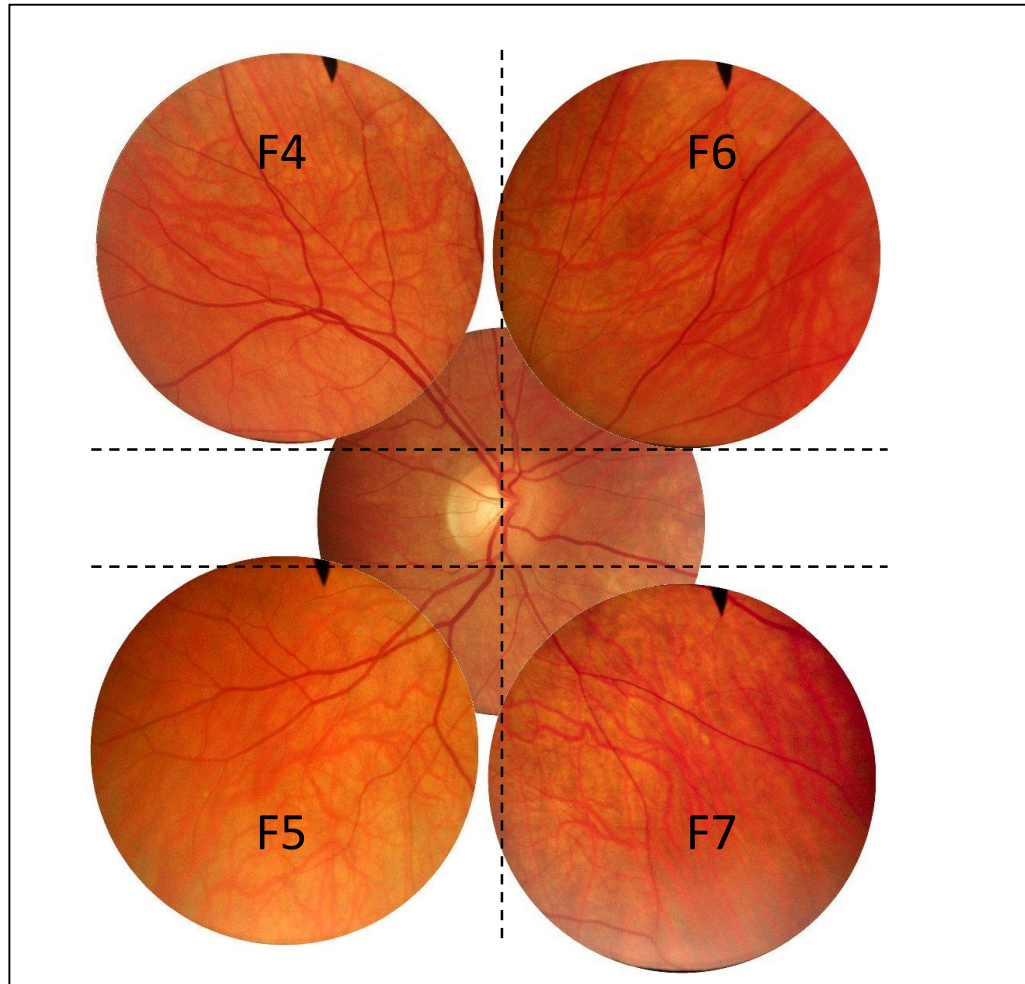
Optic disc would be 'below' F4 and F6 and 'above' F5 and F7 in viewfinder and final image

7-field 'modified ETDRS' – Zeiss etc.



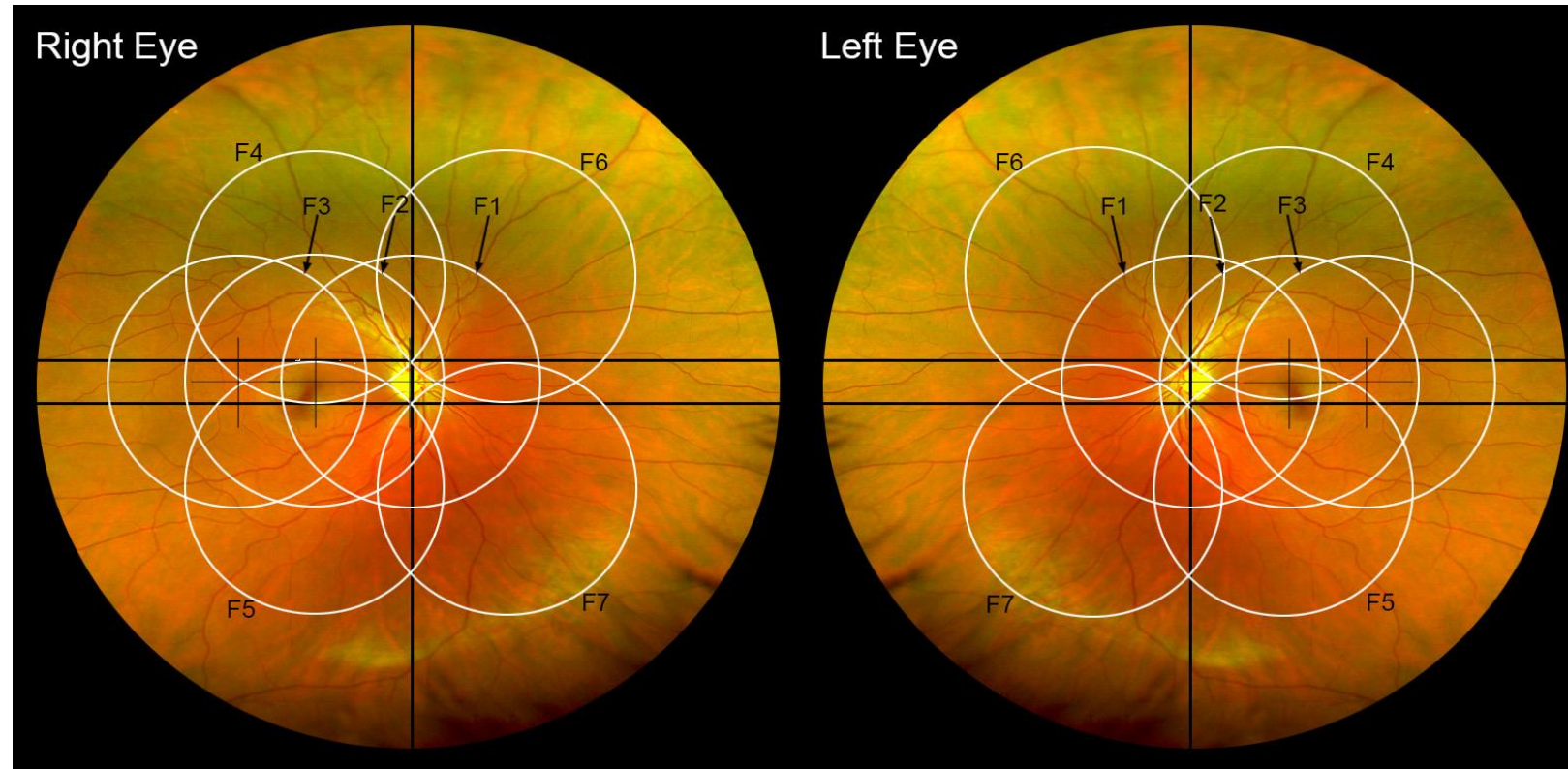
- F1 (disc-centred) – disc in the centre of field of view
- F2 (fovea-centred) – actually position the fovea about $\frac{1}{8}$ to $\frac{1}{4}$ DD temporally
- F3 (temporal) – position the fovea $\frac{1}{2}$ way between optic disc and field centre
- F4 (superior temporal) – disc is positioned outside bottom centre of view before the final horizontal movement to F4 (disc must not be visible in the final image)
- F5 (inferior temporal) – disc is positioned outside top centre edge of view...
- F6 (superior nasal) – disc is positioned outside bottom centre edge of view ...
- F7 (inferior nasal) – disc is positioned outside top centre edge of view ...
- Don't forget the fundus reflex image!

7-field 'modified ETDRS' – Zeiss etc.



These are the four peripheral fields when producing circular images. **Optic disc would be 'below' F4 and F6 and 'above' F5 and F7 in viewfinder and final image**

7-field 'modified ETDRS' – Topcon etc.



