EDNA Study Procedures

A EDNA CASE REPORT FORMS

CRF VOLUME 2 18/01/2018

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

CRF Volume 2 start date D D / M M / Y Y Y Y

EDNA CRF Contents

This study is funded by the
NIHR Health Technology Assessment (HTA) Programme

NHS
National Institute for Health Research

EDNA ELIGIBILITY CRITERIA CHECKLIST

Early Detection of Neovascular Age-related macular degeneration (AMD)

Please check against these eligibility criteria for potential EDNA participants

Study Number | | | | | |

INCLUSION CRITERIA

The answer to the following questions should be 'yes':

	Yes	No
Is the patient newly referred to nAMD clinic (i.e. was their diagnostic FFA within the last 6 weeks?)	❑	❑
Does this patient have confirmed nAMD in one eye (by FFA) and an unaffected second eye?	❑	❑
Is the patient about to commence or recently commenced anti VEGF therapy in the first eye?	❑	❑
Is the patient aged 50 - 95	❑	❑

EXCLUSION CRITERIA

If the answer to any of these criteria is 'yes' – this patient is to be excluded

	Yes	No
Patient with a history of nAMD in both eyes	❑	❑
Patient with nAMD in the study eye detected at baseline	❑	❑
Patient with a presenting visual acuity worse than 68 letters	❑	❑
Patient has retinal pathology in the study eye which can confound subsequent assessments (e.g. diabetic retinopathy, macular hole)	❑	❑
Patient not undergoing regular monitoring in standard of care	❑	❑
Patient cannot give informed consent	❑	❑
Patient is unable to undergo a Fundus Fluorescein angiography (FFA) test	❑	❑
Patient had diagnostic FFA more than 6 weeks ago	❑	❑

Is the patient eligible? Yes ☐ No ☐

If YES, which eye is the study eye? Right eye ☐ Left eye ☐

SIGNATURE AND NAME (BLOCK CAPITALS) OF PERSON COMPLETING FORM

Signature_____ PRINT NAME_____

Date | D | D | / | M | M | / | Y | Y | Y | Y |

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

CONVERSION CHART FOR VISUAL ACUITY

LogMAR	Snellen			Letters
-0.3	6/3	20/10	10/5	100
-0.2	6/3.8	20/12.5	10/6	95
-0.1	6/4.8	20/16	10/8	90
0	6/6	20/20	10/10	85
0.1	6/7.5	20/25	10/12.5	80
0.2	6/9.5	20/32	10/16	75
0.3	6/12	20/40	10/20	70
0.4	6/15	20/50	10/25	65
0.5	6/19	20/63	10/31.5	60
0.6	6/24	20/80	10/40	55
0.7	6/30	20/100	10/50	50
0.8	6/38	20/125	10/62.5	45
0.9	6/48	20/160	10/80	40
1	6/60	20/200	10/100	35
1.1	3/38 6/75	20/250	10/125	30
1.2	3/48 6/95	20/320	10/160	25
1.3	3/60 6/120	20/400	10/200	20
1.4	3/75 6/150	20/500	10/250	15
1.5	2/60 6/190	20/600	10/300	10
1.6	1/60 6/240	20/1200	10/600	5

Edna
Early Detection of Neovascular Age-related macular degeneration (AMD)

The Baseline Appointment Checklist

#	Task	Initials	Date
	AT THE APPOINTMENT		
1.	Eligibility confirmed (eligibility checklist)		
2.	Written informed consent taken (copy given to patient)		
3.	Study number entered and LEFT/RIGHT study eye marked on with EDNA stickers		
4.	Baseline Demographics and history completed on CRF		
5.	Amsler completed by patient		
6.	Baseline Clinical Measurements taken • Biomicroscopy • FFA • Visual acuity • OCT • Fundus examination • Bloods taken (optional)		
7.	Next Appointment made/date noted		
	ADMIN TASKS TO BE COMPLETED ASAP		
8.	GP letter sent		
9.	Consent form copies filed appropriately		
10.	Update clinical log hardcopy		
11.	Relevant data (Clinical log, Consent form and Baseline CRF) entered into EDNA Website https://w3.abdn.ac.uk/hsru/edna/		
12.	Relevant imaging data uploaded to CARF		
13.	Bloods sent to Queens University Belfast (if applicable)		
14.	Patient Demographics removed and stored separately		
15.	EDNA hardcopy CRF filed securely		

NOTES/QUERIES

Need help? Contact the Study office in Aberdeen! ☎

PLEASE TEAR ME OUT WHEN COMPLETE

Edna
Early Detection of Neovascular Age-related macular degeneration (AMD)

BASELINE CRF DEMOGRAPHICS

Study Number | | | | | |

***PATIENT DETAILS* (Sticker may be used below)**

Title Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other

First name

Surname

Date of birth D D / M M / Y Y Y Y

Address

Contact Telephone Number

Hospital Number (England & Wales)
CHI Number (Scotland)
H&C Number (NI)

CONSULTANT DETAILS

Initials Surname

GP DETAILS

Initials Surname

Address

PLEASE tear out this sheet once completed and store securely and separately to the main CRF

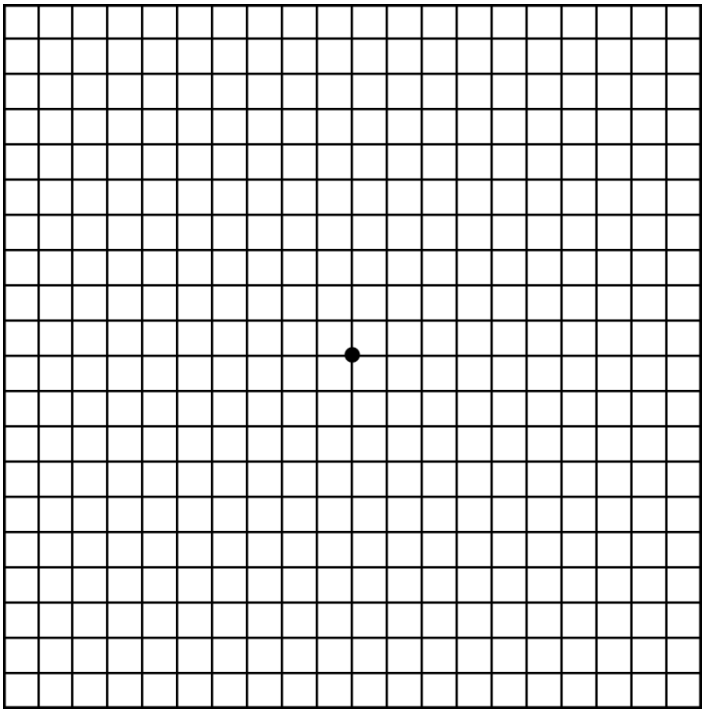
Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

NB: Amsler Tests within EDNA are to be completed on the **EDNA study eye ONLY**



Instructions for Use

1. **Wear the glasses you would normally use when reading.**
2. **Hold the chart at the distance at which you would read a book. Cover the eye in which you are getting injections so that you are looking at the chart with your EDNA study eye.**
3. **Fix your gaze on the centre black dot.**
4. **Keeping your gaze fixed on the black dot, try to see if any lines are distorted or missing.**
5. **If you notice that the lines are not straight or blurred please mark the region of the chart that is abnormal with a pen or pencil; If the lines on the chart look normal tick this box** ☐
6. ***Always* keep the Amsler's Chart the *same distance* from your eyes each time you test.**

Please turn over ➡

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Thank you

Please hand this booklet back to your clinician (Nurse or Doctor) now; the rest of this form is for them to fill in.

BASELINE VISIT CRF

Study Number | | | | | |

Date of Study Visit | D | D | / | M | M | / | Y | Y | Y | Y |

Confirm EDNA Study Eye: Right ☐ Left ☐

Drug used in treated eye:
Lucentis ☐
Eylea ☐
Avastin ☐

PATIENT HISTORY

Smoking History: Current ☐ Ex-Smoker ☐ Never smoked ☐

Hypertension Yes ☐ No ☐
Cardiovascular Disease Yes ☐ No ☐
Diabetes Yes ☐ No ☐
Nutritional Supplements Yes ☐ No ☐ If yes, name supplement _____

Family History of AMD Yes ☐ No ☐
(parents/siblings)

BMI Weight (kg) _____ Height (cm) _____
Not recorded ☐ Not recorded ☐

BLOOD SAMPLE COLLECTION

Blood Sample Collected? Not consented ☐ Yes ☐ No ☐ If no why?_____

SLIT LAMP BIOMICROSCOPY OF STUDY EYE

Does the patient have a cataract? Yes ☐ No ☐

If phakic, grade as per AREDS grading sheet (please tick box)

	0	1	2	3
NS				
PSC				
Cortical				

BASELINE DIAGNOSTIC TESTS

- **Does the FFA confirm absence of nAMD in EDNA study eye?**

Yes ☐ No ☐ (***If no this patient is INELIGIBLE***)

- **AMSLER TEST**

Is there any distortion or scotoma in study eye? Yes ☐ No ☐

Even if yes to the above, the patient is still eligible but Amsler should not be performed at subsequent visits.

- **VISUAL ACUITY**

No of letters RE ☐ No of letters LE ☐ *(If study eye <68 letters this patient is INELIGIBLE)*

Indicate the VA method used (tick only one below)

Unaided		Pinhole		Patient's Glasses		Refraction	

- **OCT FINDINGS IN STUDY EYE (SELECT ONLY ONE)**

Normal ☐
Early AMD ☐
Late AMD ☐ *(if late AMD this patient is INELIGIBLE)*

- **FUNDUS EXAMINATION OF STUDY EYE ONLY (SELECT ONLY ONE)**

No AMD ☐
Early AMD ☐
Late AMD ☐ if late AMD select type: ☐ geographic atrophy *(this patient is eligible if fulfilling VA requirements in the study eye)*

☐ exudative nAMD *(this patient is INELIGIBLE)*

Any other significant co-morbidity? Yes ☐ No ☐ If yes please detail_____

SIGNATURE AND NAME (BLOCK CAPITALS) OF PERSON COMPLETING FORM

Signature_____ PRINT NAME_____

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

The 18 month Appointment Checklist:

***** Remember at 18 months you should collect all 5 EDNA tests and the FFA *****

#	Task	Initials	Date
1.	Study ID entered and study eye marked with stickers		
2.	Patient questionnaire completed by patient		
3.	Amsler completed by patient (*unless positive at baseline*)		
4.	Visual acuity completed using same method as baseline		
5.	OCT completed		
6.	Fundus examination completed INCLUDING colour photos		
7.	FFA completed (+ clinician diagnosis if FFA is negative/inconclusive)		
8.	*OPTIONAL* – OCTA completed if available		
9.	If FFA result or clinician diagnosis is nAMD take blood and mark blood tube as 'exit visit' and send to Belfast (if consented to blood collection)		
10.	Next appointment date noted (if no nAMD detected)		
11.	CRF data entered into EDNA Website 18 month visit https://w3.abdn.ac.uk/hsru/edna/		
12.	Imaging data uploaded to CARF (all images – colour photos, OCT, FFA + optional ICG and OCTA if conducted)		
13.	EDNA hardcopy patient data filed securely		

Note about STUDY EXIT.

If FFA result or clinician diagnosis is nAMD this is the study end-point for EDNA. This will be automatically detected on the study website and there is ***no need*** *to complete a change of status form.*

NOTES/QUERIES

Need help? Contact the Study office in Aberdeen! ☎

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

How is your vision in the untreated eye, compared with the last visit?

Please see below four possible answers. We would ask you to tick one box (only)

About the same or better	A bit worse	Worse	Much worse

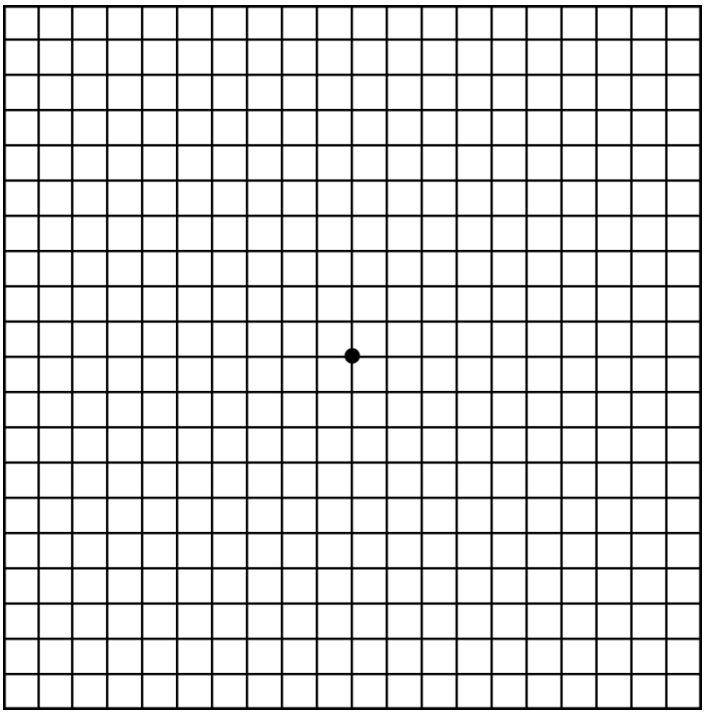
Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

NB: Amsler Tests within EDNA are to be completed on the **EDNA study eye ONLY**



Instructions for Use

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2. **Hold the chart at the distance at which you would read a book. Cover the eye in which you are getting injections so that you are looking at the chart with your EDNA study eye.**
3. **Fix your gaze on the centre black dot.**
4. **Keeping your gaze fixed on the black dot, try to see if any lines are distorted or missing.**
5. **If you notice that the lines are not straight or blurred please mark the region of the chart that is abnormal with a pen or pencil; If the lines on the chart look normal tick this box** ☐
6. ***Always* keep the Amsler's Chart the *same distance* from your eyes each time you test.**

Please turn over ➡

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Thank you

Please hand this booklet back to your clinician (Nurse or Doctor) now; the rest of this form is for them to fill in.

EDNA 18 MONTH VISIT CRF

TO BE COMPLETED at 18 months for all participants who remain in the study

Study Number | | | | | |

Date D D / M M / Y Y Y Y

Confirm Study Eye: Right ☐ Left ☐

1. PATIENT SELF- REPORTED VISION (STUDY EYE)

Has patient reported vision much worse on EDNA vision questionnaire?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

2. AMSLER TEST (STUDY EYE)

Is there a new area of distortion or blank spots where previously there was none or clear evidence of an increase in the area of distortion or scotoma?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

3. VISUAL ACUITY (using the method recorded on the baseline CRF)

No of letters RE:_____ No of letters LE: _____

Has visual acuity reduced by 10 letters or more in STUDY EYE since baseline study visit?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

4. OCT (STUDY EYE)

Does OCT in STUDY EYE show signs of neovascular AMD?

SRF on OCT Yes ☐ No ☐ Neovascular PED on OCT Yes ☐ No ☐

IRF on OCT Yes ☐ No ☐ Any other reason for OCT being positive? Yes ☐ No ☐

If yes please give reason _____

OCT not done ☐ If not done give reason _____

5. FUNDUS EVALUATION (STUDY EYE)

Method of assessment:

Colour fundus photography? Yes ☐ No ☐ Slit lamp biomicroscopy? Yes ☐ No ☐

Clinical signs of nAMD on Fundus? Yes ☐ No ☐ Not done ☐

If not done give reason _____

FLUORESCEIN ANGIOGRAPHY (FFA) * ALL PATIENTS TO HAVE FFA at 18 months *

Date FFA performed ☐☐ ☐☐ ☐☐☐☐

1. Does the FFA confirm Neovascular AMD in STUDY eye?
   - Yes ☐ No ☐ Inconclusive ☐ Not done ☐ If not done state reason_____

2. If No or Inconclusive in 1 is your clinical diagnosis Neovascular? Yes ☐ No ☐
   If Yes, what is the reason? _____

   - If No in 2 (i.e. no nAMD) then continue with EDNA monitoring.

3. If Yes in 1 or 2 (i.e. diagnosis Neovascular AMD) this is the end point for EDNA monitoring.
   Was treatment started today? Yes ☐ No ☐

4. If this is the end point for EDNA monitoring please collect bloods (if patient consented to this at baseline)

   Bloods taken? Yes ☐ No ☐ Not consented ☐

6. PATIENT FOLLOW-UP

Has this patient got a next appointment date? Yes☐ No ☐ If yes what is this date?_____
If no has this patient been discharged today? Yes☐ No☐

SIGNATURE AND NAME (BLOCK CAPITALS) OF CLINICIAN COMPLETING FORM

Signature _____PRINT NAME_____

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

The 36 month Appointment Checklist:

***** Remember at 36 months you should collect all 5 EDNA tests and the FFA *****

This is the final appointment for EDNA

#	Task	Initials	Date
1.	Study ID entered and study eye marked with stickers		
2.	Patient questionnaire completed by patient		
3.	Amsler completed by patient (*unless positive at baseline*)		
4.	Visual acuity completed using same method as baseline		
5.	OCT completed		
6.	Fundus examination completed INCLUDING colour photos		
7.	FFA completed (+ clinician diagnosis if FFA is negative/inconclusive)		
8.	*OPTIONAL* – OCTA completed if available		
9.	Bloods taken and marked on tube as 'exit visit' and send to Queen's University Belfast (if patient consented to blood collection)		
10.	Advice given about next appointment outside of EDNA		
11.	CRF data entered into EDNA website 36 month visit https://w3.abdn.ac.uk/hsru/edna/		
12.	Imaging data uploaded to CARF (all images – colour photos, OCT, FFA + optional ICG and OCTA if conducted)		
13.	EDNA hardcopy patient data filed securely		

NOTES/QUERIES

Need help? Contact the Study office in Aberdeen! ☎

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

How is your vision in the untreated eye, compared with the last visit?