These are field positions for cameras which cut off top and bottom:

F1, 2 and 3 are identical
F4 and F6 are lower
F5 and F7 are higher
Optic disc would be 'within' the viewfinder before horizontal positioning for F4, F5, F6 and F7

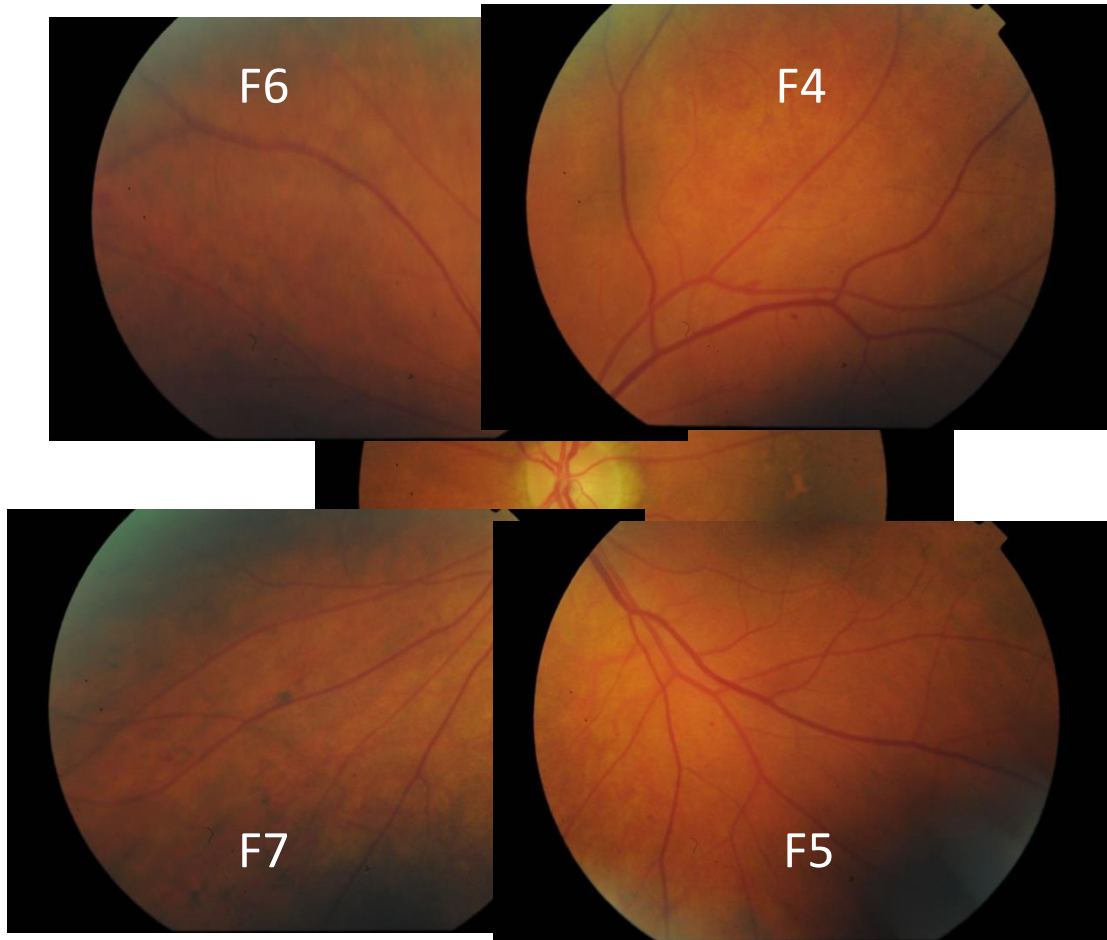
But not in the image

7-field 'modified ETDRS' – Topcon etc.



- F1 (disc-centred) – disc in the centre of field of view
- F2 (fovea-centred) – actually position the fovea about $\frac{1}{8}$ to $\frac{1}{4}$ DD temporally
- F3 (temporal) – position the fovea $\frac{1}{2}$ way between optic disc and field centre
- F4 (superior temporal) – disc is positioned at bottom centre edge of view before the final horizontal movement to F4 (disc must not be visible in the final image)
- F5 (inferior temporal) – disc is positioned outside top centre edge of view ...
- F6 (superior nasal) – disc is positioned outside bottom centre edge of view ...
- F7 (inferior nasal) – disc is positioned outside top centre edge of view ...
- Don't forget the fundus reflex image!

7-field 'modified ETDRS' – Topcon etc.



These are the four peripheral fields for cameras which cut off top and bottom:
F1, 2 and 3 are identical
F4 and F6 are lower
F5 and F7 are higher
Optic disc would be 'within' the viewfinder before horizontal positioning for F4, F5, F6 and F7
But not in the image

Image quality of 7F images



Site staff who will be reading the images will also assess overall quality

We recognise that 7F imaging may be new to many people. There are no chances for repeat imaging, so please try to get the fields correct first time

Please ensure however that every field is in focus

This is important for all fields but absolutely essential for F1 and F2

If you are not happy with an image or field, work with your patient to get extra images whilst the session is taking place. Submit only the best.



Export of 7F images

Export of the 7F images is totally manufacturer-dependent.

The EMERALD 7-field imaging guideline provides details of procedures required for export from the camera systems that sites have reported they may use:

- Topcon ImageNet

- Topcon iBase

- Zeiss Visupac

- OIS Winstation

- Canon Eyecap

3-field wide angle images from Optos



The Optos instruments produce nominal 200° ultra wide-angle images

Each site will already be regular users of one of these or, if you have only recently been supplied with one, will need to get some practice in as soon as possible

The Optos uses lasers to produce 'composite' colour retinal images:

- Green laser - 'red free' retina and autofluorescence

- Red laser - deeper retinal structures

- IR laser - choroid

3-field Optos wide-angle

We need 3 retinal fields in composite colour: Superior , Central and Inferior

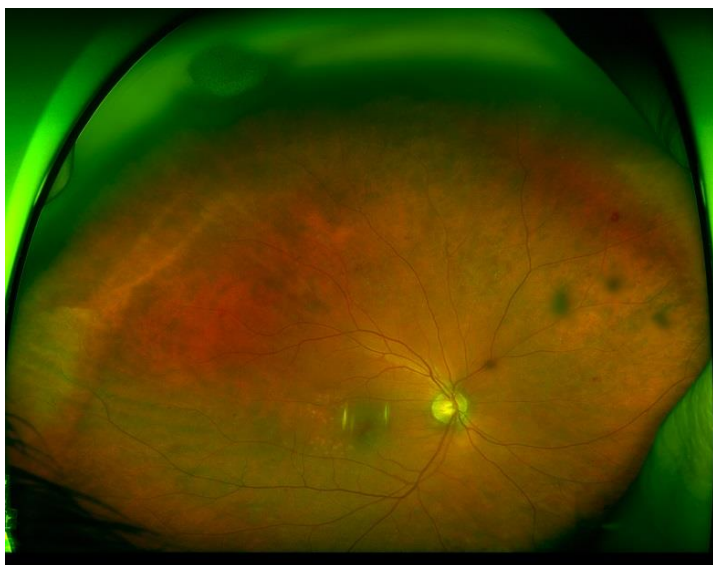


Image quality of 3F images

Site staff who will be reading the images will also assess overall quality

We recognise that Optos 3F imaging may be new to many people. There are no chances for repeat imaging, so please try to get the fields correct first time

We don't really need to worry too much about focus but fields are difficult

You will need to move the patient's chin up and down and even rotate the patient's head slightly to get the correct fields

For the superior and inferior fields – unlikely you will go 'too far' up or down!

Hold the lids and try to avoid artefacts. Submit only the best



Export of 3F images

All Optos 3-field images must be exported in DICOM format.

The patient's identity must be anonymized within the Optos prior to export of the DICOM files and subsequent submission to CARF

Optos instruments use two possible review platforms:

- V² Vantage Pro

- Optos Advance

Details of the required procedures for both of these are provided in the 3-field imaging guideline



Spectralis OCT scans

The pathway of standard care, especially for DMO patients, includes OCT scans

We are asking sites to use the following Spectralis scan capture procedure when imaging **all** EMERALD patients:

Pre-set volume scan P-Pole:

high speed, 30x25°, 61 lines, 120µm separation

Please ensure all eligible eyes are scanned on all patients

Export of OCT scans



The patient's identity must be anonymized within the Spectralis prior to export of the E2E file and submission to CARF.

- Create a desktop folder into which files can be exported
- Use folder name format : "SiteID_SubjectID_DateofVisit"
So: 20_1234_26Jan2012 (NB: use DDMMYYYY please)
- Select patient to be exported, double-click on name to load scans
- Select the scans you need – right click on scans to Export/as E2E
- Send the E2E file to the folder above and complete the data fields

Submission of images/scans to CARF



The Central Angiographic Reading Centre (CARF), Queen's University Belfast are acting as the repository and re-provider of all retinal images and scans