Please see below four possible answers. We would ask you to tick one box (only)

About the same or better	A bit worse	Worse	Much worse

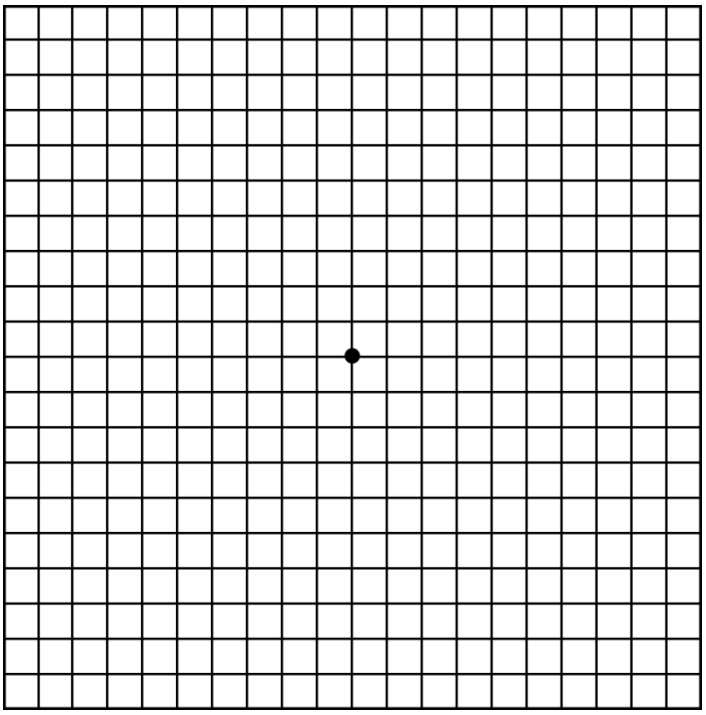
Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

NB: Amsler Tests within EDNA are to be completed on the **EDNA study eye ONLY**



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6. ***Always* keep the Amsler's Chart the *same distance* from your eyes each time you test.**

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Thank you

Please hand this booklet back to your clinician (Nurse or Doctor) now; the rest of this form is for them to fill in.

36 MONTH VISIT CRF

TO BE COMPLETED at 36 months for all participants who remain in the study

Study Number | | | | | |

Date D D / M M / Y Y Y Y

Confirm Study Eye: Right ☐ Left ☐

36 MONTH VISIT – Bloods taken? Yes ☐ No ☐ Not consented ☐

1. PATIENT SELF- REPORTED VISION (STUDY EYE)

Has patient reported vision much worse on EDNA vision questionnaire?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

2. AMSLER TEST (STUDY EYE)

Is there a new area of distortion or blank spots where previously there was none or clear evidence of an increase in the area of distortion or scotoma?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

3. VISUAL ACUITY (using the method recorded on the baseline CRF)

No of letters RE:_____ No of letters LE: _____

Has visual acuity reduced by 10 letters or more in STUDY EYE since baseline study visit?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

4. OCT (STUDY EYE)

Does OCT in STUDY EYE show signs of neovascular AMD?

SRF on OCT Yes ☐ No ☐ Neovascular PED on OCT Yes ☐ No ☐

IRF on OCT Yes ☐ No ☐ Any other reason for OCT being positive? Yes ☐ No ☐

If yes please give reason _____

OCT not done ☐ If not done give reason _____

5. FUNDUS EVALUATION (STUDY EYE)

Method of assessment:

Colour fundus photography? Yes ☐ No ☐ Slit lamp biomicroscopy? Yes ☐ No ☐

Clinical signs of nAMD on Fundus? Yes ☐ No ☐ Not done ☐

If not done give reason _____

FLUORESCEIN ANGIOGRAPHY (FFA) * ALL PATIENTS TO HAVE FFA at 36 months *

Date FFA performed D D / M M / Y Y Y Y

1. Does the FFA confirm Neovascular AMD in STUDY eye?
   - Yes ☐ No ☐ Inconclusive ☐ Not done ☐ If not done state reason_____

2. If No or Inconclusive in 1 is your clinical diagnosis Neovascular? Yes ☐ No ☐
   If Yes, what is the reason? _____

6. PATIENT FOLLOW-UP

Has this patient got a next appointment date? Yes ☐ No ☐ If yes what is this date?_____
If no has this patient been discharged today? Yes ☐ No ☐

SIGNATURE AND NAME (BLOCK CAPITALS) OF PERSON COMPLETING FORM

Signature_____PRINT NAME_____

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

The Routine Follow up Appointment Checklist:

#	Task	Initials	Date
1.	Study ID entered and study eye marked with stickers		
2.	Patient questionnaire completed by patient		
3.	Amsler completed by patient *(unless positive at baseline)*		
4.	Visual acuity completed using same method as baseline		
5.	OCT completed		
6.	Fundus examination completed (including colour photos if any tests trigger FFA)		
7.	Next appointment date noted		
8.	FFA requested (*if triggered by results of 2-6 above*)		
9.	FFA results entered (*if triggered by results of 2-6 above*)		
10.	*OPTIONAL* – OCTA completed if FFA triggered		
11.	Bloods taken and marked on tube as 'exit visit' and send to Queen's University Belfast (*if FFA result is positive and consent to bloods given*)		
12.	Relevant imaging data entered to CARF -*if FFA triggered (colour photos, OCT, FFA +optional ICG and OCTA if conducted*)		
13.	CRF data entered into EDNA website https://w3.abdn.ac.uk/hsru/edna/		
14.	EDNA hardcopy patient data filed securely		

Note about STUDY EXIT.
If FFA result or clinician diagnosis is nAMD this is the study end-point for EDNA. This will be automatically detected on the study website and there is ***no need*** *to complete a change of status form.*

NOTES/QUERIES

Need help? Contact the Study office in Aberdeen! ☎

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

How is your vision in the untreated eye, compared with the last visit?

Please see below four possible answers. We would ask you to tick one box (only)

About the same or better	A bit worse	Worse	Much worse

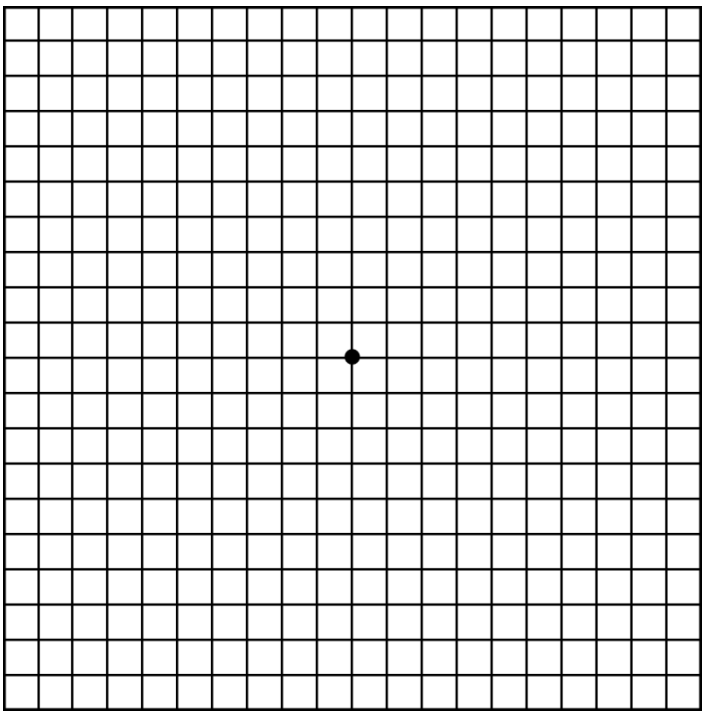
Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Study Number | | | | | |

Date D D / M M / Y Y Y Y

NB: Amsler Tests within EDNA are to be completed on the **EDNA study eye ONLY**



Instructions for Use

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5. **If you notice that the lines are not straight or blurred please mark the region of the chart that is abnormal with a pen or pencil; If the lines on the chart look normal tick this box** ☐
6. ***Always* keep the Amsler's Chart the *same distance* from your eyes each time you test.**

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

Thank you

Please hand this booklet back to your clinician (Nurse or Doctor) now; the rest of this form is for them to fill in.

EDNA ROUTINE FOLLOW-UP VISIT

PLEASE COMPLETE AT EACH ROUTINE CLINIC APPOINTMENT

Study Number | | | | | |

Date D D / M M / Y Y Y Y

Confirm Study Eye: Right ☐ Left ☐

1. PATIENT SELF- REPORTED VISION (STUDY EYE)

Has patient reported vision much worse on EDNA vision questionnaire?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

If YES trigger FFA

2. AMSLER TEST (STUDY EYE)

Is there a new area of distortion or blank spots where previously there was none or clear evidence of an increase in the area of distortion or scotoma?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

If YES trigger FFA

3. VISUAL ACUITY (using the method recorded on the baseline CRF)

No of letters RE:_____ No of letters LE: _____

Has visual acuity reduced by 10 letters or more in STUDY EYE since baseline study visit?

Yes ☐ No ☐ Not done ☐ If not done give reason _____

If YES trigger FFA

4. OCT (STUDY EYE)

Does OCT in STUDY EYE show signs of neovascular AMD?

SRF on OCT Yes ☐ No ☐ Neovascular PED on OCT Yes ☐ No ☐

IRF on OCT Yes ☐ No ☐ Any other reason for OCT being positive? Yes ☐ No ☐

If yes please give reason _____

If YES to any – trigger FFA

OCT not done ☐ If not done give reason _____

5. FUNDUS EVALUATION (STUDY EYE)

Method of assessment:

Colour fundus photography? Yes ☐ No ☐ Slit lamp biomicroscopy? Yes ☐ No ☐

Clinical signs of nAMD on Fundus? Yes ☐ No ☐ Not done ☐

If not done give reason _____

If YES trigger FFA

FLUORESCEIN ANGIOGRAPHY (FFA)

PLEASE COMPLETE THIS SECTION IF ANY OF THE ABOVE TESTS TRIGGER FFA

Date FFA performed ☐☐ ☐☐ ☐☐☐☐

1. Does the FFA confirm Neovascular AMD in STUDY eye?
   - Yes ☐ No ☐ Inconclusive ☐ Not done ☐ If not done state reason_____

2. If No or Inconclusive in 1 is your clinical diagnosis Neovascular? Yes ☐ No ☐
   If Yes, what is the reason? _____
   - If No in 2 (i.e. no nAMD) then continue with EDNA monitoring.

3. If Yes in 1 or 2 (i.e. diagnosis Neovascular AMD) this is the end point for EDNA monitoring. Was treatment started today? Yes ☐ No ☐

4. If this is the end point for EDNA monitoring please collect bloods (if patient consented to this at baseline)

   Bloods taken? Yes ☐ No ☐ Not consented ☐

6. PATIENT FOLLOW-UP

Has this patient got a next appointment date? Yes ☐ No ☐ If yes what is this date?_____
If no was this patient discharged today? Yes ☐ No ☐

SIGNATURE AND NAME (BLOCK CAPITALS) OF CLINICIAN COMPLETING FORM

Signature_____PRINT NAME_____

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

The Serious Adverse Event (SAE) and Death (for any reason) report form

Within the EDNA study we will record only any AE/SAE relating to collection of blood or FFA requested during involvement in the study. AEs relating to FFAs conducted prior to recruitment to the study will not be reported.

Any AE/SAE resulting from treatment to the nAMD eye during the study will not be recorded as an AE/SAE. Once an EDNA participant has nAMD in the study eye, or the end of follow- up, any subsequent AE or SAE will not be recorded.

An **adverse event** (AE) is any untoward medical event affecting a clinical study participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

A **serious adverse event** (SAE), is any AE, that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- is otherwise considered medically significant by the investigator

Reporting of deaths during the study:

Most participants in the study will be elderly, and we anticipate that 50% will be >75 years at the time of recruitment. Therefore it is expected that a proportion of the cohort will die from causes unrelated to the study over the period of follow up. Deaths unrelated to the study procedures will not be recorded as SAEs but will be recorded within the CRF.

Need help? Contact the Study office in Aberdeen! ☎

V2 18_1_18

Adverse Event/SAE & Death Report Form

To be completed for any Serious Adverse Event (SAE) that is:

- **related (resulted from administration of any of the research procedures) and**
- **expected or unexpected (unexpected events are events which are not listed in section 4 of the protocol as a possible expected serious occurrence)**

ALL DEATHS must be recorded using this Report Form

Report date ☐☐ / ☐☐ / ☐☐☐☐ **Study No** ☐☐☐☐☐

1. Type of event
(tick all that apply to the adverse event – if any boxes are ticked the adverse event is "serious")

- **Patient died** ☐
- **Life threatening** ☐
- **Hospitalisation or prolongation of existing hospitalisation** ☐
- **Congenital anomaly / birth defect** ☐
- **Persistent or significant disability or incapacity** ☐
- **Considered medically significant by the investigator** ☐

2. Date of event ☐☐ / ☐☐ / ☐☐☐☐

3. Brief details of adverse event (reference; section 4.1 of Protocol)

FFA related

Local Skin Irritation ☐

Development Erythematous Lesions on skin ☐

Anaphylaxis (generalised reaction to FFA pulmonary or otherwise) ☐

Other (please specify below) ☐

_____

Blood Related

Bruising/ Discomfort at site of puncture ☐

4. Is this an "expected" serious adverse event? Yes ☐ No ☐

5. Other relevant history (e.g. diagnostics, allergies, etc)

6. Place where adverse event took place/detected

7. Details of any intervention required

8. Assessment of whether the event was caused by study participation:

8a. Is it reasonably likely that the adverse event resulted from administration of any of the procedures required by EDNA?

Yes ☐ No ☐

8b. Please explain your decision.

9. Name and position of person (PI or a delegated medical person) confirming assessment of this event

Name

Position

9a. Date of PI assessment ☐☐ / ☐☐ / ☐☐☐☐

For CI use only

If SAE is unexpected and related, a CI assessment is required.

Does the CI confirm that this is a serious, unexpected and related SAE?

Yes ☐ **No** ☐

Date of CI assessment ☐☐ / ☐☐ / ☐☐☐☐

Edna

Early Detection of Neovascular Age-related macular degeneration (AMD)

The Withdrawal Form

Need help? Contact the Study office in Aberdeen! 

V2 18_1_18

Early Detection of Neovascular Age-related macular degeneration (AMD)

EDNA Withdrawal CRF

Study Number | | | | | |

WITHDRAWAL

Withdrew consent (tick all that apply):

To future follow-up ☐

To use of existing data collected ☐

To use of existing blood collected ☐

OTHER REASON

Please give details _____

SIGNATURE AND NAME (BLOCK CAPITALS) OF PERSON COMPLETING FORM

Signature_____ PRINT NAME_____

Date D D / M M / Y Y Y Y

V1.1 24_07_15

B. EDNA study procedures

EDNA Study Procedures.

Contents

1. Guidelines for completion of Baseline clinical measurements and completing baseline CRF

DRUG USED

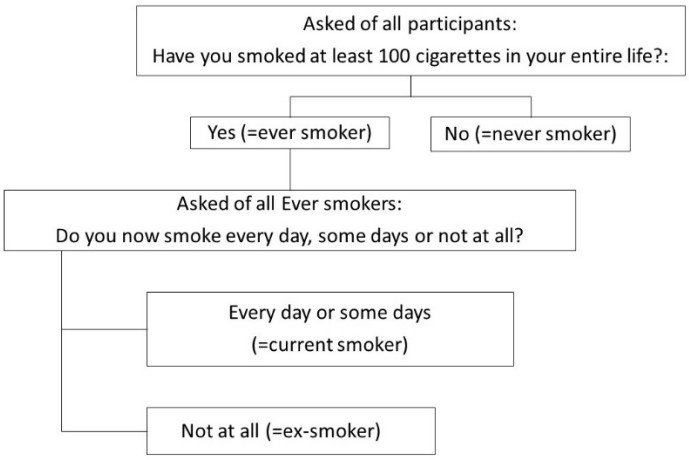
Please record which is the treatment drug for the non-EDNA study eye.

PATIENT HISTORY

In order to collect the patient's history please review the medical notes and ask the patient. If either the notes or the patient are positive, record as positive on the CRF.

- Smoking History:

Smoking History will determined by asking two questions:



- Hypertension

Record yes if patient has a history of having been diagnosed as having high blood pressure or taking antihypertensives.

- Cardiovascular Disease

Record yes if patient has any of the following cardiovascular disease: angina, heart attack, transient ischaemic attacks (TIA) and stroke.

- **Diabetes**

Record yes if diagnosed as having diabetes by GP or hospital

- **Nutritional Supplements**

Ask patient if they are taking any of the following: vitamins, lutein and zeaxanthin, fish oil

- **Family History of AMD**

Record yes if parents or siblings have been diagnosed with AMD.

- **BMI**

Please measure the participant's height and weight and record on the CRF. In exceptional circumstances, if height/weight cannot be measured then self-reported height and weight can be entered.

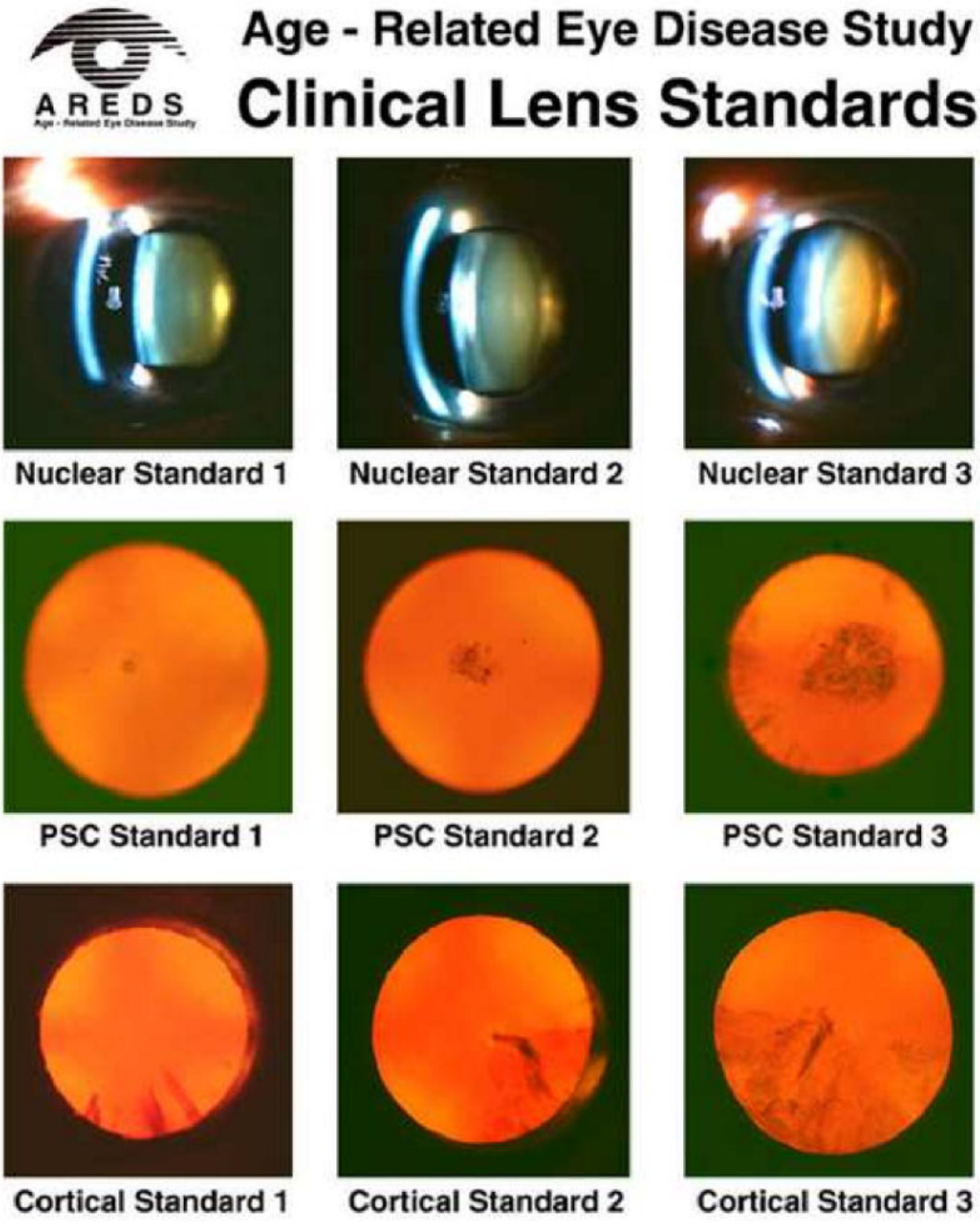
BLOOD SAMPLE COLLECTION

If the patient has consented to blood collection as part of EDNA please collect/process blood according to EDNA blood sample collection protocol.

In exceptional circumstances, if a patient has consented to blood collection and this was not done at the baseline appointment, it can be collected at the next routine clinic visit.

SLIT LAMP BIOMICROSCOPY

Using a Slit Lamp evaluate the state of the lens according to the following pictorial standards.



Taken from http://www.sciencedirect.com/science/article/pii/S0161642010002459

BASELINE DIAGNOSTIC TESTS

The following assessments may be performed at the baseline study visit if data from the routine visit is not available in order to establish a baseline for all the comparator technologies at study entry.

- FFA

A fluorescein angiogram conducted on referral should confirm that the patient has no signs of nAMD in the EDNA study eye. If an FFA has already been conducted, there is no need to repeat an FFA for EDNA but the results of baseline FFA should be checked to ensure the patient is eligible at baseline.

- Amsler test

The patient should complete the Amsler within the EDNA CRF for the EDNA study eye according to the instructions on the CRF clearly explained to them. Make sure the patient is aware of the eye to be occluded. Please emphasize that the eye to be tested is the EDNA study eye and the eye to be occluded is the fellow eye which is on active treatment for nAMD.

After completion, record on the baseline CRF whether there are any distortion or scotoma marks on the Amsler grid.

If the patient has a baseline distortion or scotoma they are still eligible to take part in EDNA. However, no further Amsler tests need to be collected as part of EDNA follow-up.

- Visual acuity

Visual acuity should be measured using a LogMAR/EDTRS chart calibrated for the distance used and recorded in number of letters read for both eyes. A logMAR/EDTRS conversion chart is within the CRF.

Whether the BCVA is undertaken using pinhole/refraction/unaided/using habitual refraction should also be recorded.

N.B. The same method should be used for all follow-up appointments so if follow-up visions are routinely performed using a different method to baseline please record baseline VA using the routine follow-up method.

- OCT findings in study eye

No validation is required to conduct the OCT for the EDNA study. Please follow the CARF protocol for image acquisition. If an enhanced depth imaging (EDI) scan of the choroid is collected this can be submitted as an optional extra. Any study team member who can interpret tomograms can complete this section of the CRF. The patient is ineligible if baseline OCT shows signs of late AMD. Section 3.2.5 of the EDNA protocol gives further details of possible abnormalities which may be detected by clinical interpretation of the OCT.

- Fundus examination of study eye

This can be either assessed by a Slit Lamp clinical examination or from fundus photography.

We recommend that colour fundus photography includes fields 1 and 2 comprising of the central macula. If a wide field camera is used a single image is sufficient.

The examination of the eye and or the colour fundus images with completion of the CRF can be made by any appropriately qualified member of the study team.

No AMD	No drusen or pigmentary irregularities or only small hard drusen
Early AMD	Soft drusen and/or pigmentary irregularities
Late AMD	Exudative Neovascular AMD or Geographic atrophy: if Geographic atrophy with sufficient vision (VA≥68) patient is eligible. If exudative nAMD patient is ineligible.

Please record any other significant co-morbidity.

READING CENTRE INFORMATION

Please complete the table and upload the relevant baseline images to the reading centre (CARF) using the documentation provided to photographers by CARF.

2. Guidelines for completion of follow-up measurements and completing routine follow-up CRF

As detailed in the EDNA protocol, a routine follow-up CRF should be completed for each routine clinic visit once a patient is recruited to EDNA. At each visit, results from the 5 EDNA diagnostic tests should be entered. If any test is not conducted this should be recorded as 'not done'.

If any diagnostic test triggers an FFA as described below, please ensure all 5 EDNA diagnostic test results are recorded and request FFA within one month.

PATIENT SELF-REPORTED VISION

Whenever possible, patient self-reported vision should be collected **before** the patient completes the AMSLER chart.

The patient should be given the EDNA questionnaire and asked to tick only one box making it clear that they are completing this for the EDNA study eye which is the eye they are not having injections in.

If the patient reports vision 'much worse' this should trigger an FFA.

AMSLER

In patients who reported any distortion at baseline, the Amsler test does not need to be completed at follow-up.

In all other patients an Amsler should be completed at each routine follow-up appointment within the EDNA CRF for the EDNA study eye according to the instructions on the CRF clearly explained to them. Make sure the correct eye is covered throughout

After completion, a clinician should assess whether there is any clearly reported distortion/scotoma in which case an FFA should be triggered.

If an Amsler has previously triggered a negative FFA, any subsequent Amsler test should be assessed by a clinician. If the Amsler does not show any clear evidence of an increase in the area of distortion or scotoma then an FFA should not be triggered. However, if the clinician judges that there is clear evidence of an increase in the area of distortion or scotoma then an FFA should be triggered.

VISUAL ACUITY

Visual acuity should be recorded for both eyes, using the standard practice method as used on the patient at baseline, at each follow-up visit.

If the visual acuity in the EDNA study eye has reduced by 10 letters or more from the baseline measurement then an FFA should be triggered.

OCT

No validation is required to conduct the OCT for the EDNA study. Please follow the CARF protocol for image acquisition. If an enhanced depth imaging (EDI) scan of the choroid is collected this can be submitted as an optional extra . Any study team member who can interpret tomograms can complete this section of the CRF.

If any signs of neovascular AMD are found these should be recorded on the CRF and an FFA should be triggered.

FUNDUS EVALUATION

The fundus evaluation should be interpreted by an appropriately trained individual. Fundus evaluation can be by slit lamp biomicroscopy and/or colour fundus photography.

If either slit lamp and/or photography show clinical signs of nAMD on Fundus an FFA should be triggered.

FLUORESCEIN ANGIOGRAPHY (FFA)

This section only needs to be completed if at any routine follow-up, any of the 5 EDNA diagnostic tests triggers an FFA as described above.

Please ensure all 5 EDNA diagnostic test results are recorded on the routine follow up CRF.

An FFA should be requested within one month and the FFA section of the CRF then completed.

If the FFA confirms neovascular AMD, this is the end-point for EDNA monitoring.

If the FFA does not confirm neovascular AMD or is inconclusive but the responsible clinician diagnoses neovascular AMD, this is the end-point for EDNA monitoring.

In all other cases, please continue EDNA monitoring until 36 months.

3. Guidelines for completion of the 18 month research appointment and CRF

For all patients who have not exited EDNA due to conversion to nAMD in the EDNA study eye a study visit should be arranged at 18 months post recruitment.

At each study visit all 5 EDNA diagnostic tests should be conducted and results entered. An FFA should also be conducted for all patients (see below).

PATIENT SELF-REPORTED VISION

Whenever possible, patient self-reported vision should be collected **before** the patient completes the AMSLER chart.

The patient should be given the EDNA questionnaire and asked to tick only one box making it clear that they are completing this for the EDNA study eye which is the eye they are not having injections in.

AMSLER

In patients who reported any distortion at baseline, the Amsler test does not need to be completed at follow-up.

In all other patients an Amsler should be completed at each routine follow-up appointment within the EDNA CRF for the EDNA study eye according to the instructions on the CRF clearly explained to them. Make sure the correct eye is covered throughout

After completion, a clinician should assess whether there is any clearly reported distortion/scotoma and record on the CRF.

VISUAL ACUITY

Visual acuity should be recorded for both eyes, using the standard practice method as used on the patient at baseline, at each follow-up visit.

OCT

No validation is required to conduct the OCT for the EDNA study. Please follow the CARF protocol for image acquisition. If an enhanced depth imaging (EDI) scan of the choroid is collected this can be submitted as an optional extra. Any study team member who can interpret tomograms can complete this section of the CRF.

If any signs of neovascular AMD are found these should be recorded on the CRF.

FUNDUS EVALUATION

The fundus evaluation should be interpreted by an appropriately trained individual. Fundus evaluation can be by slit lamp biomicroscopy and/or colour fundus photography.

If either slit lamp and/or photography show clinical signs of nAMD on Fundus this should be recorded on the CRF.

FLUORESCEIN ANGIOGRAPHY (FFA)

All patients who have not exited the study should have a study visit FFA at 18 months.

If the patient has had a negative FFA within the two months preceding the 18month visit there is no need to repeat the FFA and the data from the preceding FFA can be recorded on the CRF.

If the patient does not attend at 18 months an FFA should be performed at the next available timepoint.

Please ensure all 5 EDNA diagnostic test results are also recorded on the 18month CRF.

If the FFA confirms neovascular AMD, this is the end-point for EDNA monitoring.

If the FFA does not confirm neovascular AMD or is inconclusive but the responsible clinician diagnoses neovascular AMD, this is the end-point for EDNA monitoring.

In all other cases, please continue monitoring under routine practice until 36 months.

4. Guidelines for completion of 36 month (exit) research appointments and CRF

For all patients who have not exited EDNA due to conversion to nAMD in the EDNA study eye a final study visit should be arranged at 36 months post recruitment. This is the end-point for EDNA monitoring.

At each study visit the 5 EDNA diagnostic tests should be conducted and results entered. An FFA should also be conducted for all patients.

BLOOD SAMPLE COLLECTION

If the patient consented to blood collection as part of EDNA please collect/process blood according to EDNA blood sample collection protocol.

PATIENT SELF-REPORTED VISION

Whenever possible, patient self-reported vision should be collected **before** the patient completes the AMSLER chart.

The patient should be given the EDNA questionnaire and asked to tick only one box making it clear that they are completing this for the EDNA study eye which is the eye they are not having injections in.

AMSLER

In patients who reported any distortion at baseline, the Amsler test does not need to be completed at follow-up.

In all other patients an Amsler should be completed at each routine follow-up appointment within the EDNA CRF for the EDNA study eye according to the instructions on the CRF clearly explained to them. Make sure the correct eye is covered throughout

After completion, a clinician should assess whether there is any clearly reported distortion/scotoma and record on the CRF.

VISUAL ACUITY

Visual acuity should be recorded for both eyes, using the standard practice method as used on the patient at baseline, at each follow-up visit.

OCT

No validation is required to conduct the OCT for the EDNA study. Please follow the CARF protocol for image acquisition. If an enhanced depth imaging (EDI) scan of the choroid is collected this can be submitted as an optional extra. Any study team member who can interpret tomograms can complete this section of the CRF. If any signs of neovascular AMD are found these should be recorded on the CRF.

FUNDUS EVALUATION

The fundus evaluation should be interpreted by an appropriately trained individual. Fundus evaluation can be by slit lamp biomicroscopy and/or colour fundus photography.

If either slit lamp and/or photography show clinical signs of nAMD on Fundus this should be recorded on the CRF.

FLUORESCEIN ANGIOGRAPHY (FFA)

All patients who have not exited the study should have a study visit FFA at 36 months.

If the patient has had a negative FFA within the two months preceding the 36 month visit there is no need to repeat the FFA and the data from the preceding FFA can be recorded on the CRF.

If the patient does not attend at 36 months an FFA should be performed at the next available timepoint.

Please ensure all 5 EDNA diagnostic test results are also recorded on the 36 month CRF.

This is the end-point for EDNA monitoring.

C. READING CENTRE GRADING DEFINITIONS

Study Name: EDNA
Document Title: Supplement 2 - Colour Fundus Grading Definitions and Rules

Prepared By

Document Owner(s)	Project/Organization Role	Signature	Date
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Reviewed By

Document Reviewer	Project/Organization Role	Signature	Date
Barbra Hamill	Ophthalmic Image Grader	[redacted]	01MAY2017

Approved By

Name	Project/Organization Role	Signature	Date
Prof Tunde Peto	Director of CARF	[redacted]	01MAY2017

Project Closure Report Version Control

Version	Date	Author	Change Description
1.0	01MAY2017	David Parry	Created Document

Initials	Name	Title	Functional Role
DGP	David Parry	Mr	Senior Ophthalmic Image Grader
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Revision History

Revision	Date	Author	Section	Page	Reason for Change
1.1	09/07/2020	CJ			EDNA only protocol

Contents

1.0 Colour Fundus Imaging

Colour fundus images are provided and graded at all visits. They should also be used by graders to assist in the grading of FFA images. The following document contains information related to the appearance of AMD features on colour photographs. The presence of absence of features is graded on colour images.