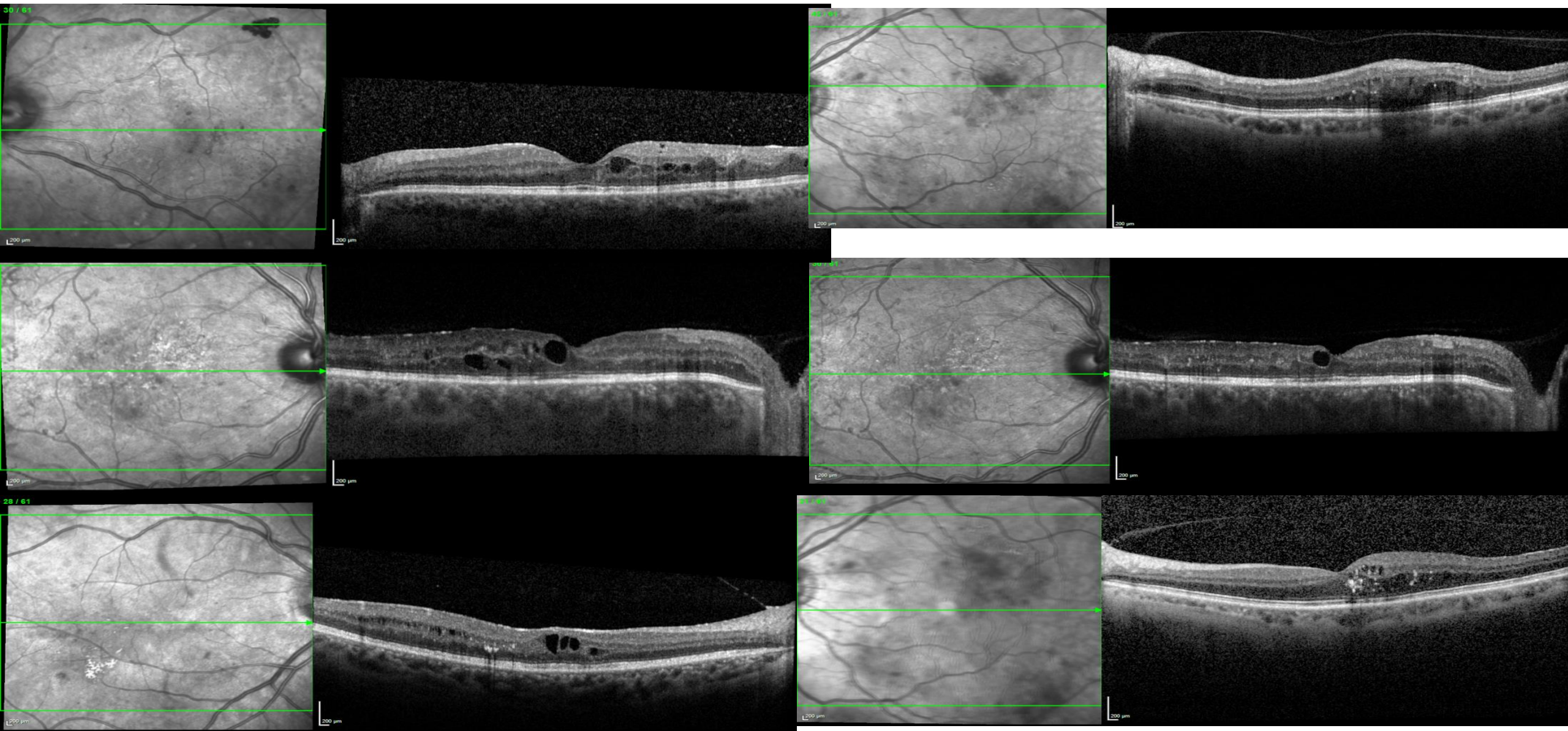
They are not reading any scans or images – you are!

All 7F and 3F images and the OCT scans are (ideally) to be uploaded via secure FTP to CARF within **7 days** of image capture please, using the procedures detailed in the trial manuals and protocols. If you cannot use this method for any reason – please contact CARF directly

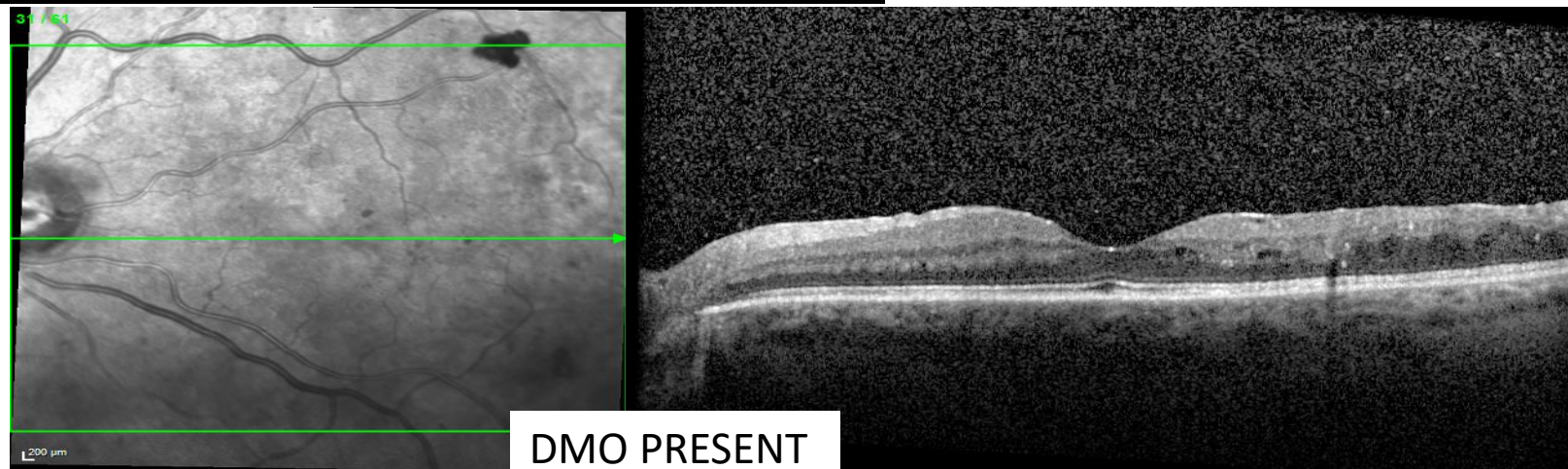
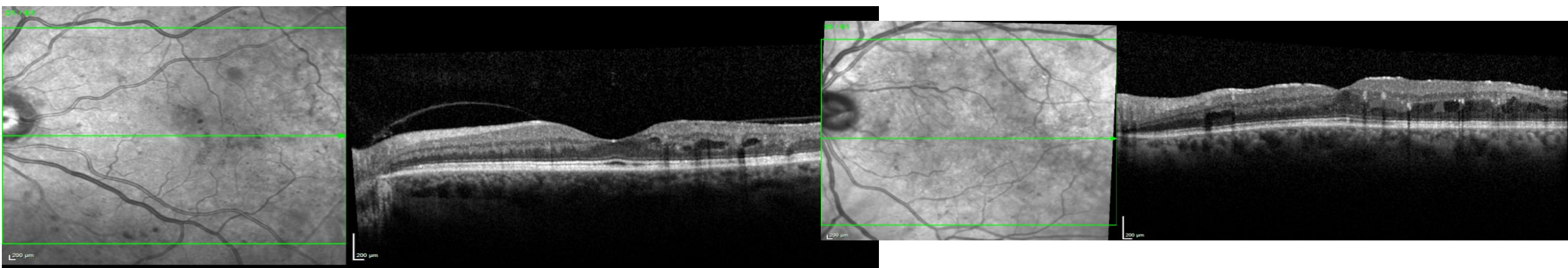
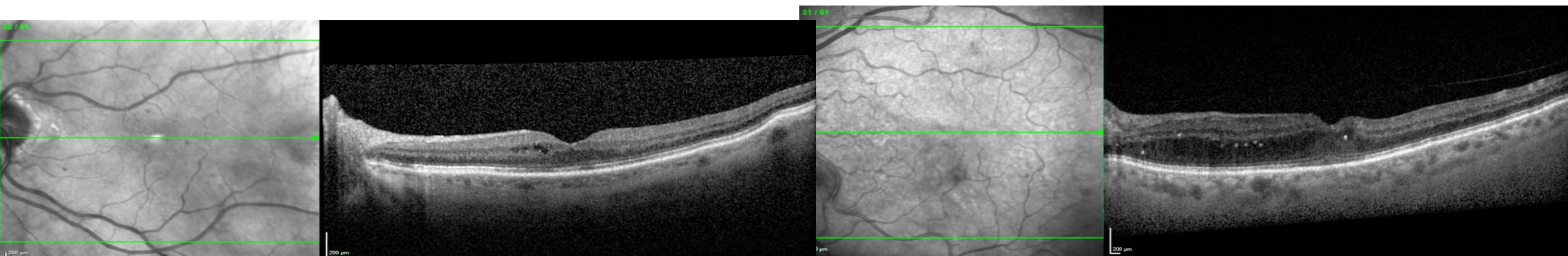
Every submission to CARF must be accompanied by an emailed Transmittal Log to let CARF know that images have been transferred and what to expect