However, graders must remember that if that you can **only grade what you see**. For example, if a certain lesion characteristic is identified in the colours but cannot be identified on any of the FFA images then that feature should not be graded as present on the FFA grading form. If however, the grader questions the presence of a particular lesion component on FFA, the colour can be used as a method of verification.

2.0 Image Quality

The image quality questions that are on the grading form are covered in the NetwORC Appendix's B Image Quality and C Artefact's for more info.

If the image quality is poor on the colour images, please do use the FFA images to confirm any feature of nvAMD.

3.0 Exudative AMD Present

The presence of exudative AMD is based on the presence of any of the following features (excluding atrophy outside the lesion). If exudative AMD is not present, any questions relating to exudative AMD will not be visible.

- CNV
- Blood
- Exudates
- PED*
- SRF*

*If stereo images are supplied

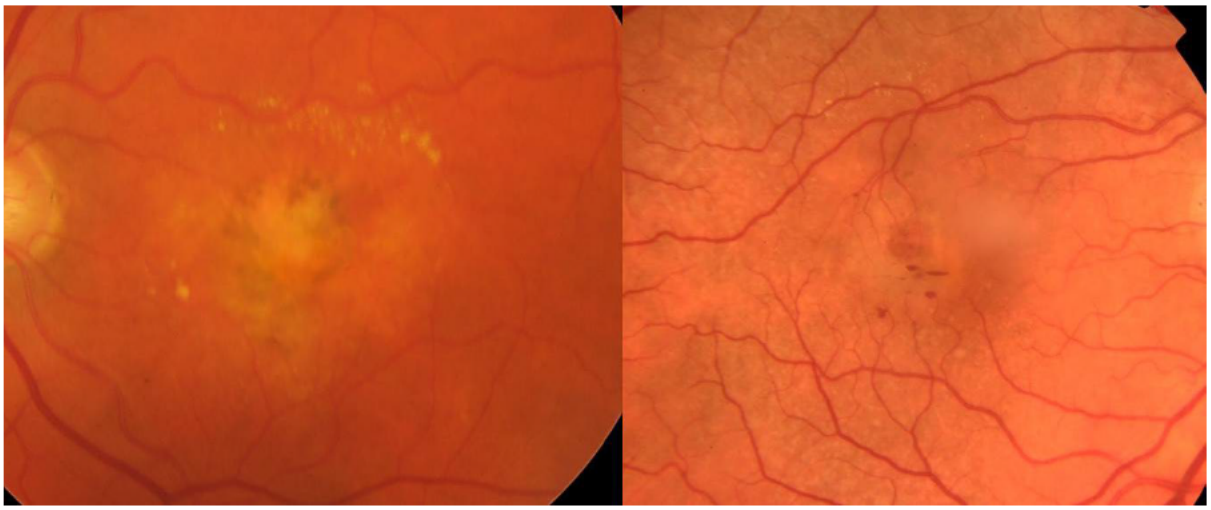

Fig 1. Exudative AMD

Grade Options
Yes
No
Cannot Grade (CG)

3.1 Atrophy

This section covers both atrophy within the lesion and atrophy outside the lesion (or in the absence of a lesion). Graders should assess all colour images given. Atrophy should be graded as present if the following apply:

Area in question is at least 175um in diameter

AND:

Any two of the following are characteristics are identified:

- Choroidal vessels visible
- Well defined margins
- Scalloped edges

Grade Options
Yes
No
Cannot Grade

3.1.1 Atrophy - Extra-lesional

Atrophy outside the lesion is a sharply defined drop-out of the RPE and choriocapillaris (which must be at least 175 µm in diameter), exposing the underlying large choroidal vessels.

Several patterns characterise the appearance of atrophy outside the lesion. For example, it can appear as one patch, with its size varying from meeting the minimum criteria, through to very large. Often it begins as several smaller oval/round lesions surrounding the fovea.
If large atrophic areas are present, they often have scalloped edges (the scalloped edges are the last evidence that individual atrophic patches existed prior to fusion into one large patch.)
An area of atrophy outside the lesion must be at least 175 µm. In addition to size, two of the three following characteristics must be present:

- Visibility of choroidal vessels
- Well defined margins
- Scalloped edges

In the absence of other features, the presence of a sharp edge only does not constitute atrophy outside the lesion. In such cases, the RPE should be re-evaluated.
Where there is a pale RPE, it can be difficult to spot hypo-pigmentation and the edges of the atrophy because of reduced contrast. An indicator of the limits of atrophy can be found by picking a choroidal vessel and following it for colour change.
The single greatest characteristic difference between hypo-pigmentation and atrophy is pigment loss, which allows the larger choroidal vessels to be seen. The choroid can have some pinkness.

Information Only

Staging of atrophy, as per Jane Armstrong, Wisconsin, London meeting January 2007.

Mild: Two features, scalloped edge, well defined margins but choroidal vessels may not be visible.
Moderate: Three features, with small choroidal vessels visible.
Severe: Three features, with large choroidal vessels visible.

N.B. All Three stages are graded positive for atrophy on above grading protocol definitions.

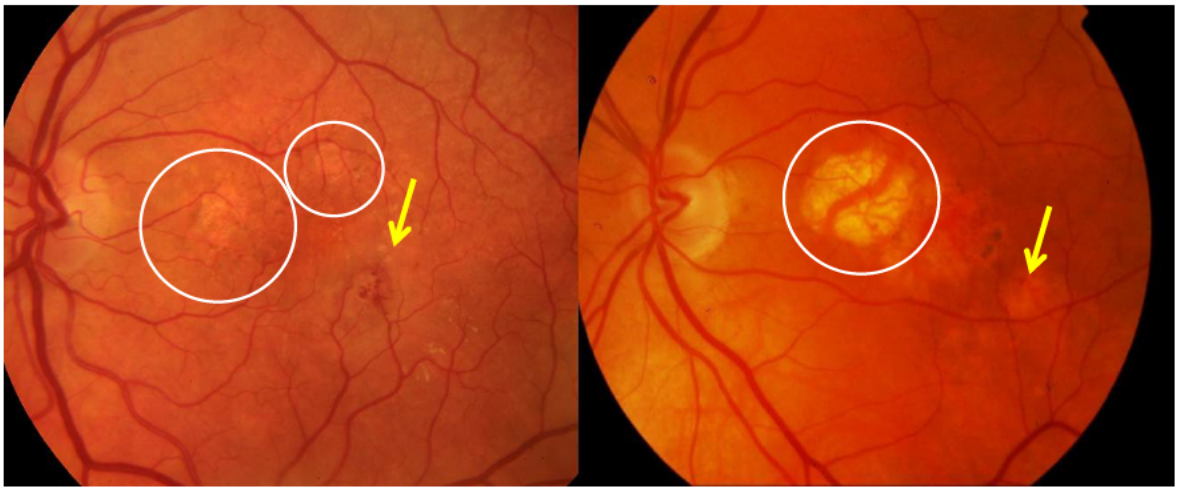

Fig 2. Extra-lesional atrophy. Extra-lesional atrophy (white circles) and nvAMD lesion (yellow arrows)

Grade Options			
Yes	If Yes:		
No	Is Atrophy	Unifocal / Multifocal	
CG	Location	Sub-foveal / Juxta-Foveal / Extra-foveal	
	Total Area	*Enter value from drawing*	mm²

3.1.3 Atrophy - Intra-lesional

This is an area within the total lesion which may previously been occupied by active lesion, is at least 175um in diameter and has atrophic properties such as visibility of choroidal vessels, well defined margins.

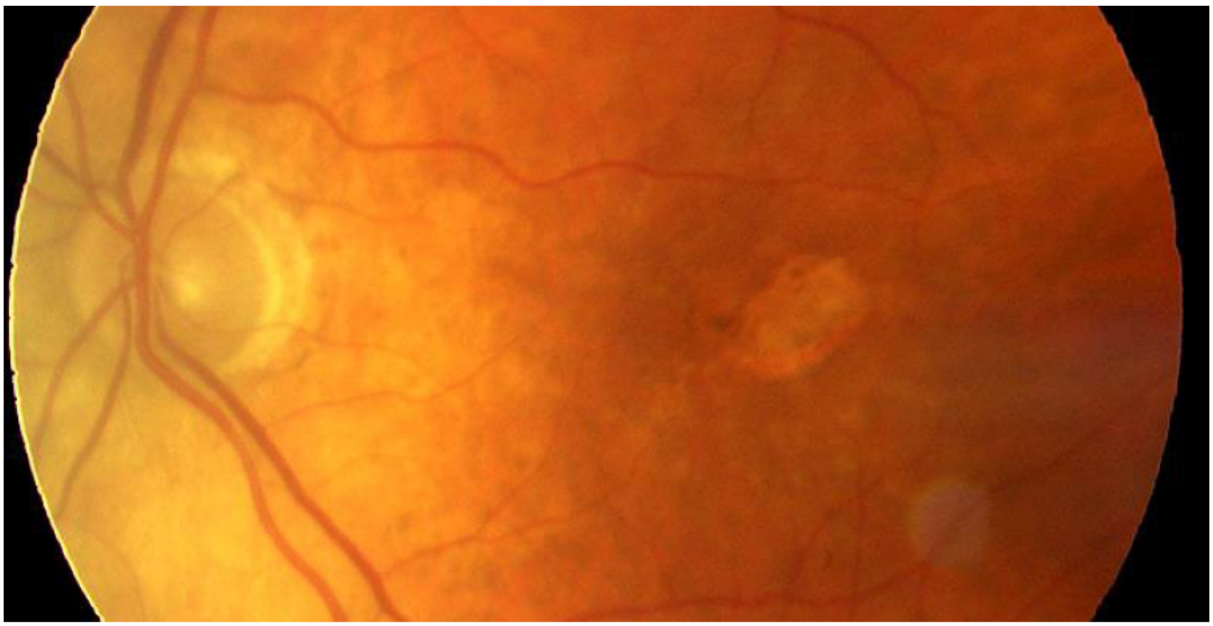

Fig 3. Intra-lesional atrophy

Grade Options			
Yes	If Yes:		
No	Is Atrophy	Unifocal / Multifocal	
CG	Location	Sub-foveal / Juxta-Foveal / Extra-foveal	
	Well defined	Yes/No	
	Total Area	*Enter value from drawing*	mm²
Total of all atrophy		*Auto add Extra & Intra-lesional values*	mm²

3.2 Drusen

Drusen must be graded for presence both within and outside the grid. If at least one druse (of any size) is visible anywhere on the fundus images provided, then drusen should be recorded as present. If drusen are present within the grid then the most severe type of drusen present must be

determined. This is based on size (choices are <63µm, 63-125µm and >125µm) and lesion circles can be used to aid this grading. Graders must also record the most frequent type of drusen present within the grid; <63µm, 63-125µm >125µm or crystalline.

Graders must also record the presence of drusen OUTSIDE the grid and if any reticular pseudodrusen are present (anywhere on the fundus image).
Drusen are oval, slightly elevated, yellowish deposits of variable size, usually located in the plane of the RPE. Drusen are classified according to minimum diameter. It is assumed that all drusen are round or oval in shape and that a single druse is no more than twice as long as it is wide.

Drusen are yellowish coloured and may contrast sharply with the surrounding RPE, though sometimes being only slightly paler than the RPE and easily overlooked. To detect small drusen, careful examination of well-focused stereo photographs is required.
Drusen can exhibit certain other morphological characteristics and may also be referred to under the following terms.

Hard Drusen

These are seen as small, punctuate, hard-edged, white dots very deep in the retina. These small white deposits are on Bruch's membrane, and appear to project through the retinal pigment epithelial (RPE) layer. Hard, distinct drusen can sometimes be seen within larger soft drusen. The image below shows hard drusen <63 µm in size.

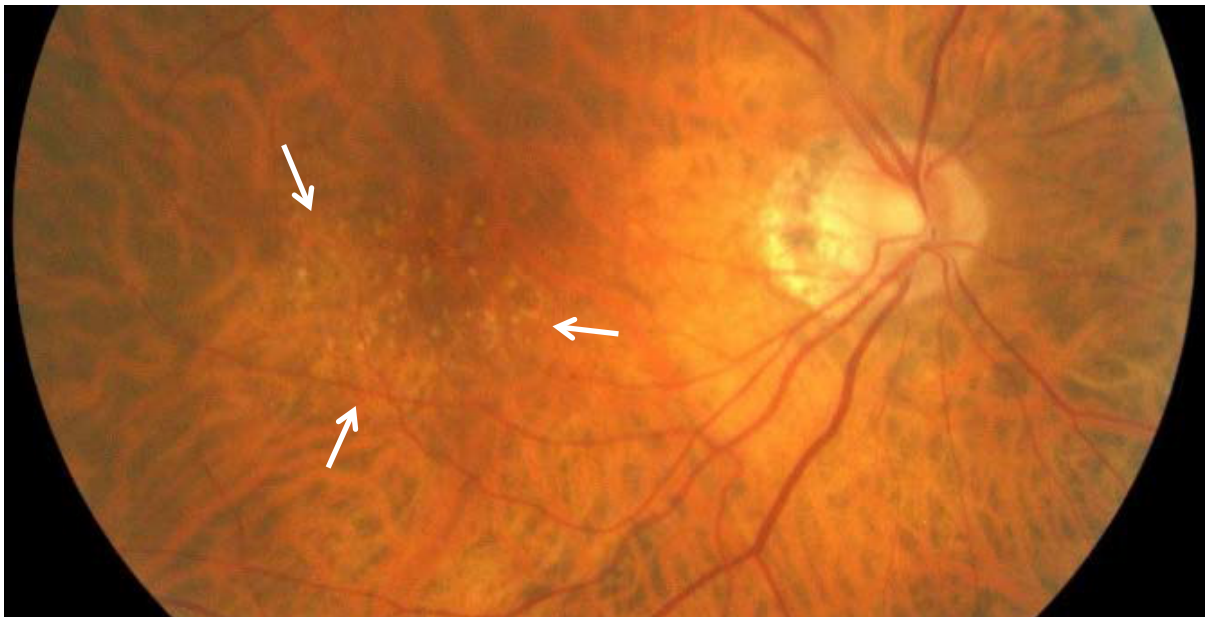

Fig 4. Hard Drusen

Soft Drusen

Typically these drusen are yellow-white in colour, with visible thickness (nodular elevated appearance), clearly defined edges, and a relatively uniform density (colour) from centre to periphery (even if their substance is minimal). The image below shows soft drusen >125 µm in size.

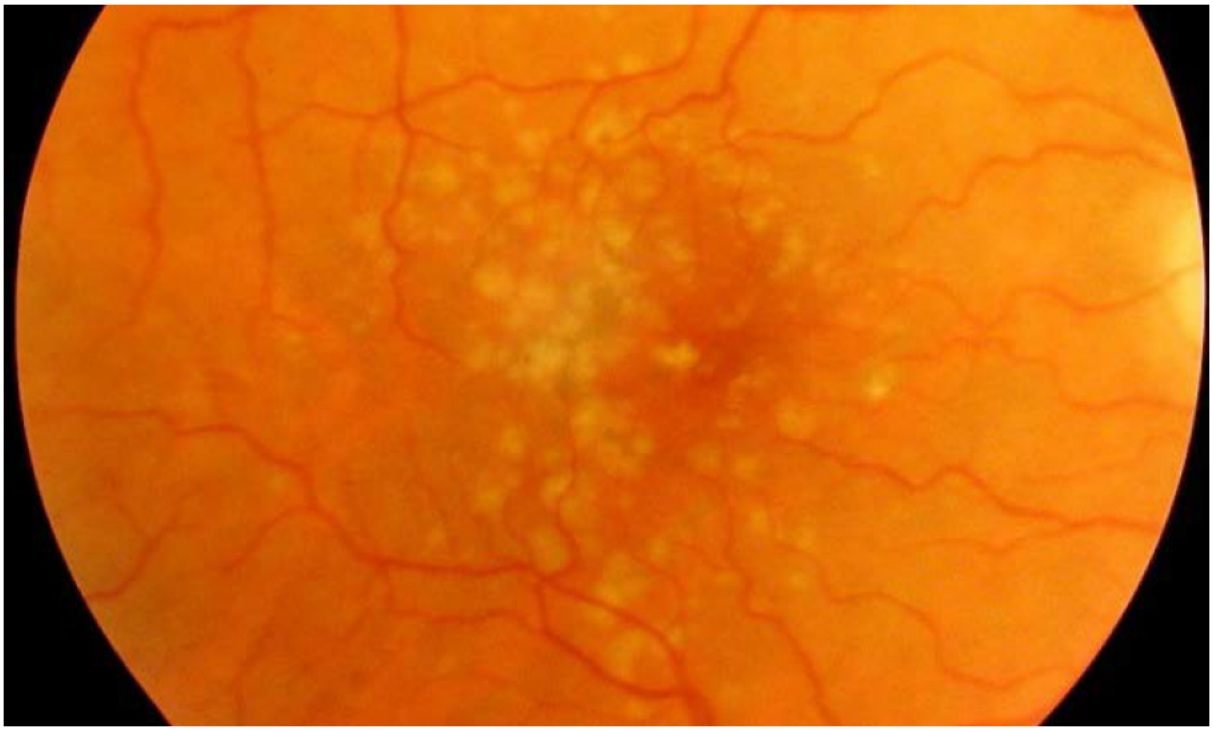

Fig 5. Soft Drusen

Discreet Calcific Refractile/Crystalline Drusen.

Eyes with refractile drusen were identified by visualisation of reflective white glistening dots within drusen in the posterior pole.

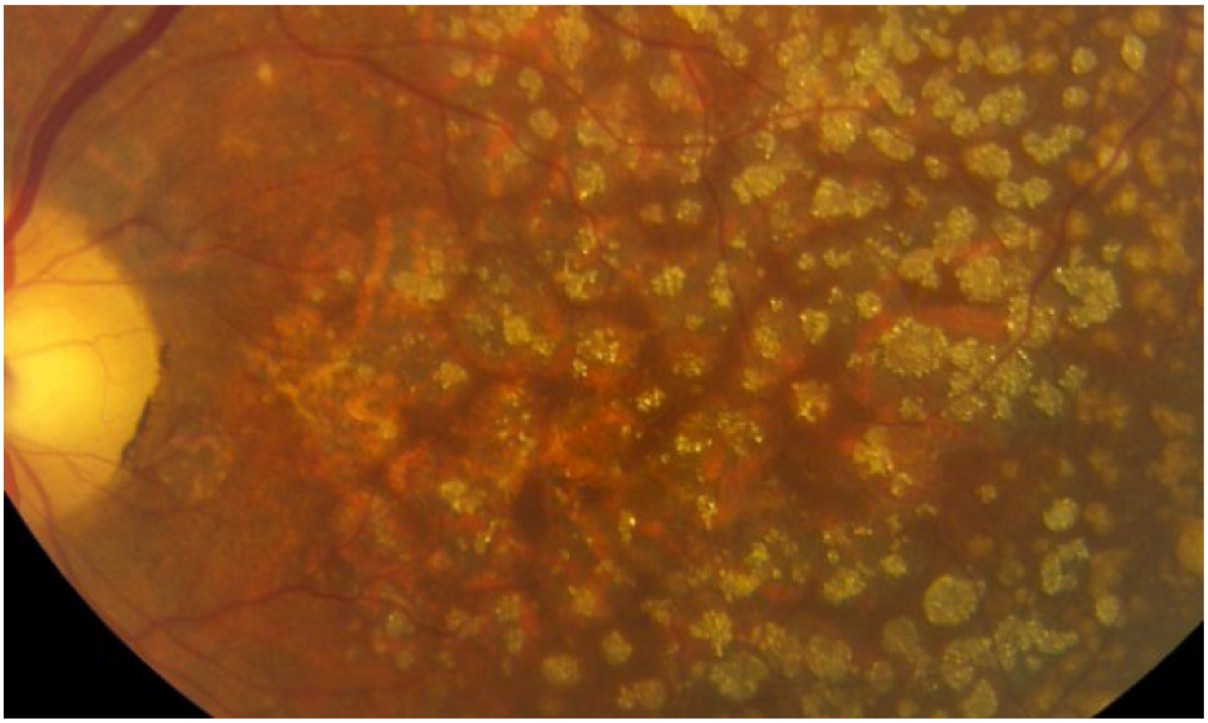

Fig 6. Discreet calcific refractile/crystalline drusen

Reticular Pseudodrusen (RPD)

For the presence/absence of this feature it is important to assess colour, infra-red, multicolour and OCT images as the sensitivity of identifying the feature from colour fundus photographs is poor. In colour, RPD can be identified as yellow interlacing networks ranging from 125µm to 250 µm in width or lesions that occur in regular and well-defined domains. In Autofluorescence RPD are defined as "clusters of ill-defined hypo-autofluorescent lesions interspersed against a background of mildly increased AF occurring in a regular and well-defined array". RPD in infra-red is defined as "clusters of ill-defined hypo-reflective lesions interspersed against a background of mild hyper-reflectance".
RPD on OCT is defined as discrete accumulation of material anterior to the RPE often occurring as sharp peaks visible within the layers corresponding to the outer regions of the photoreceptors.

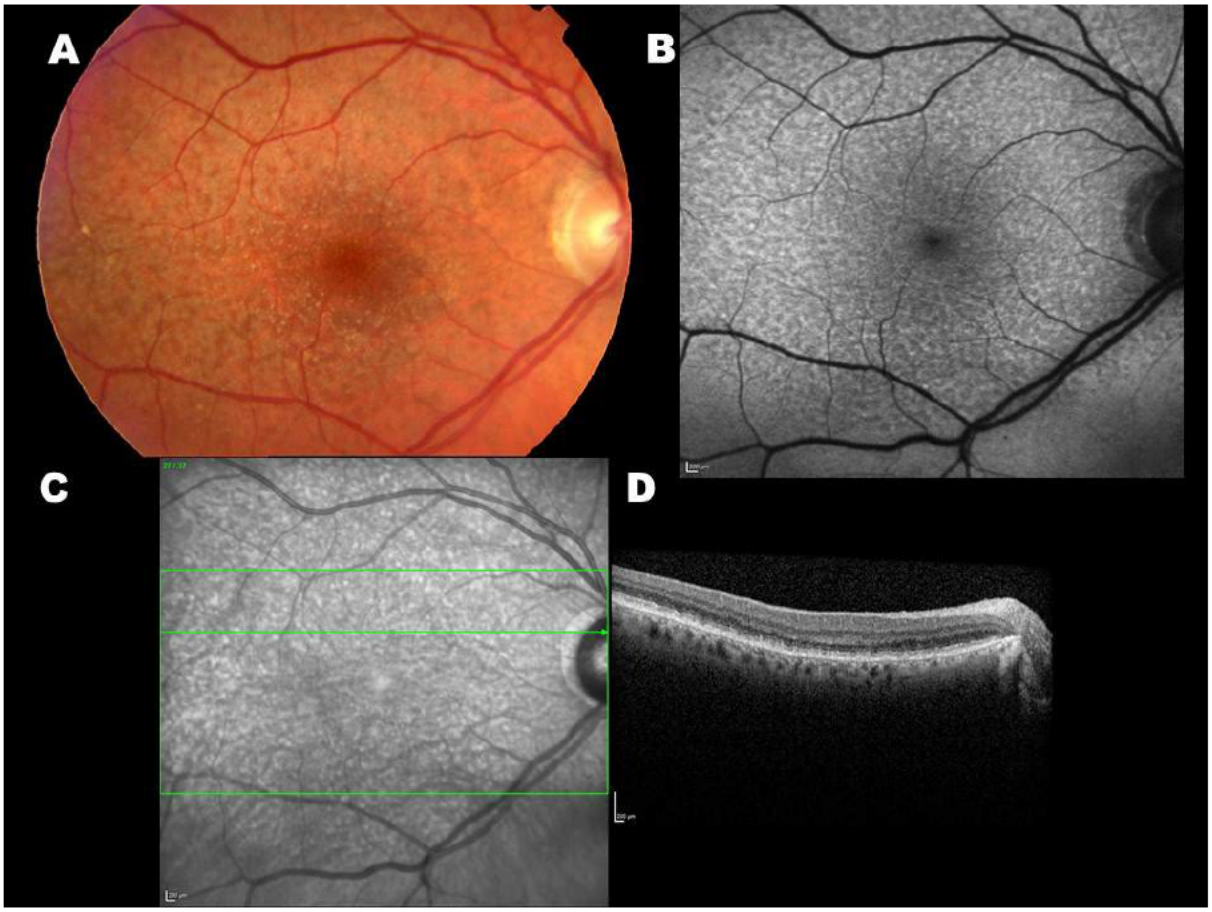

Fig 7. Visibility of reticular pseudodrusen on various imaging modalities: (A) Colour Fundus Photograph (B) Red-free (C) Blue Autofluorescence (D) Infra-red and corresponding OCT line through the fovea centre

Grade Options		
Yes	If Yes:	
No	Are there drusen inside the grid	Yes / No
CG	Most severe drusen inside the grid	<63µm / 63-125 µm / >125 µm

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	Most frequent drusen inside the grid	63µm / 63-125 µm / >125 µm / Crystalline
	Are there drusen outside the grid	Yes / No
	Reticular drusen	Yes / No
	If reticular then location	Inside grid / Outside grid/ Both

3.3 Retinal Pigment Epithelium (RPE) Pigmentary Changes

Hyper-pigmentation is the term used to describe an increase in the intensity of pigment. Disturbances of the RPE can lead to the deposition of granules or clumps of grey or black pigment in or beneath the retina.

Graders should be aware that hyper-pigmentation may be a result of previous traumatic, inflammatory, toxic or congenital processes, and may be distinguished on the basis of its association with scarring and location. Halos of pigment surrounding drusen should be excluded from consideration, as should peripapillary deposits. When evaluating an eye for pigment related to exudative AMD, graders should be aware of interference from dirt on the monitor or camera, or from other artefacts. Grading station monitors and stereo-view stereo viewers should therefore be cleaned regularly to avoid such artefacts.

It may be useful to note that it is rare to find hyper-pigmentation and hypo-pigmentation if an eye has just a few hard distinct drusen present. It is more usual to find that the area under and surrounding long-standing soft drusen has pigmentary irregularities. Often spots of hyper-pigmentation are surrounded by a pale zone of hypo-pigmentation.

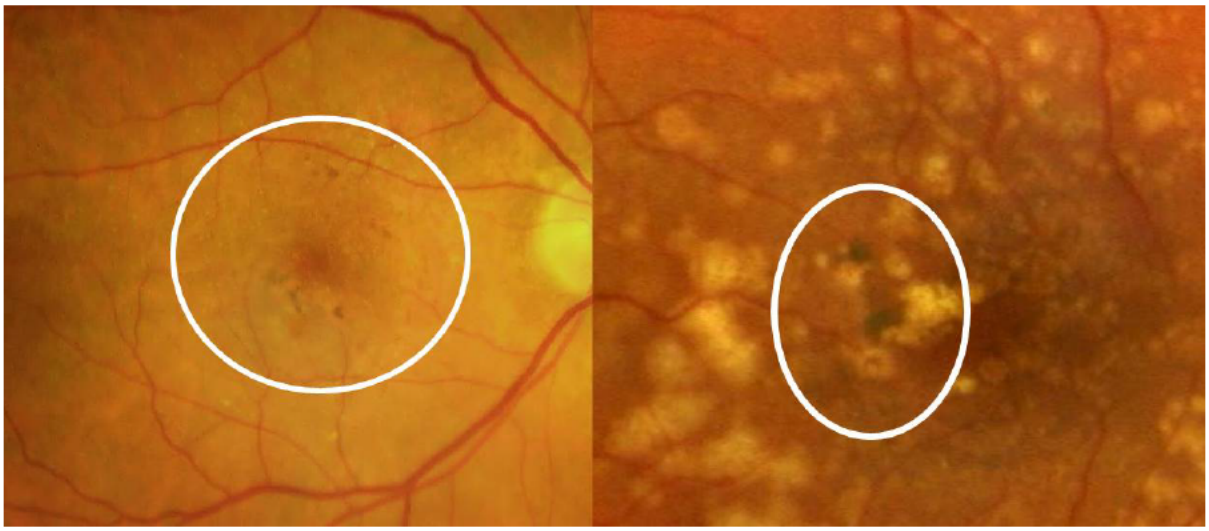

Fig 8. RPE pigment changes

Grade Options		
Yes	If Yes:	
No	Is Pigment	Hyper-pigment / Hypo-pigment / Both
CG		

3.4 Epiretinal Membrane

An epiretinal Membrane is a thin membrane that develops as from a proliferation of repair cells that then fibroses over and contract as they contract what is known as a macular pucker or ripple effect.

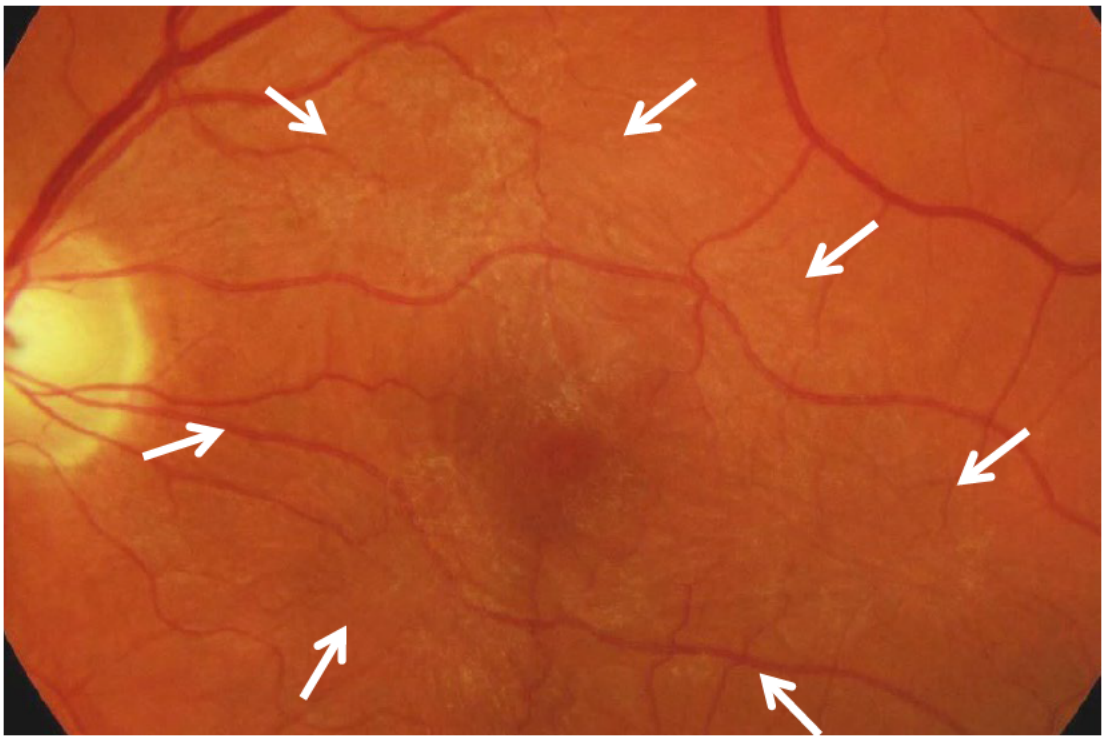

Fig 9. Epiretinal Membrane

Grade Options
Yes
No

4.0 Other Pathologies

If other pathologies are present then the grader must identify them if possible. If they are unsure or the particular pathology is not listed, they should use the 'Other' selection and add a comment.

4.1 Macular Hole (Any Stage)

A macular hole is a small break in the macula, located in the retina. These are typically not seen clearly on colour fundus images, but can be better seen on Multi-colour and OCT.

There are three stages to a macular hole:

- Foveal detachments (Stage I)
- Partial-thickness holes (Stage II)

•Full-thickness holes (Stage III)
Any stages should be graded as present.