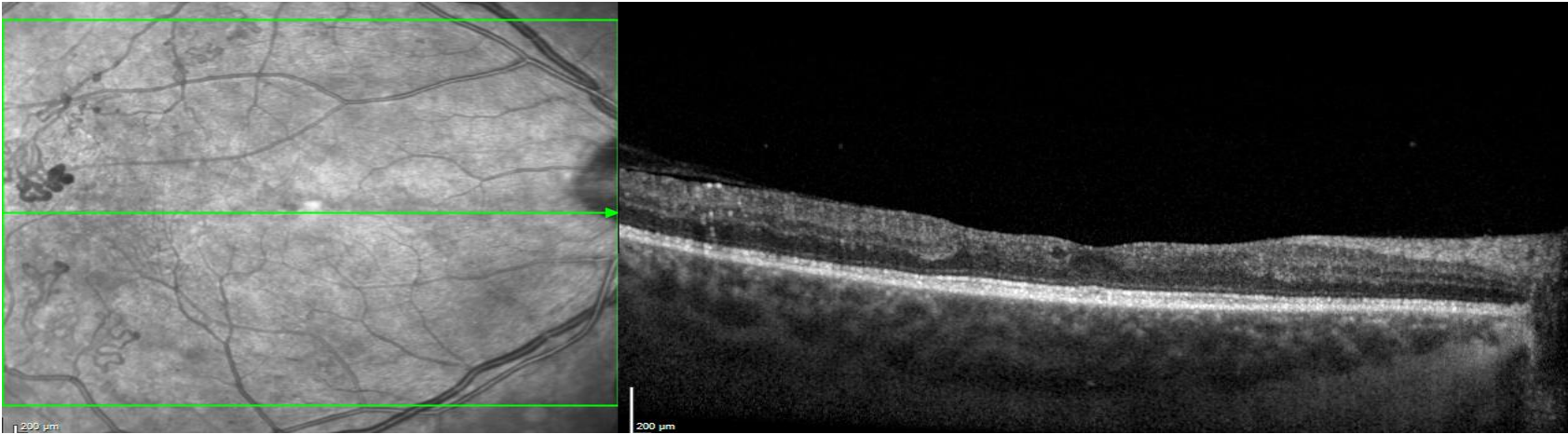
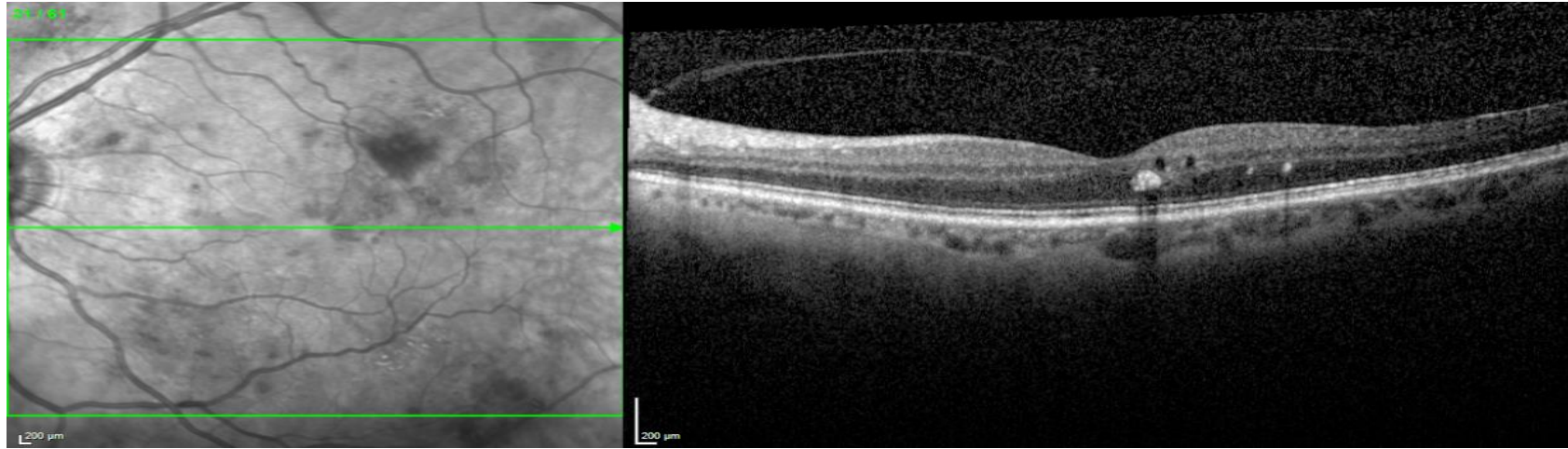
Case Reviews