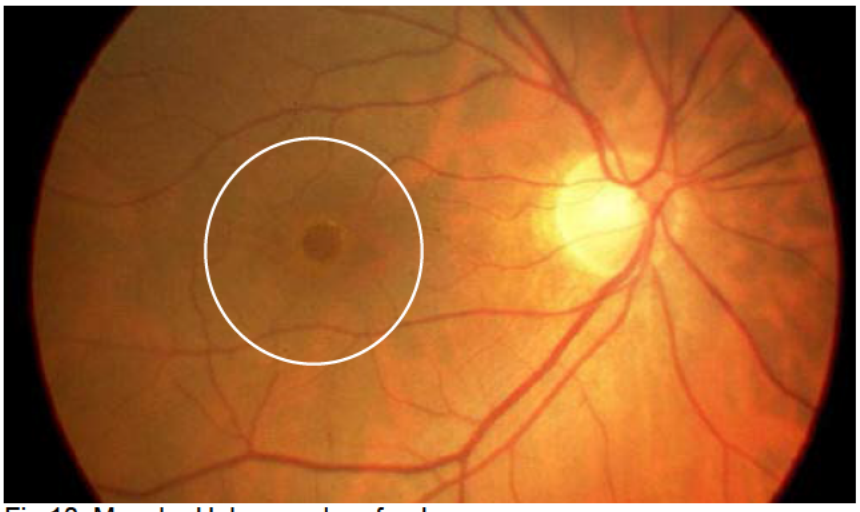

Fig 10. Macular Hole on colour fundus

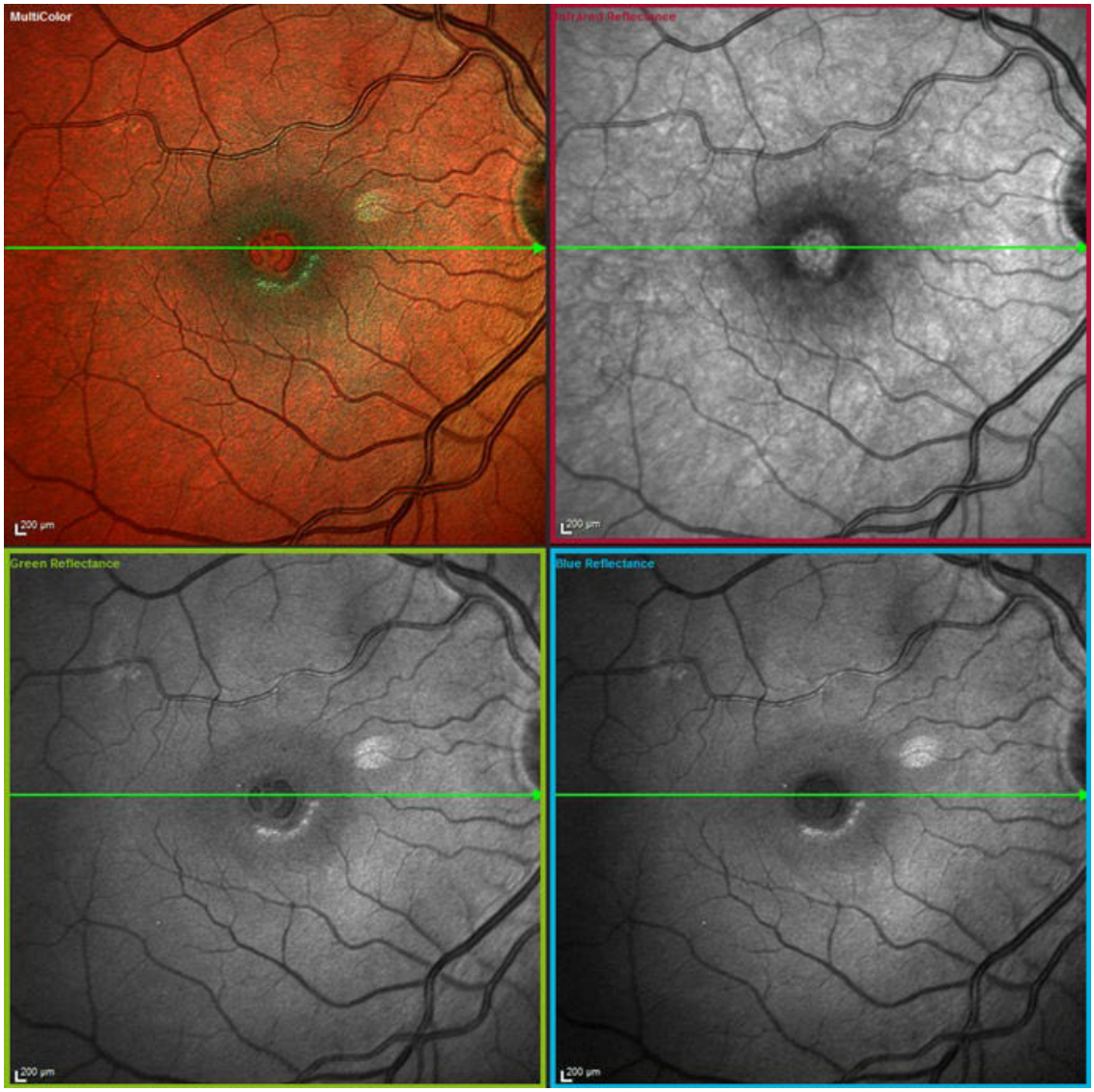

Fig 11. Macular Hole on Multi-colour

4.2 Diabetic Retinopathy/Maculopathy

Diabetic Retinopathy is a pathological state of the retinal microvasculature, which typically occurs in people with diabetes mellitus. Features include micro-aneurysms (MA), which are small round red dots (blood) that are associated with the retinal micro-vessels, IRMA (Intra-Retinal Microvascular Anomalies), or small polyps of retinal circulation, which may or may not leak. Diffuse leakage from the RPE in diabetic maculopathy may cause exudate, SRF and/or CMO, also associated with small or large blot haemorrhages.

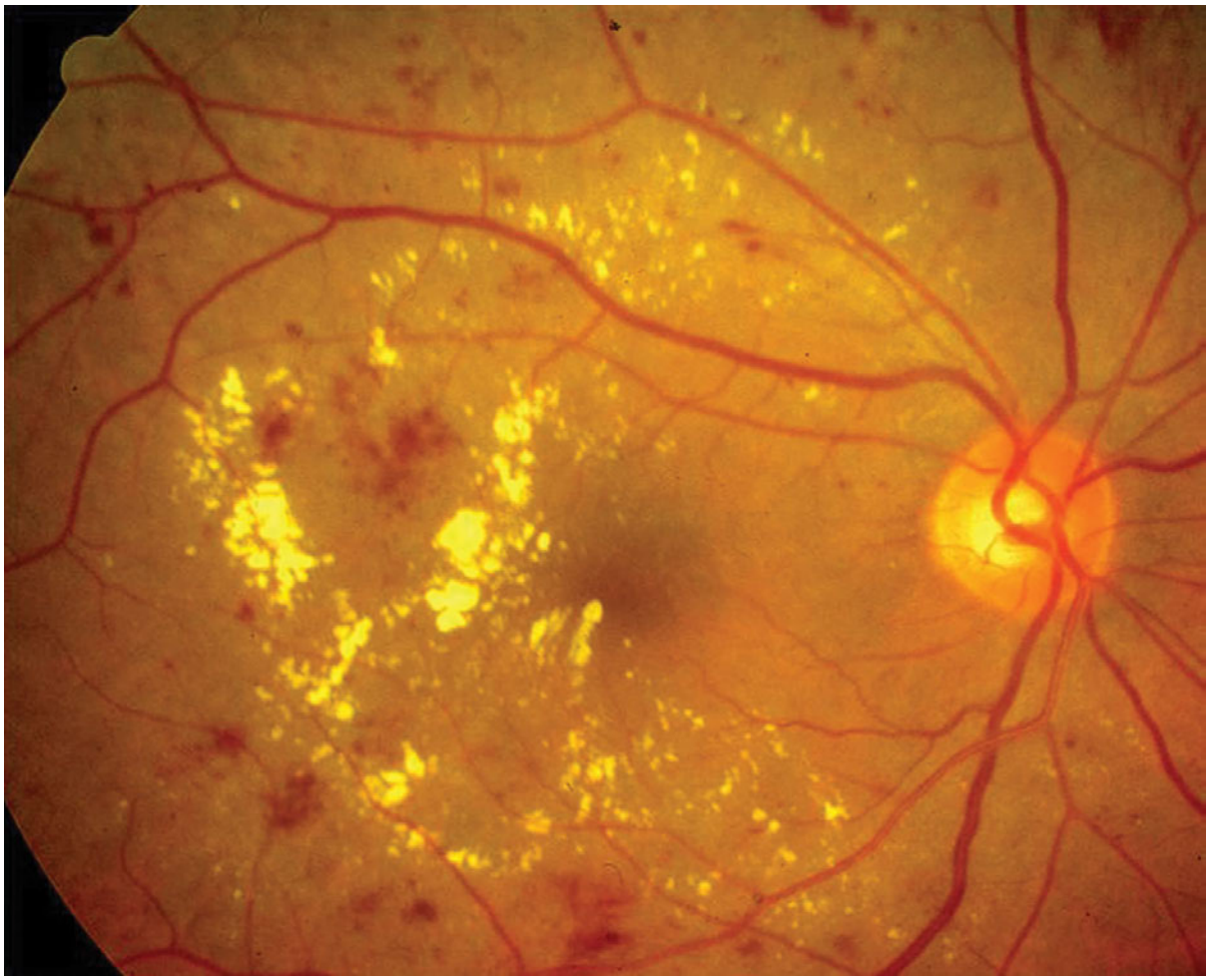

Fig 12. Diabetic Retinopathy

4.3 Laser Scars

Laser scars characteristically appear as 50 to 200 micron diameter lesions in the macula or 300-600 micron lesions in the periphery. They are round or oval, yellowish-white with variable black pigment centrally.

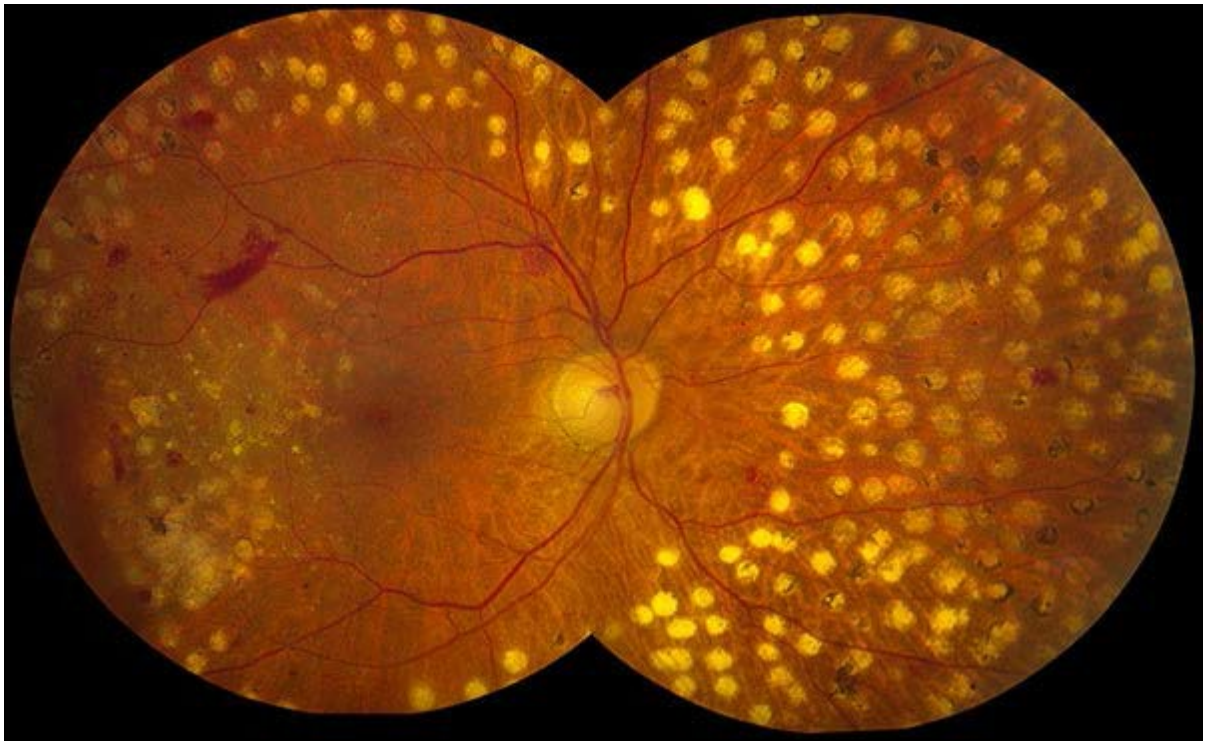

Fig 13. Laser Scars

4.4 Macular Telangiectasia

Disease characterised by dilatation and tortuosity of retinal blood vessels, multiple aneurysms, vascular leakage and the deposition of exudates. Tends to involve areas outside the fovea (i.e. juxta- or extra-foveal). It may also be associated with heavy pigment clumping, particularly in triangular shapes associated with the blood vessels, which typically are of wide calibre and dip down at right angles to level of the RPE.

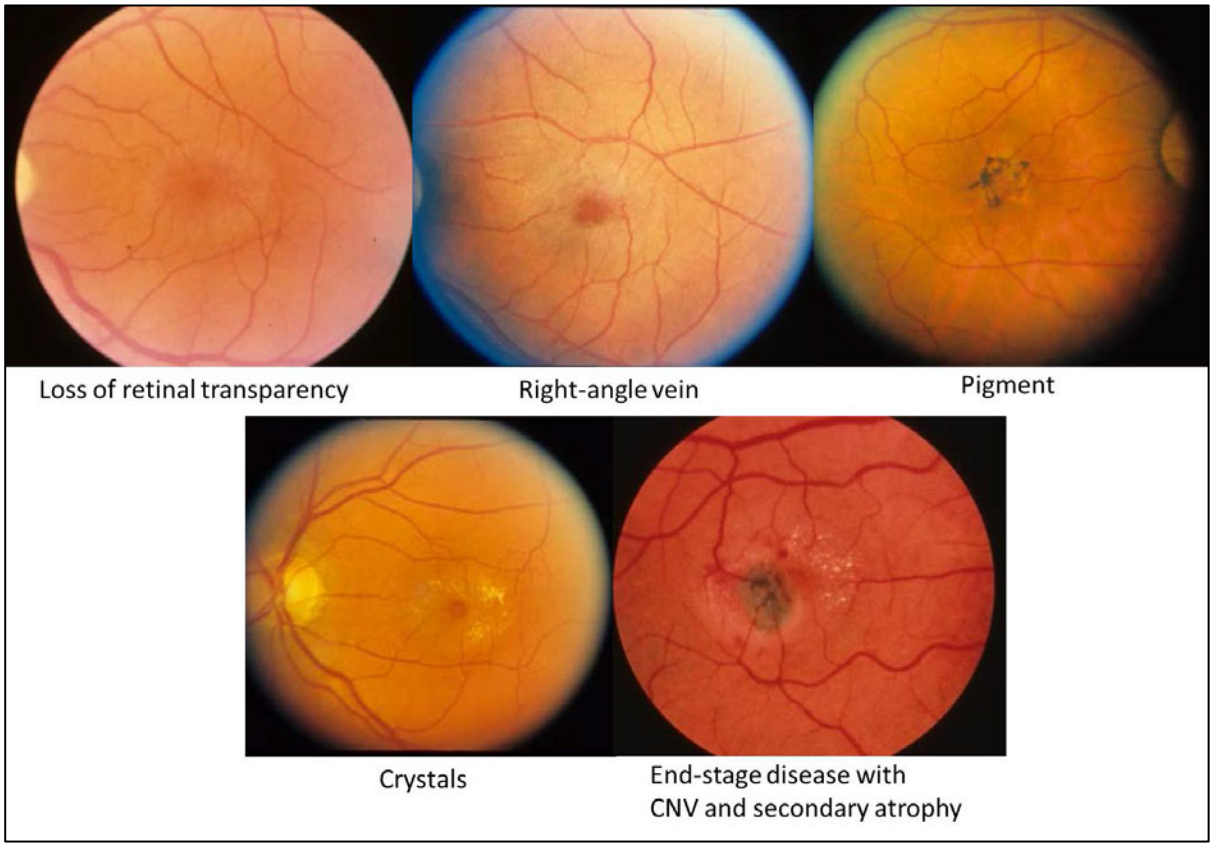

Fig 14. Macula Telangiectasia

4.4 Naevus/Melanoma

A naevus (plural, naevi) in the eye is a common, benign, pigmented growth, similar to a mole on skin. A naevus can occur either in the front of the eye, around the iris or coloured part of the eye, or beneath the retina in the back of the eye. A naevus beneath the retina is called a choroidal naevus.
A melanoma is thought to develop from a pre-existing melanocytic naevus, or may occur spontaneously. The colour varies from darkly pigmented to amelanotic. It is usually dome-shaped. If it breaks through Bruch's membrane (which effectively forms a blood/neural tissue barrier between the vascular choroid and the retinal layer) as it grows, it appears mushroom-like.

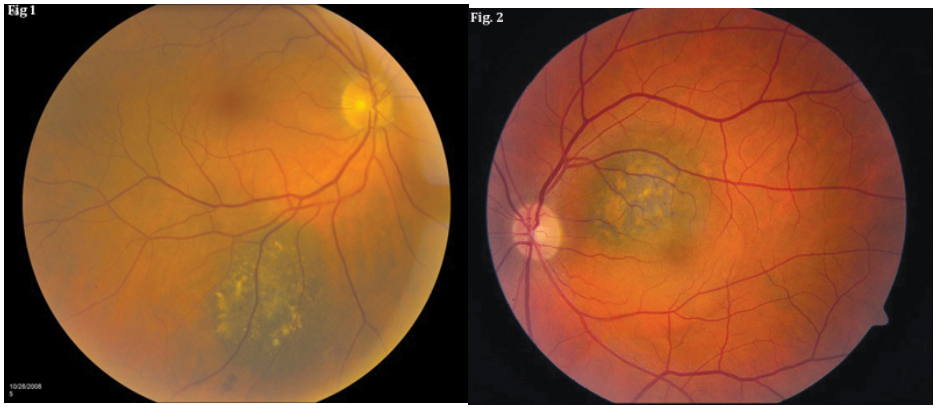

Fig 15. Choroidal naevus with drusen (L). Choroidal melanoma with orange pigment and subretinal fluid (R).

4.5 Any Other Pathology Not Listed (comment)

If any other abnormalities are observed or the disease pathology is unknown please record in the other comments box. If unknown please ensure to check adjudication.