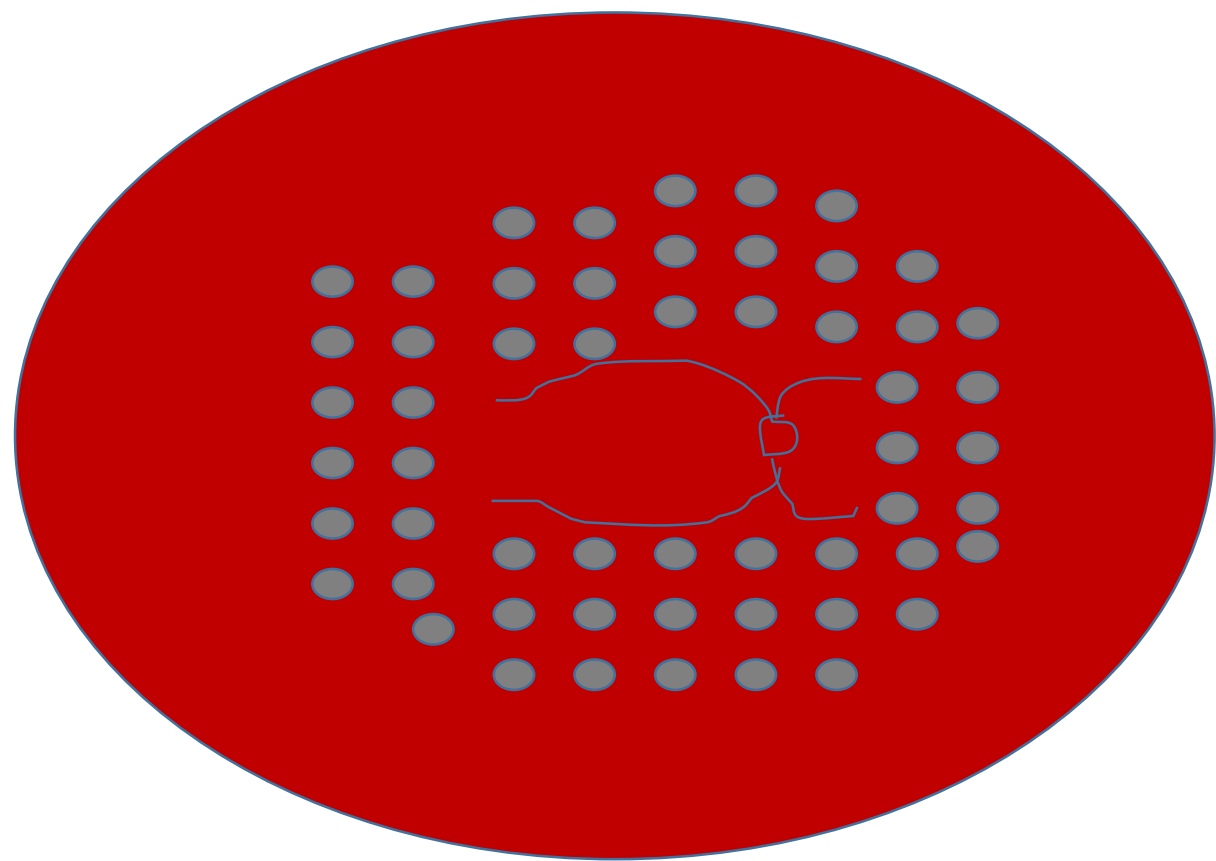
DMO PRESENT



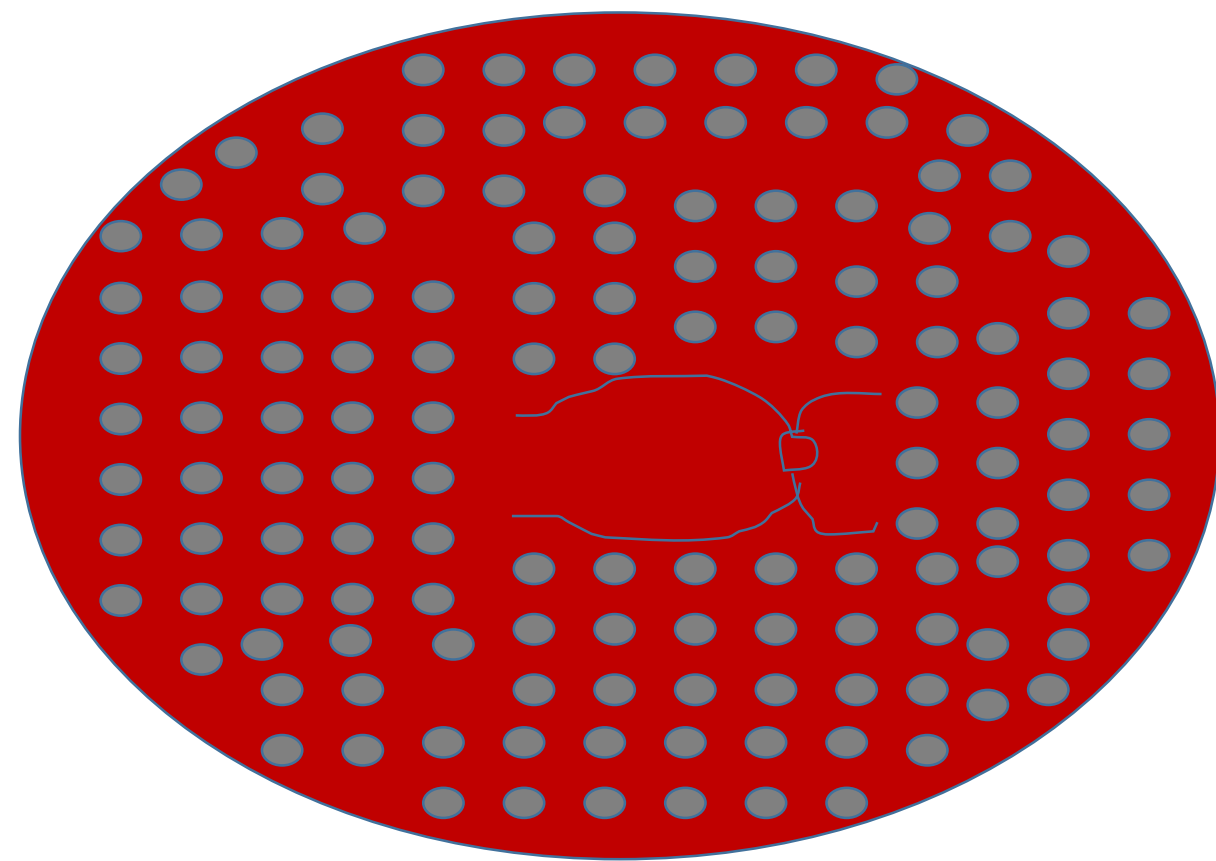
DMO PRESENT



DMO ABSENT



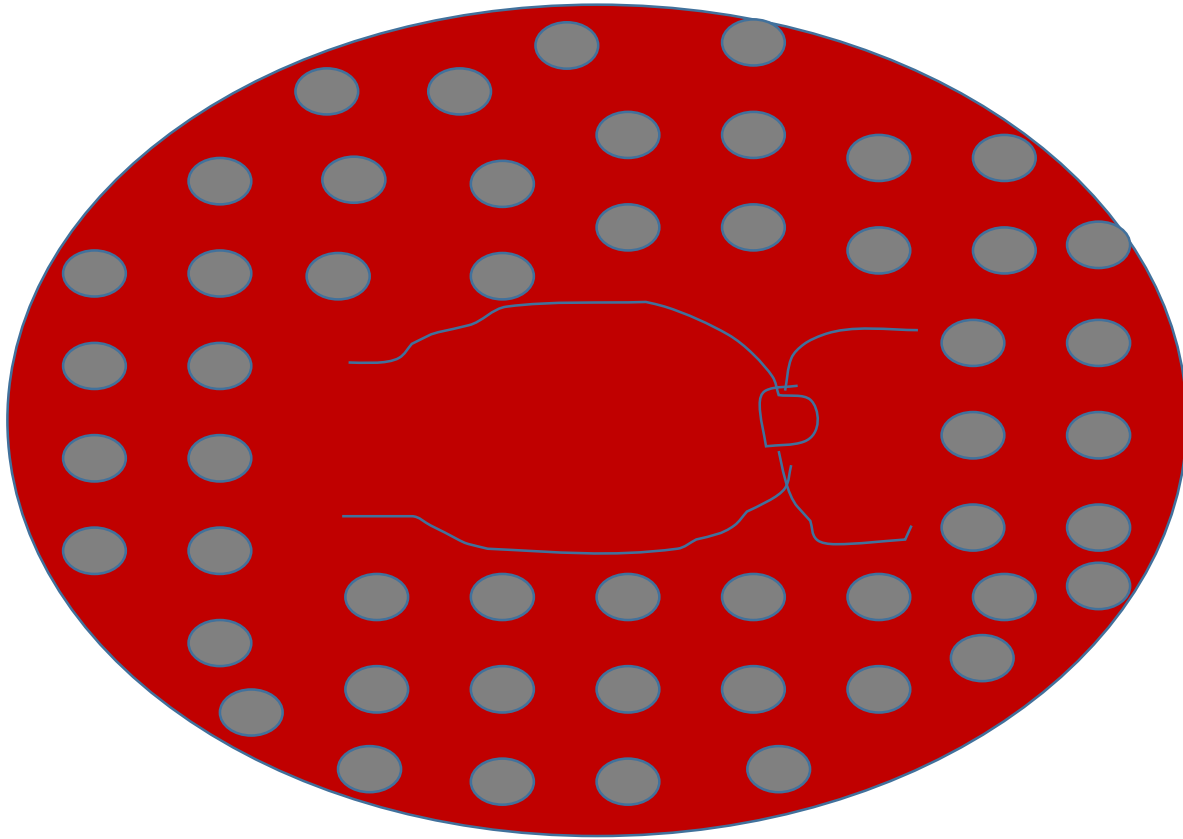
INCOMPLETE PRP



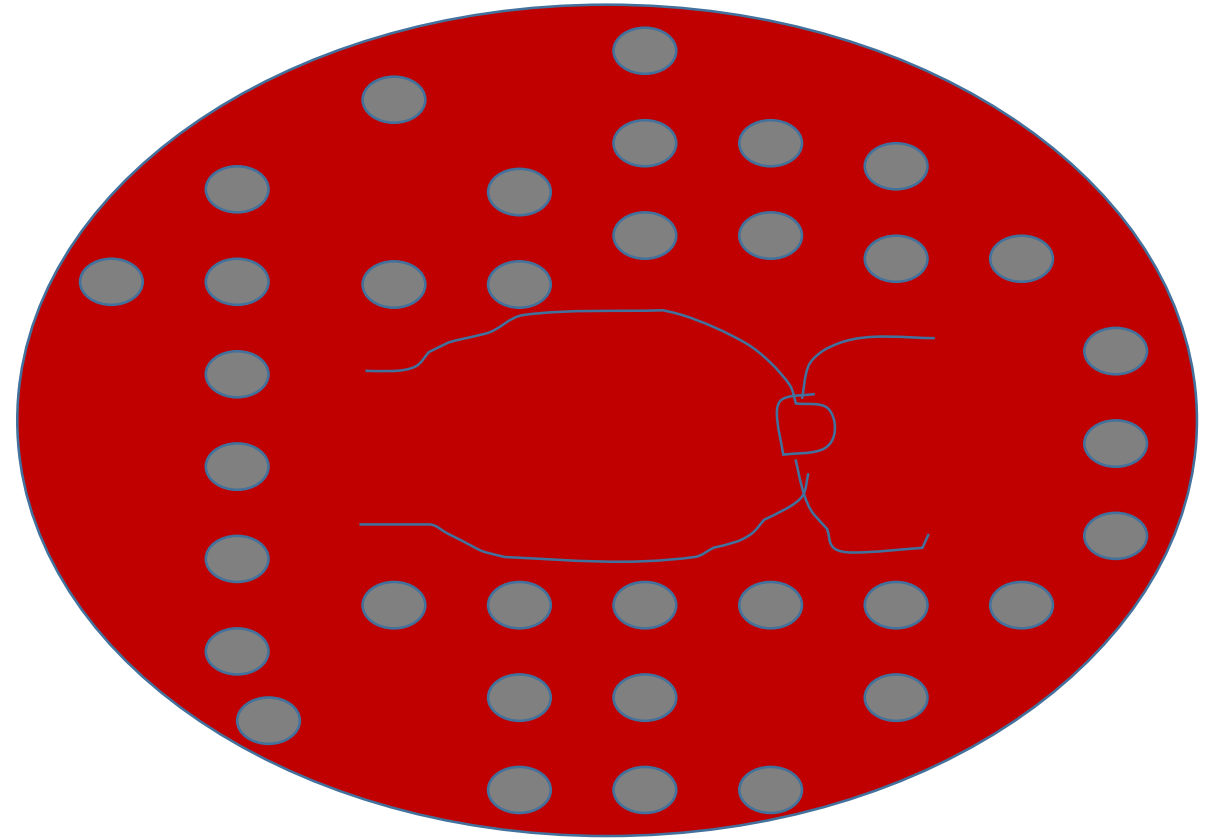
COMPLETE PRP



If full PRP and fine NVD or NVE and
No pre-retinal (subhyaloid) or vitreous
haemorrhage: PDR INACTIVE



COMPLETE PRP as seen with 7 fields ETDRS

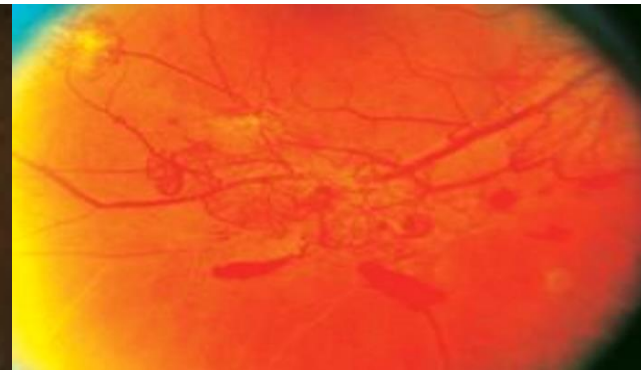
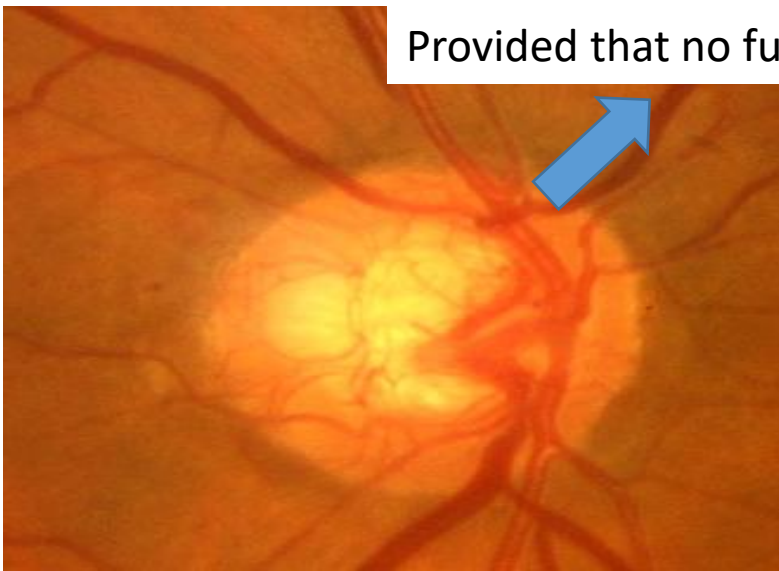