Study Name: EDNA
Document Title: Supplement 3 – Fundus Fluorescein Angiogram (FFA) Grading Definitions and Rules

Prepared By

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Project Closure Report Version Control

Version	Date	Author	Change Description

Initials	Name	Title	Functional Role
DGP	David Parry	Mr	Senior Ophthalmic Image Grader

Revision History

Revision	Date	Author	Section	Reason for Change
1.0	0XX FEB 2017	DGP		Created Protocol

1.1	09/07/2020	CJ		EDNA only protocol

Contents

1.0 Fluorescein Angiogram (FFA)

Graders must assess the full set of FA images provided for grading. If any other pathology is present in conjunction with AMD, the grader should mark the presence of this in the 'Other Pathology' section of the colour grading. If the pathology observed is not listed, the grader should select 'Other' from the list and enter a comment.

1.1 Exudative Age Related Macular Degeneration (nvAMD)

AMD is a disorder of the macular area of the retina, most often clinically apparent after 50 years of age. AMD is a condition characterised by the accumulation of membranous debris on both sides of the retinal pigment epithelium (RPE) basement membrane, without indication that they are secondary to another disorder. Clinical manifestations include drusen, atrophy of the RPE/choriocapillaris, RPE detachment and choroidal neovascularisation (CNV).

Early AMD is defined as the absence of the signs of advanced AMD and the presence of drusen and RPE pigmentary abnormalities.

Late AMD is defined as the presence of signs of exudative AMD or geographic atrophy. Exudative AMD can also be referred to as 'neo-vascular' or 'disciform' or 'wet' AMD.

Exudative AMD must be graded as 'YES' if any of the following are present in the macula:

- Choroidal neovascularisation
- Serous retinal fluid (SRF)
- Intra-retinal or sub-retinal exudates
- Haemorrhage
- Sub-retinal fibrosis or atrophic scar
- Retinal pigment epithelial detachment (PED).

Active CNV or RAP should be graded as 'YES' if grader can identify fluid, blood, leakage of fluorescein from a CNV (not just staining) or the presence of exudate.

The grader should also note the calibration used for the FFA images. (see Appendix A for details on how to calibrate images)

The options on Exudative AMD present are in two parts:

First part is whether nvAMD is present or not and this can be active with the features mentioned above.

Is Exudative AMD Present:

Grade Options	
Yes	If Yes:
No	Continue to Is CNV or RAP active question
CG	

The second part covers whether there is an active CNV or RAP present, or if the lesion is inactive, such as fibrosis with no leakage of fluorescein dye in the late FFA images, just staining of the lesion.

Is CNV or RAP Active:

Grade Options	
Yes	If Yes:
No	Continue with the lesion component questions

1.2 Angiographic Features of Lesion Components

This section of the protocol will provide the definitions for all lesion components to be graded on FA and a description of how they should be graded.

1.2.1 Lesion Components

This refers to any of the features of exudative AMD for which measurements must be recorded. These components are:

- Classic CNV
- Occult CNV (FPED/LLIO)
- RAP
- Blocked Fluorescence
- RPE tear
- SPED
- Fibrosis
- Atrophy within the lesion

Total lesion is defined as the total area of all of the components mentioned above.

1.2.2 Choroidal Neovascularisation (CNV)

Choroidal Neovascularisation (CNV) is an in-growth of choroidal capillaries through a break in the outer aspect of Bruch's membrane. CNV is easily visible in FA images, unlike in colour images.

Delineating the boundaries of CNV in eyes with AMD can be quite difficult as it is often accompanied by in-growth of fibrous scar tissue, and may have a variety of complex angiographic appearances.

Traditionally, CNV has been divided into two categories; classic and occult. These can only be determined in FA images.

In this protocol, CNV is described based on when it typically appears on the FFA run.

1 - Area of early bright hyperfluorescence: Classic and RAP
2 - Area of mid-late hyperfluorescence: FPED and LLIO

Lesion types with an area of early bright hyperfluorescence

This category will contain classic CNV and RAP lesions.

1.2.2.1 Classic CNV

Classic CNV is typically recognised by the appearance of a well-demarcated area or areas of hyperfluorescence which occur in the early phase of the angiographic sequence. The hyperfluorescence represents the presence of fluorescein dye in the abnormal vascular complexes. Initially, restricted by the walls of the vasculature, the hyperfluorescent dye may take on the form of vascular profiles (lacy network) or may appear as areas of homogenous but well delineated hyperfluorescence. In later phases of the angiogram, progressive pooling of fluorescein dye which has leaked out of the CNV into the overlying sub-sensory retinal space usually obscures the boundaries of the initially well demarcated region of hyperfluorescence.

In the slow-filling form of classic CNV, the vessels should be discernible in the early phase of the angiogram, but may not be well visualised until about 2 minutes after dye injection, with late-phase leakage into the overlying sub-retinal space 5 and 10 minutes after injection. A flat rim of blocked fluorescence is also common.

‘Older’ classic lesions also tend to be more blocked in the centre, showing more activity at their borders than in the central region; it is therefore possible that although there is early hyperfluorescence, the centre of the classic lesion may hypofluoresce, and smooth leakage may also be present.

- Classic CNV should be measured during the early fill phase, before leakage breaks the boundaries of the classic lesion. Images selected before 30 seconds (20-30 seconds) are recommended as this is the earliest time that everything is filled, yet not all the classic CNV indents have gone. (By 40 seconds the indented edge observed at 25-30 seconds has disappeared and the leakage is also brighter and passes its own margins. CNV should therefore be measured after the new vessels are filled, but before leakage begins).
- If there are two or more classic lesions present, quite often there is something connecting them (feeder vessel). All areas of classic CNV should be measured and added together.

- Areas that might be considered to have little or no leakage and are surrounded by classic CNV should be included as part of the classic CNV, providing there is an arc of at least 270 degrees of classic CNV surrounding the area of non-leakage.
- Slow-filling classic can sometimes be confused with FPED. If a grader is unsure if a lesion is slow-filling classic or occult, it is advised that the grader observe how the lesion changes over time (at 30 seconds, 1 minute, 5 minutes and 10 minutes). If there is leakage and it does not look Occult, it can be graded as Classic. The grader needs to check if RPE is flat or elevated on stereo images, this is best seen at around 2-3 mins before profuse leakage really starts, to determine if FPED is present or absent.

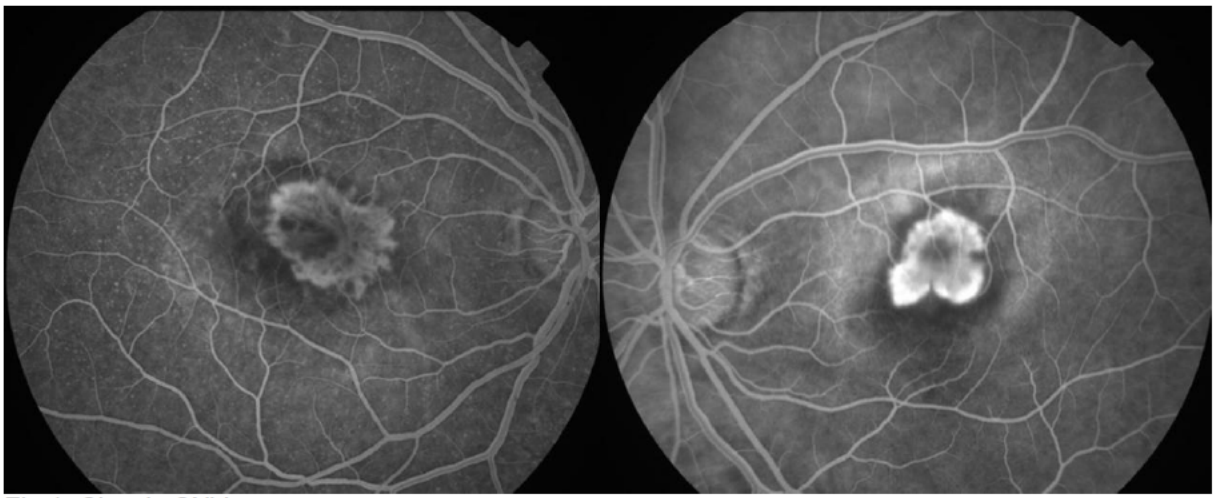

Fig 1. Classic CNV

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.2.2 Retinal Angiomatous Proliferation (RAP)

Angiomatous proliferations originate from the retina and extend posteriorly into the sub-retinal space, eventually communicating in some cases with choroidal new vessels. RAPs are considered to be a distinct sub-group of neovascular AMD. In CNV, venules erode through the RPE and infiltrate the sub-RPE and sub-retinal spaces. CNV also communicates with the retinal circulation (referred to as a retinal-choroidal anastomosis (RCA). RAPs on the other hand, begin as fronds of intra-retinal neovascularisation, (Yannuzzi Stage 1). These fronds may grow into the sub-retinal space causing serous retinal pigment epithelial detachments (SPEDs) (Yannuzzi Stage 2) and ultimately anastomose with choroidal neovascular complexes (Yannuzzi Stage 3). RAP can be accompanied by drusen, exudate and lipid.

[See appendix A for Yannuzzi descriptions and sample drawings]

When looking for a RAP vessel, it is important to look at a very early stereo pair of the transit run, ideally up to 30 secs, and appreciate an elevated perifoveal retinal vessel which doesn't taper, but instead does a very sharp right angled turn usually downwards towards the RPE.

This vascular complex then goes on to leak profusely in the later images. This needs to be present and identified before we can confidently diagnose RAP, however other secondary clues can also

be helpful, such as superficial intra-retinal haemorrhages, exudates and SRF/SPED/FPED etc. Appearance of a retinal-retinal anastomosis is also a strong indicator of RAP.

RAP should be measured on an early frame before there is evidence of leakage. If more than one RAP lesion is present, all RAP lesions should be measured and the areas summed for RAP area.

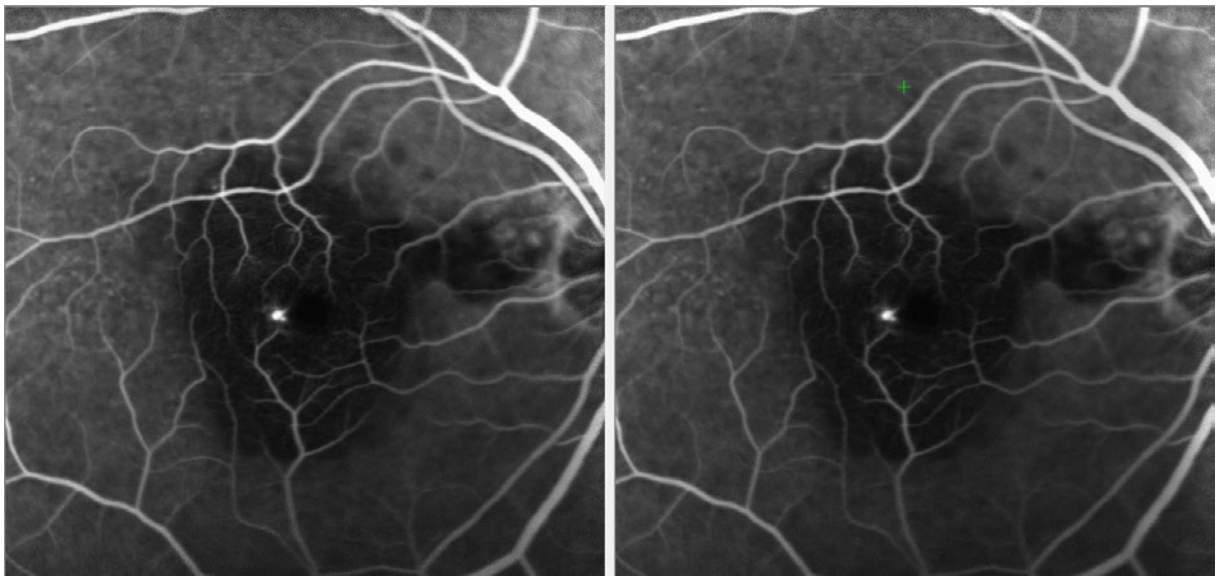

Fig 2. RAP. Early FFA (stereo), note small hyperfluorescent spot centrally

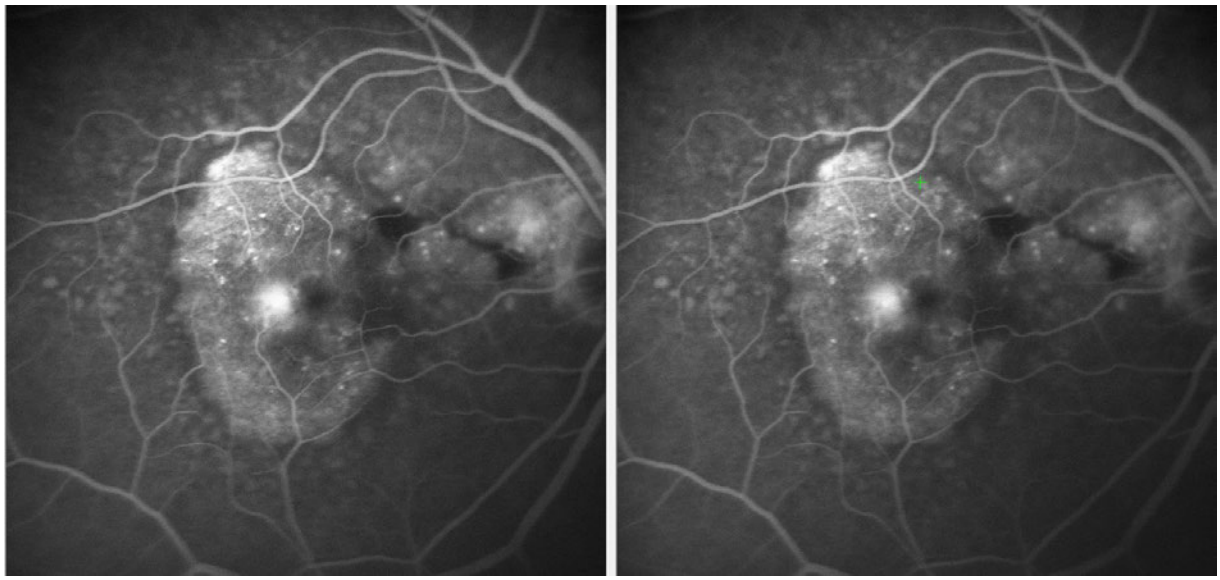

Fig 3. RAP. Late FFA (stereo)

Extra Notes on RAP Measurement

When drawing an FPED that has multiple RAPs within its area, then the sum of the areas of RAP should be subtracted from the area of FPED. For example, if the total area of FPED is 2mm² (measured around the boundary of FPED), and the area of multiple RAP within is 0.5mm², then the area of FPED should be recorded as 1.5mm² and the area of RAP as 0.5mm².

Grade Options

Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

Lesion types with an area of mid-late hyperfluorescence

This category will contain both occult CNV types; FPED and LLIO. If the grader identifies PFED or LLIO, this should be graded under the Occult CNV lesion component.

The appearance of occult CNV varies widely, and it may be difficult to define the extent or to be confident of its presence. Occult patterns usually only start to show from approximately the one minute images. Typically, occult CNV lesions leak less than classic CNV.
Occult CNV is generally speckled, and may show only fluorescein staining.

The identification of occult CNV in which irregular elevation of the RPE is usually present, is facilitated by stereoscopic viewing of the images, this is best viewed at around 2-3 min. There are two forms of hyperfluorescence which are identified as 'occult' forms of CNV: fibrovascular pigment epithelial detachment (FPED) & late leakage of indeterminate origin (LLIO).

[Graders should take care when they observe such stippled hyperfluorescence as it may be transmission defect. To check, graders should refer to the colour images and check for signs of RPE hypo-pigmentation. RPE atrophy can look like occult CNV. It is also important not to confuse stippled hyperfluorescence with drusen. Hard drusen fluoresce brightly in the early phase of the angiogram and then slowly fade. Soft drusen fluoresce more slowly and remain fluorescent for longer.]

1.2.2.3 Fibrovascular Pigment Epithelial Detachment (FPED)

This is a type of occult neovascularisation in which areas of usually irregularly or undulating elevated stippled hyperfluorescence are seen on stereoscopic angiography within 1 to 2 minutes after fluorescein injection (early or mid-phases). These areas are neither as discrete nor as bright as areas of classic CNV in the transit phase of the angiogram. By 10 minutes after injection, there is persistent fluorescein staining or leakage within the sub-sensory retinal space overlying this detachment.

Both the contours of the elevation and the border of the elevation (at its base) tend to be irregular. The borders of elevated RPE often slope gradually downward to surrounding flat RPE so that the demarcation between elevated RPE and flat RPE cannot be easily determined.

Frequently, the intensity of fluorescence at the boundary of the elevated RPE is quite irregular, with some areas fading relative to the fluorescence of the remaining areas of elevated RPE (making it difficult to distinguish the boundaries of fading occult CNV fluorescence from the fading fluorescence of the surrounding RPE).