INCOMPLETE PRP

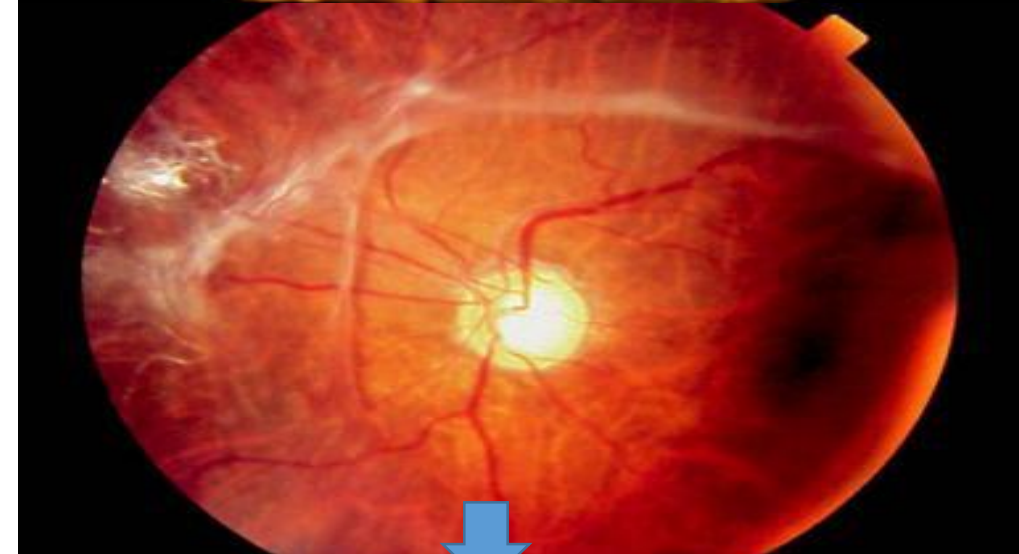
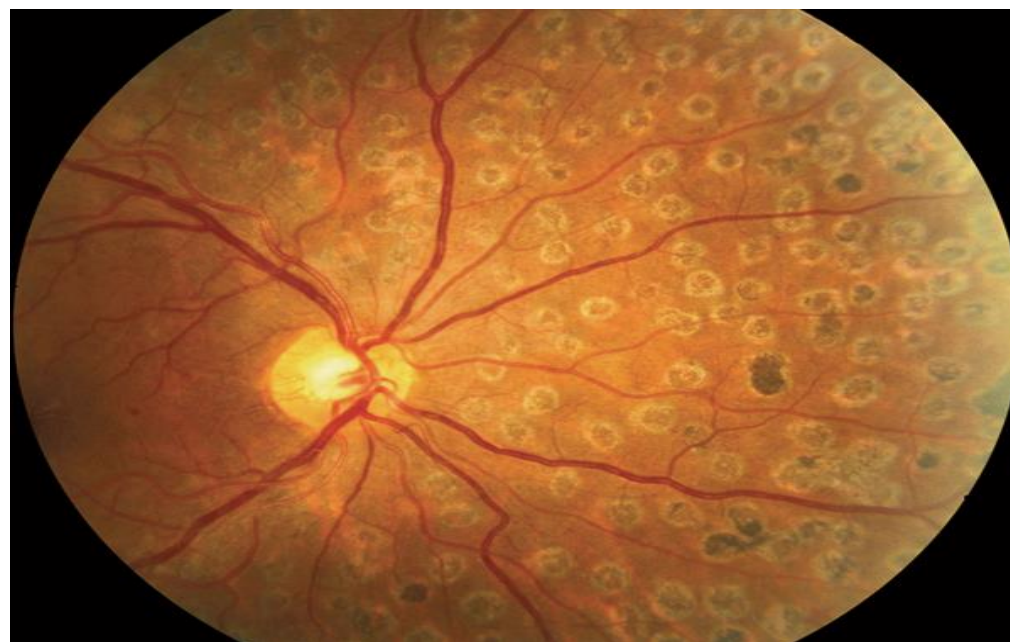


(If full PRP (like drawn) and fine NVD or NVE and no pre-retinal (subhyaloid) or vitreous haemorrhage, PDR can be considered INACTIVE

Provided that no full PRP



Active PDR



If PRP present: Inactive

Inactive PDR



Northern Ireland Clinical Trials Unit:
Overview of processes and procedures

Screening & Recruitment



Potential patients identified through:

- Patient electronic databases
- Referral letter
- At their routine clinical appointment
- At A&E

If identified via electronic database or letter of referral, potential participants may be approached via telephone or invitation letter

- post out patient information sheet
- minimum of 24 hours to decide whether or not to participate

Identified at clinic

- PIS provided
- patient can agree to participate on the day if desired, or further visit arranged

Screening Log



- Record all patients screened (recruited or not)
 - Screening ID: format SXXXXXX;
 - first 2 XX after S are for the site number (these will be allocated)
 - The last 2 XX are for the screening number within the site
 - should be allocated sequentially
 - Record the following information:
 - Screening number
 - Date PIS provided
 - Screening date
 - Recruitment date (if applicable) and patient ID number
 - Reason (s) for non -recruitment

Belfast Health & Social Care Trust										Northern Ireland Clinical Trials Unit (NICTU)																			
Principal Investigator (PI):										Site Name:										Site No:									
Screening Number	Date Patient Information Sheet Provided			Screening Date			Recruited?		Date Recruited			Patient Number (If Recruited)			Reason(s) for Non-Recruitment (see overleaf)														
	DD	MM	YY	DD	MM	YY	<input type="checkbox"/>	Yes	DD	MM	YY				1														
	DD	MM	YY	DD	MM	YY	<input type="checkbox"/>	Yes	DD	MM	YY																		
	DD	MM	YY	DD	MM	YY	<input type="checkbox"/>	Yes	DD	MM	YY																		

- PI or designee required to submit screening logs to the NICTU monthly

Informed Consent



- The PI (or designee) taking informed consent must be **GCP trained**, suitably **qualified** and **experienced** and have been **delegated** this duty by the PI on the EMERALD delegation log.
- The participant's medical notes will be annotated by PI to confirm that participant has provided written informed consent and have been recruited onto the EMERALD study.
- The PI (or designee) is responsible for ensuring all participants are given a participant information sheet, and given adequate time to review and ask questions.
- Original Informed consent form (ICF):
 - One to be given to Patient
 - One to be retained in the Investigator Site File
- Copy of ICF:
 - One to be filed in patient's medical notes
- There are **two consent forms** for this study: the **study consent form** and the **focus group discussions consent form**.
- (There is a separate consent form for Healthcare professionals who agree to take part in focus group discussions)
- Consent forms and Patient Information leaflets will be emailed to each site. They must be populated with local trust headers and printed at site.

Study Title: "Effectiveness of Multimodal imaging for the Evaluation of Retinal Oedema And new vessels in Diabetic Retinopathy (EMERALD)"

PATIENT CONSENT FORM

Patient's name:

Please initial
each box

1. I confirm that I have read, or had read to me, and understand the Patient Information Sheet for the above study. I have had the opportunity to ask questions and these have been fully answered.

☐

2. I confirm that I have had sufficient time to consider whether or not to participate in the study

☐

3. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my legal rights or medical care being affected.

☐

4. I understand the study is being conducted by the Belfast Health and Social Care Trust in conjunction with researchers from Queen's University Belfast and that my personal information will be held securely on NHS/HSC Trust and Queens University Belfast premises and handled in accordance with the provisions of the Data Protection Act 1998.

☐

Copies: 1 original for patient. 1 original in Investigator Site File. 1 copy on Patient's Medical Records

5. I understand that data collected as part of this study and relevant sections in my medical records may be looked at by authorised individuals from NHS/HSC Trust and Queens University Belfast where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.

☐

6. I understand that the information gathered as a result of this study will be published. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications.

☐

7. I agree for anonymised photographs of my eyes (photographs without my name but with a code) to be transferred to Queen's University and to the EMERALD website and used for this study and for other studies as well as for other purposes.

☐

8. I agree that if I withdraw from the study any outstanding data can be collected and data already collected from me can be used for the EMERALD study and for other studies as well as for other purposes.

☐

9. I agree to take part in the above study.

☐

Name of Participant
(please print)

Signature

Date

Name of Person Taking
Consent (please print)

Signature

Date

Copies: 1 original for patient. 1 original in Investigator Site File. 1 copy on Patient's Medical Records



<LOCAL TRUST HEADER TO BE INSERTED HERE>>

Study Title: "Effectiveness of Multimodal imaging for the Evaluation of Retinal Oedema And new vessels in Diabetic Retinopathy (EMERALD)"

Focus Group Discussions

PATIENT CONSENT FORM – Focus Group Discussions

Patient's name: _____

Please initial
each box

1. I confirm that I have read, or had read to me, and understand the Patient Information Sheet for the above study. I have had the opportunity to ask questions and these have been fully answered. ☐
2. I confirm that I have had sufficient time to consider whether or not to participate in focus group discussions. ☐
3. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason and without my legal rights or medical care being affected. ☐
4. I understand the study is being conducted by the Belfast Health and Social Care Trust in conjunction with researchers from Queen's University Belfast and that my personal information will be held securely on NHS/HSC Trust and Queens University Belfast premises and handled in accordance with the provisions of the Data Protection Act 1998. ☐

Copies: 1 original for patient. 1 original in Investigator Site File. 1 copy on Patient's Medical Records

EMERALD Patient Consent Form- Focus Group Discussions Version 1.0 FINAL 31/05/2017

5. I understand that data collected as part of this study and relevant sections in my medical records may be looked at by authorised individuals from NHS/HSC Trust and Queens University Belfast where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information. ☐
6. I understand that the information gathered as a result of this study will be published. Confidentiality and anonymity will be maintained and it will not be possible to identify me from any publications. ☐
7. I agree for my views and opinions that I have expressed during the focus group discussions, to be audio-recorded and transcribed and used for this study and for other studies as well as for other purposes. ☐
8. I agree that if I withdraw from the study any outstanding data can be collected and data already collected from me can be used for the EMERALD study and for other studies as well as for other purposes. ☐
9. I agree to take part in the focus group discussions for the EMERALD study. ☐

Name of Participant
(please print)

Signature

Date

Name of Person Taking
Consent (please print)

Signature

Date

Copies: 1 original for patient. 1 original in Investigator Site File. 1 copy on Patient's Medical Records

EMERALD Patient Consent Form- Focus Group Discussions Version 1.0 FINAL 31/05/2017



Confirmation of Eligibility: Patient Registration Form



- Principal Investigator (PI)/Delegated Ophthalmologist Responsibilities:
 - Establish if the patient is eligible based on the inclusion & exclusion criteria
 - If eligible, indicate 'yes' on the form
 - If not eligible, indicate 'no'
 - PI to print name and provide signature and date
- Patients screened and not recruited to the study should be documented on the screening log, including the reason for not being enrolled on the trial
- Eligibility must also be documented in patient medical notes e.g.
 - *"This subject meets all the inclusion criteria and none of the exclusion criteria and is therefore eligible for entry into the EMERALD trial. Eligibility confirmed by <medically qualified doctor confirming eligibility>, recorded in notes by <healthcare professional> <date>"*

Adverse Events



Adverse event (AE)

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.

Mild blurriness or visual disturbance immediately following imaging is not an AE and should not be reported

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

Recording & Reporting AEs

AEs (not related to underlying medical conditions)

Adverse events assessed for:

- Seriousness
- Expectedness
- Relatedness
- PI or designee will record all AEs that occur at the EMERALD study visit.
- Recorded in CRF and participant medical notes
- Completed AE CRF sent to NICTU
- All AEs assessed by the PI or designee as being related and unexpected will be followed up until resolved or considered stable
- CRF updated with the date and time of resolution.

Recording & Reporting: SAE



- Reported to the NICTU using the SAE form no later than 24 hours after becoming aware of the event
- Copy of completed SAE kept in patients' medical notes and a copy filed in section 13 of the ISF along with all related correspondence.
- SAEs should be sent to: clinicaltrials@nictu.hscni.net
- Follow up all SAEs to resolution and report date of resolution on SAE follow up form.

Recording & Reporting: SAE



Onward Reporting

- NICTU will inform Sponsor and REC and all study sites about any SAEs
- SAE will be reported to REC if the event was deemed:
 - A) Related – it resulted from the administration of any research procedures, and
 - B) Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.
 - Within 15 days of CI becoming aware of the SAE

Urgent Safety Measures

- PI/designee may take appropriate urgent safety measures to protect participants from any immediate hazards to their health or safety.
- Site should phone NICTU on 028 90635794 and send follow up email to clinicaltrials@nictu.hscni.net
- NICTU responsible for onward reporting to REC and Sponsor.

Protocol Deviations and Serious Breaches



Protocol compliance will be monitored by CTU who will undertake monitoring visits to ensure trial protocol is adhered to and that necessary paperwork is being completed appropriately.

What is a deviation?

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

What is a serious breach?

- Defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:
 - (a) the safety or physical or mental integrity of the subjects of 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 and sponsor within one working day of becoming aware of the breach.
- A 'notification of serious breach of trial protocol or GCP form' can be found in the ISF.
- Please refer to section 6.4 of the Investigator Site File for guideline

Investigator Site File: SOP TM02 Training



TM02 Investigator Site File (ISF) and Essential Documents

- Essential documents are those which individually and collectively permit evaluation of the trial conduct and the quality of the data produced.
- Compliance of the trial with GCP and regulatory requirements can also be assessed through review of the TMF & essential documents
- NICTU delegated management of the TMF for the EMERALD trial
- PI at site responsible for set up & maintenance of all essential documents in the ISF.
- PI is responsible for providing the NICTU personnel with any new or amended documents as the trial progresses and as requested throughout the trial, until closure.
- The PI may delegate this activity to member of the research team. Should be documented on the delegation log.

SOP TM02 Training



Establishing an ISF

- NICTU responsible for providing the PI with an ISF
- Must be retained in a secure location with restricted access.
- ISF contains an index at beginning of file, it is a guide
 - not all documents may be applicable, mark NA on index.
 - If document is applicable but filed elsewhere, file notes should be added to the applicable sections
- Will contain copies of the document version control logs which should list all approved versions of the protocol, PIS, ICF
- Remote SIV- the site will be asked to confirm that all essential documents and approvals are in place, then will be given confirmation to commence recruitment.

SOP TM02 Training



Maintaining the ISF

- PI or delegate is responsible for updating the ISF with any new documentation as trial progresses and applicable forms completed
 - Staff training documented on Study Training Log
 - Updates to Delegation Log notified to CTU and other departments
 - Previous versions of the protocol and other essential documents marked as superseded
- Ensure all filing is completed in a timely manner with documents filed chronologically within each section with the most recent at the front
- ISF made available for monitoring visits, audits or inspections by regulatory authorities- will form the basis for inspection/audit

SOP TM02 Training



After completion of the Trial

- Once the trial is finished PI responsible for reviewing ISF to ensure all documents present.
- NICTU will complete a final close out review and issue relevant documentation.
- PI must archive the ISF, unless otherwise agreed with the NICTU.
- NICTU will issue each site with guidance on archiving, period of time as defined by sponsor.
- ISF can only be archived once all close out actions are completed.

Data Collection



- Sites will be provided with a CRF per patient to collect data required by the protocol
 - Patient CRF
 - Graders CRF – Contains all grading forms
- Instructions on CRF completion found at start of document.
 - One copy patient medical notes
 - One copy kept at site
 - One copy sent to CTU
 - A tracking form must accompany the CRF as it is sent.

Data Collection

Belfast Health & Social Care Trust

EMERALD

NI Clinical Trials Unit (NICTU)



Protocol Number: 17020NL-AS

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

PATIENT CASE REPORT FORM (CRF)

Site Number:

--	--

Participant Initials:

--	--

Screening Number:

S						
---	--	--	--	--	--	--

Participant number:

--	--	--	--

Please retain one copy of completed Case Report Forms (CRFs) on site, file one copy in the patient notes and return original copies by post to the NICTU at the following address:

NICTU
EMERALD STUDY
1st Floor Elliott Dynes Building
The Royal Hospitals
Grosvenor Road
BELFAST, BT12 6BA

For any administrative queries please contact the NICTU:

Telephone: (028) 9063 5974

Email: EMERALD@nictu.hscni.net

PLEASE READ ALL THE INSTRUCTIONS CAREFULLY THROUGHOUT

Belfast Health & Social Care Trust

EMERALD

NI Clinical Trials Unit (NICTU)

Protocol Number:

17020NL-AS

Participant Initials

--	--

Participant Number

--	--	--	--

Site Number

--	--

MEDICAL HISTORY

Please put a tick in box for each question. Please answer all questions.

Visit Date:

D D	/	M M	/	Y Y Y Y
-----	---	-----	---	---------

DEMOGRAPHICS

Patient Gender:

☐ Male ☐ Female
☐ Other (if the participant doesn't identify as male or female please tick other)

Patient Date of Birth:

D D	/	M M	/	Y Y Y Y
-----	---	-----	---	---------

ETHNICITY

Please state Patient's
Race/ Ethnicity:

White	<input type="checkbox"/>	Hispanic	<input type="checkbox"/>
Black	<input type="checkbox"/>	Asian	<input type="checkbox"/>
Middle Eastern	<input type="checkbox"/>	Other please specify below:	<input type="checkbox"/>

OPHTHALMIC HISTORY

Please state the date that the patient was first
diagnosed with DMO:

RE	MM / YYYY	Date Unknown <input type="checkbox"/>
N/A		
LE	MM / YYYY	Date Unknown <input type="checkbox"/>
N/A		

Please state the date the patient was diagnosed
PDR:

RE	MM / YYYY	Date Unknown <input type="checkbox"/>
N/A		
LE	MM / YYYY	Date Unknown <input type="checkbox"/>
N/A		

Previous DMO Treatments:

	RE	LE
Has the patient had previous laser grid/focal laser treatment for DMO?	Y <input type="checkbox"/> N <input type="checkbox"/>	Y <input type="checkbox"/> N <input type="checkbox"/>
Has the patient ever had Anti-VEGF Treatments for DMO?	Y <input type="checkbox"/> N <input type="checkbox"/>	Y <input type="checkbox"/> N <input type="checkbox"/>
Has the patient ever had intraocular steroid treatment for DMO?	Y <input type="checkbox"/> N <input type="checkbox"/>	Y <input type="checkbox"/> N <input type="checkbox"/>

Previous PDR Treatments:

	RE	LE
Has the patient had previous laser PRP treatment for PDR?	Y <input type="checkbox"/> N <input type="checkbox"/>	Y <input type="checkbox"/> N <input type="checkbox"/>
Has the patient ever had Anti-VEGF Treatments for PDR?	Y <input type="checkbox"/> N <input type="checkbox"/>	Y <input type="checkbox"/> N <input type="checkbox"/>

DETAILS OF PERSON COMPLETING FORM

Print name:

--

Signature:

--

Date completed:

D D	/	M M	/	Y Y Y Y
-----	---	-----	---	---------



CRF Submission Schedule



- The CRF should be completed and submitted to the CTU in accordance with the submission schedule
- A tracking form must accompany the CRF as it is sent.

The Case Report Form (CRF) for the EMERALD trial should be completed and submitted to the Clinical Trials Unit (CTU) in accordance with the submission schedule below:

Form / Visit	To be submitted
CRF	Within 2 weeks after visit date
Off Study	As soon as possible after event
Protocol Deviation	As soon as possible after event
Withdrawal of consent	As soon as possible after event
AEs	As soon as possible after event
SAEs	SAE forms should be submitted by email (clinicaltrials@nctu.hscni.net) within 24 hours of becoming aware of the event. Original copies should be submitted as soon as possible thereafter.
Questionnaires	Within 1 week after visit date
Sign-off	On completion of final visit

NOTE:

The CRF should be submitted to the CTU:
Northern Ireland Clinical Trials Unit
1st Floor Elliott Dynes Building
Royal Victoria Hospital
Grosvenor Road
Belfast, BT12 6BA

Monitoring



- To ensure:
 - the rights, safety and well being of the trial participants are protected
 - the reported trial data are accurate, complete and verifiable from source documents
 - the trial is in compliance with the approved protocol, GCP and applicable regulatory requirements
- First interim visit will occur no later than 6 months from the recruitment of the first patient
- Annual visits thereafter until study close out
- A close-out visit will be arranged at each site once the final patient recruited at the site has completed all follow-up

Monitoring



- Visits will involve:
 - Review of compliance to protocol and trial specific guidelines
 - Review of the Investigator Site File
 - Review consent forms & eligibility checklists
 - Review of AE/SAEs
- The CRF is the source data; please have this available
- Please ensure a member of the team is available to deal with queries
- Investigator available at the end of the visit for a feedback meeting

Archiving



- The PI is responsible for archiving essential documents at the study site.
- Unless otherwise directed ensure that all study records are archived appropriately on conclusion of the study and retained for 5 years. Patient medical files should be retained for 15 years.

Delegation log



- All members of staff working on the EMERALD trial must be trained on the protocol and signed onto the delegation log before completing any research tasks
- Activities can be delegated by the PI to appropriately trained members of the team but the PI **must** have oversight
- Only people who will be actively involved in the EMERALD trial are to sign delegation log (staff changes to be notified to NICTU)
- PI must be listed first on the delegation log
- Must have been trained in a task prior to being delegated that task on the delegation log

Delegation Log



Delegation Log

NICTU

PROTOCOL ACRONYM:		PRINCIPAL INVESTIGATOR (PI):	
PROTOCOL NO:		SITE:	

Name(Print)	Initials	Job Title	Delegated Tasks ¹	Research Personnel (Sign & Date)	Start Date	Investigator (Sign & Date)	End Date	Investigator (Sign & Date)

1. Protocol Training
2. Obtain Informed Consent
3. Screening/ Inclusion/Exclusion Criteria
4. Confirmation of Eligibility
5. Recruitment/Registration/Randomisation of Patients
6. Physical Examinations/Clinical Evaluations
7. Sample Handling
(includes obtaining and processing)

8. IMP Accountability
9. IMP Prescribing
10. IMP Dispensing
11. IMP Administration
12. Recording and Reporting AE/SAE
13. Unblinding
14. Source Document Entry
(i.e. medical notes)

15. CRF/eCRF Completion
16. CRF/eCRF Signature
17. Maintaining Investigator Site File (ISF)
18. Data Query Completion
19. Archiving

21. Other:
22. Other:
23. Other:
24. Other:

² This signature indicates that the individual confirms that he/she has been adequately trained in the task and feels confident to take on the responsibility.

- The CI may also be the PI for single site studies
- A copy of the Delegation Log should be sent to the Clinical Trials Unit and other departments within the participating site (e.g. Pharmacy), as any updates to staff and tasks delegated occur.

Delegation Log

EXAMPLE DOCUMENT

NICTU

PROTOCOL ACRONYM:	EMERALD	PRINCIPAL INVESTIGATOR (PI):	A. BLACK.
PROTOCOL NO:	12020NL-AS	SITE:	BELFAST.

Name(Print)	Initials	Job Title	Delegated Tasks ¹	Research Personnel (Sign & Date)	Start Date	Investigator (Sign & Date)	End Date	Investigator (Sign & Date)
A. Black	A. B.	PRINCIPAL INVESTIGATOR	1, 2, 3, 4, 5, 6, 12, 14, 15, 16, 17, 18, 19	A. Black.	25/08/17	A. Black.		
B. WHITE	B. W.	PHOTOGRAPHER	6, 15-17	B. white	25/08/17	A. Black.		
C. BLUE	C. B.	GRADER	15, 16, 18	C. Blue	25/08/17	A. Black.		
D. PINK	D. P.	GRADER	" " "	D. Pink	25/08/17	A. Black.		
E. RED	E. R.	AS ABOVE	AS ABOVE	E. Red.	" " "	" "		

NOT ACCEPTABLE

NOT ACCEPTABLE

NOT ACCEPTABLE

1. Protocol Training
2. Obtain Informed Consent
3. Screening/ Inclusion/Exclusion Criteria
4. Confirmation of Eligibility
5. Recruitment/Registration/Randomisation of Patients
6. Physical Examinations/Clinical Evaluations
7. Sample Handling (includes obtaining and processing)

8. IMP Accountability
9. IMP Prescribing
10. IMP Dispensing
11. IMP Administration
12. Recording and Reporting AE/SAE
13. Unblinding
14. Source Document Entry (i.e. medical notes)

15. CRF/eCRF Completion
16. CRF/eCRF Signature
17. Maintaining Investigator Site File (ISF)
18. Data Query Completion
19. Archiving

20. Other:
21. Other:
22. Other:
23. Other:


² This signature indicates that the individual confirms that he/she has been adequately trained in the task and feels confident to take on the responsibility.

- The CI may also be the PI for single site studies
- A copy of the Delegation Log should be sent to the Clinical Trials Unit and other departments within the participating site (e.g. Pharmacy), as any updates to staff and tasks delegated occur.

Training Log



- All members of staff working on the EMERALD trial must be trained on the protocol and document this on a study training log.
- All other relevant training e.g.– Grading images, imaging protocols, uploading images to CARF must also be documented on training log for each staff member.
- Staff members previously documented as having received training on the protocol, guidelines and SOPs can provide training to new members of staff.

		Study Training Log					
PROTOCOL ACRONYM:				PRINCIPAL INVESTIGATOR (PI):			
PROTOCOL NO:				SITE:			
Date of Training	Name of Trial Personnel ¹	Signature of Trial Personnel	Nature of Training (specify any trial documents including version number)	Name of Trainer ¹	Signature of Trainer ²		

Trial Supplies



- Before recruitment begins at your site, you will be provided with:
 - Investigator Site File (ISF)
 - Case Report Form (CRF) folders
 - Trial Manual
 - Electronic copies of CF, PIS, invitation letter



Trial Team



- ❖ **Chief Investigator** Professor Noemi Lois



- ❖ Northern Ireland Clinical Trials Unit (NICTU)

Trial Manager	Mrs Christine McNally
Trial Co-Ordinator	Miss Rachael Rice
Trial Administrator	Mrs Laurie Martin/Mrs Nuala Hannaway
Data Manager	Mr Andrew Jackson
Research Monitor	Catherine Campbell
CTU Manager	Ms Lynn Murphy

- ❖ **Health Economists**
Professor Norman Waugh, University of Warwick
Dr Hema Mistry, University of Warwick
- ❖ **Satisticians**
Professor Jonathan Cook, Oxford University
William Sones, Oxford University
- ❖ **Focus Groups Qualitative Assessment**
Professor Lindsay Prior, QUB
- ❖ **Training and development of photographers and graders**
Steve Aldington, Gloucester Hospital



EMERALD

Contact Details



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

Clinical Trial Manager: Mrs Christine McNally
Clinical Trial Co-ordinator: Rachael Rice

Chief Investigator:
Professor Noemi Lois n.lois@qub.ac.uk T: +44 (0) 28 90976462





Any Questions?