Stipples of hyperfluorescence are often intermixed on the surface of the elevated staining/leaking RPE. These hyperfluorescent areas are neither as discrete nor as bright as areas of classic CNV or SPEDs in the transit (early) phase of the angiogram.

If the surface of the FPED is smooth, it can usually be differentiated from an SPED by the irregular contour of its base, and the uneven pattern of hyperfluorescence. Since the elevation of the FPED tends to be lower than it is in SPEDs, and in many cases is quite subtle, good stereo effect is essential in determining their presence. Graders should view several stereo pairs to achieve the optimum stereoscopic effect for drawing the FPED.

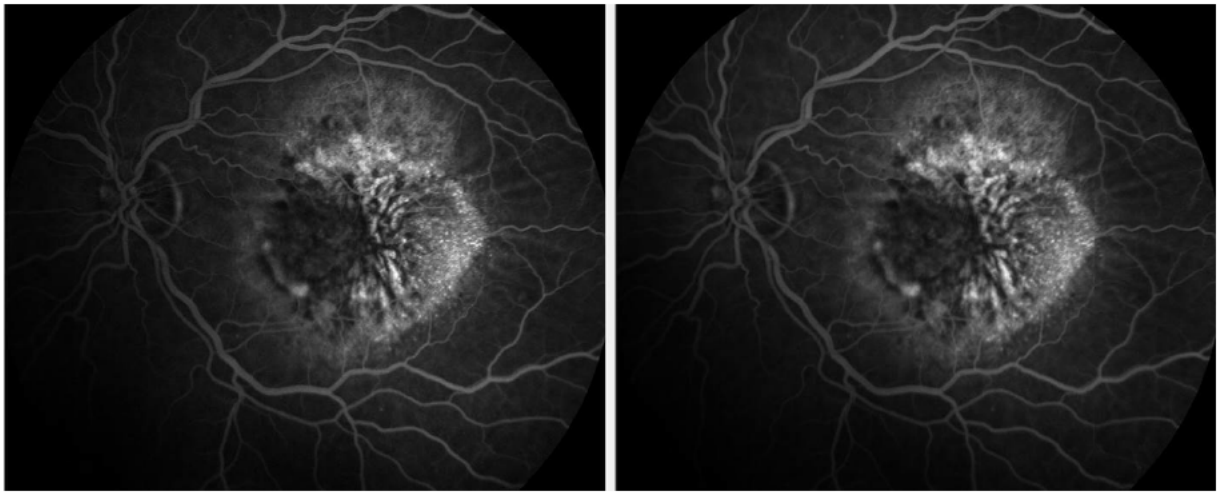

Fig 4. FVPED (Stereo)

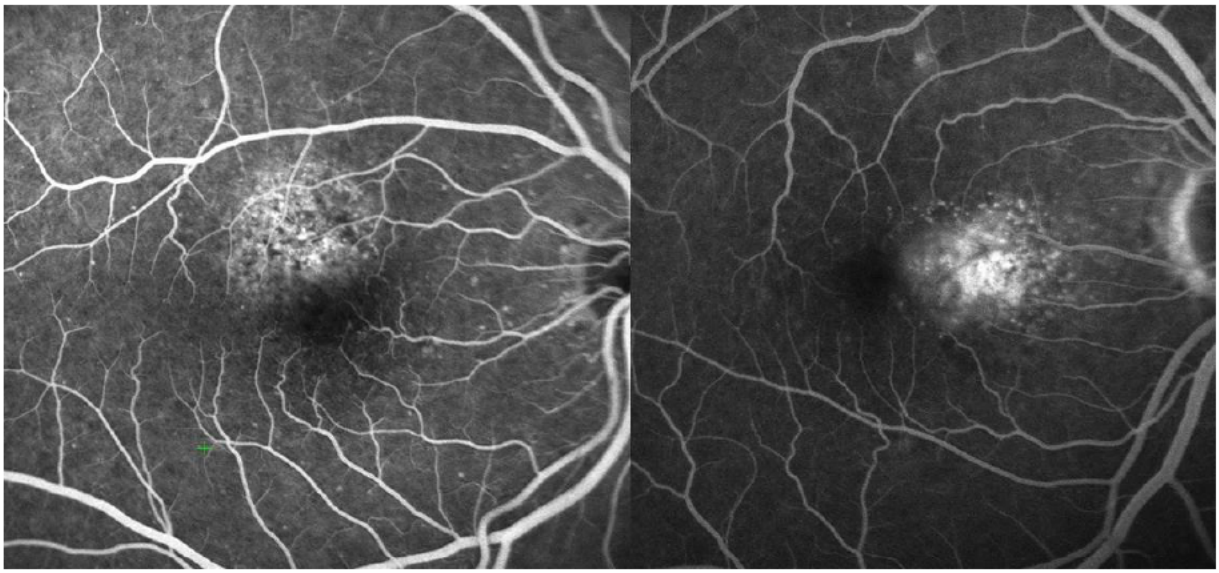

Fig 5. FVPED (note the stippled appearance)

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.2.4 Late-Phase Leakage of Indeterminate Origin (LLIO)

This is a type of occult CNV in which poorly demarcated areas of leakage appear at the level of the RPE in the later phases of the angiogram (2-5 minutes) without well-demarcated areas of hyperfluorescence discernible in the early phase of the angiogram that account for fluorescein leakage.

This type of leakage is seen as hyperfluorescence, which is brighter and deeper than the hyperfluorescence associated with fluorescein dye that has leaked in the sub-retinal space. Some useful cues are the proximity of the hyperfluorescence to the RPE. Overlying SRF is usually elevated on stereoscopic examination when compared with adjacent healthy RPE. Stereo viewing will aid in the identification of late ill-defined leakage of indeterminate origin.

[Graders should distinguish LLIO in occult CNV from slow filling classic CNV. In classic CNV with slow filling of choroidal vessels, vessels are discernible in the early phase of the angiogram.]

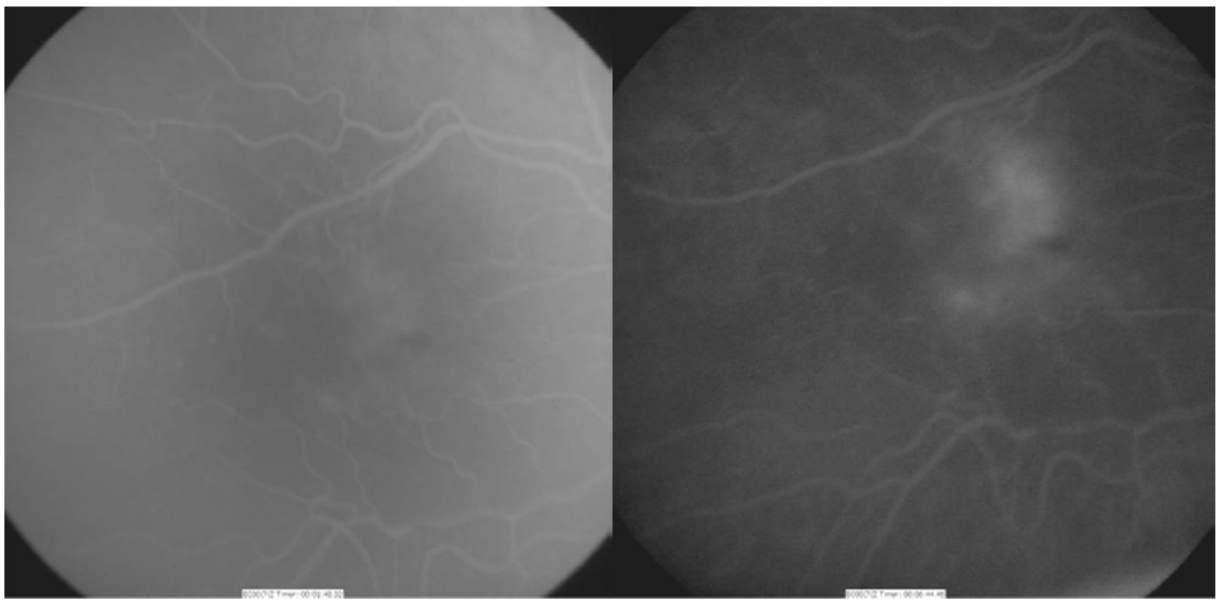

Fig 6. Occult CNV – LLIO

Occult CNV (FPED) should be observed on an image at approximately 1 minute. Occult CNV (LLIO) should be observed at the latest time possible (approximately 10-minute frame). Graders should then mentally transfer these observations to the image selected for drawing. Drawings should be made on a suitable image, preferably before 1 minute. If frames after approximately 7 minutes are not available, the grader should mark this in the image quality section.

As with classic CNV, occult CNV should be measured after the CNV is filled, but before leakage begins.

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm²
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.2.5 Extra notes on CNV Measurement

- Graders have some discretion in applying the term ‘surrounded’ when measuring CNV - in general, an arc of at least 270 degrees is considered sufficient. If a lesion appears to look like a doughnut, it is assumed that there is also CNV centrally. Similarly, if an outline can be seen for 270 degrees, it is also assumed that there is CNV centrally

- When drawing occult CNV that has a classic/RAP CNV component within its area, then the area of classic/RAP CNV should be subtracted from the area of occult CNV. For example, if the total area of CNV is 2mm² (measured around the boundary of occult CNV), and the area of classic/RAP CNV in the centre is 0.5mm², then the area of occult CNV should be recorded as 1.5mm² and the area of classic as 0.5mm²

- If blocked fluorescence due to blood is isolated from the exudative AMD lesion, and the grader is not confident that the blood is associated with the exudative AMD lesion, it should not be included when measuring the total lesion. Adjudication is recommended in these cases

- If a juxtapapillary CNV is present, grade as exudative AMD. Add the comment JPCNV

- Where a lesion has overlying blocked fluorescence then the blocked fluorescence should be included in the area of CNV as well as being marked present and measured as a separate lesion component (i.e. the total lesion area will be not be equal to the sum of CNV and blood but to the area of CNV only)

1.2.3 Blocked Fluorescence

Blocked fluorescence (BF) is categorised as either due to blood or other. Blocked fluorescence (BF) is marked as present if it lies within the total lesion and therefore may be blocking areas of active CNV.

BF can obscure CNV boundaries, making it impossible to judge how far CNV extends. BF may also lie on top of the lesion. Both of these presentations are classed as contiguous to the lesion.

Measurement of Blocked Fluorescence

Blocked Fluorescence due to blood that is contiguous (either overlying or at the edge) to the lesion should be delineated and measured and must always be included in the total lesion measurement. If the area of BF due to blood is contiguous to any area of RAP or CNV then graders must include the BF due to blood in the total active lesion.

‘Blocked Fluorescence other’ should be marked as absent or present. If present, the grader should then select whether BF other is overlying the lesion or at the edge of the lesion. ‘BF other’ that is contiguous to the lesion should be included in the total lesion measurement. If
the area of ‘BF other’ is contiguous to any area or RAP or CNV then graders must include the BF other in the total active lesion.

The measurement for BF other will be automatically calculated and stored in the database. Graders will not see this measurement. It will be based on the assumption that:

1.2.3.1 Blocked Fluorescence due to Blood

Blood manifests itself as an area of blocked fluorescence on FA. It should be graded as present if the grader evaluates that the blocked fluorescence observed is caused by blood (which has been confirmed by assessment of the colour images) and is within or at the edge of the lesion.

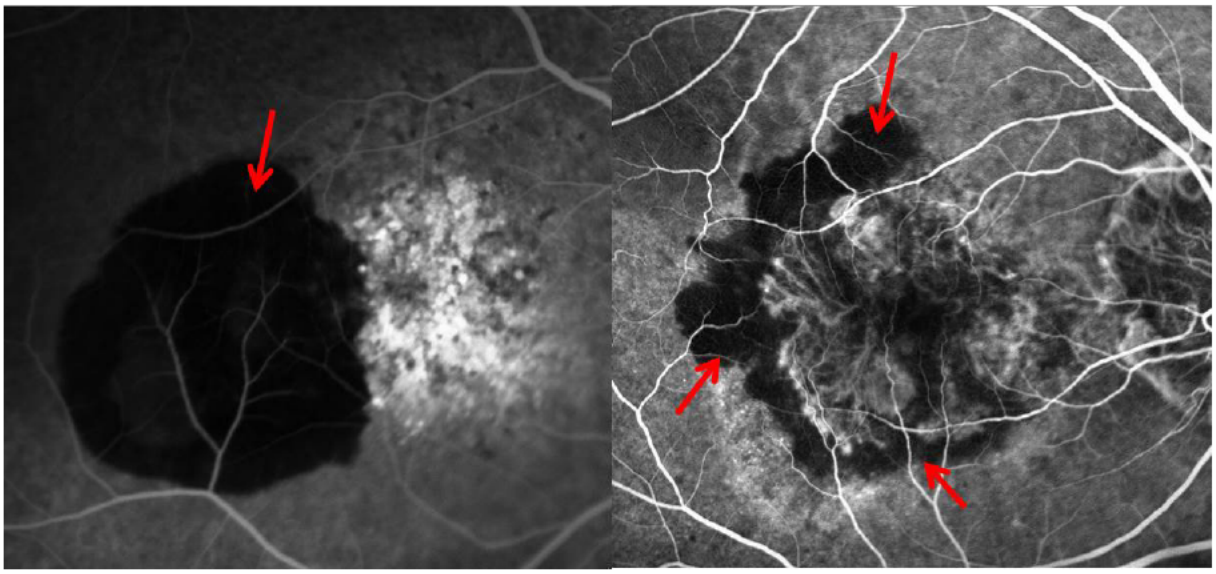

Fig 7. Blocked fluorescence due to blood

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.3.2 Blocked Fluorescence due to Other

Blocked fluorescence may also be due to hyperplastic pigment epithelium, thick exudate, pigment or fibrous tissue. It should be graded as present if the grader evaluates that the blocked fluorescence observed is caused by hyperplastic pigment epithelium, thick exudate, pigment or fibrous tissue (which has been confirmed by assessment of the colour images) and is overlying or at the edge of the lesion.

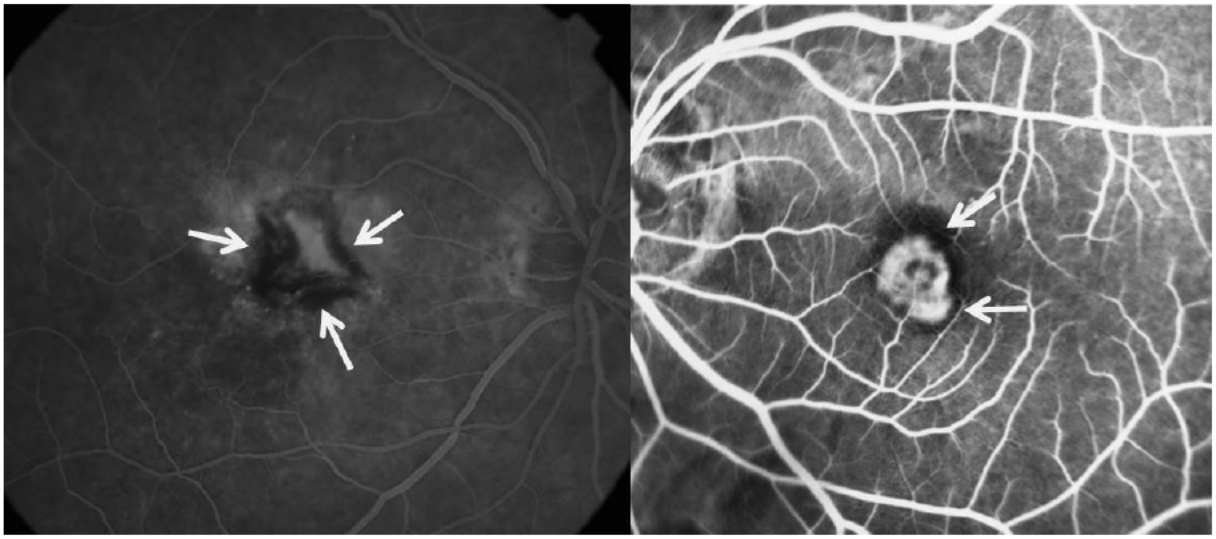

Fig 8. Blocked fluorescence due to pigment

Grade Options		
Yes	If Yes:	
No	Location	Overlying Lesion / At Edge of Lesion

1.2.4 Retinal Pigment Epithelium (RPE) Tear/Rip

Tears generally occur at the junction of attached and detached RPE, possibly as result of increased tension along the RPE. When the RPE tears, the free edge retracts and rolls back on itself. On angiography, the area devoid of RPE is hyperfluorescent and the rolled-up RPE will block the normal choroidal fluorescence.

Leakage can occur from the tissues along the free edge of the tear. However, if the tear is longstanding and any accompanying CNV is now fibrosed and inactive, there may not be any accompanying leakage. Also there may or may not be accompanying haemorrhage.

The area devoid of RPE should be measured as the area of RPE tear with the area of rolled up RPE being included in either the blocked fluorescence section or the CNV section depending on its appearance.

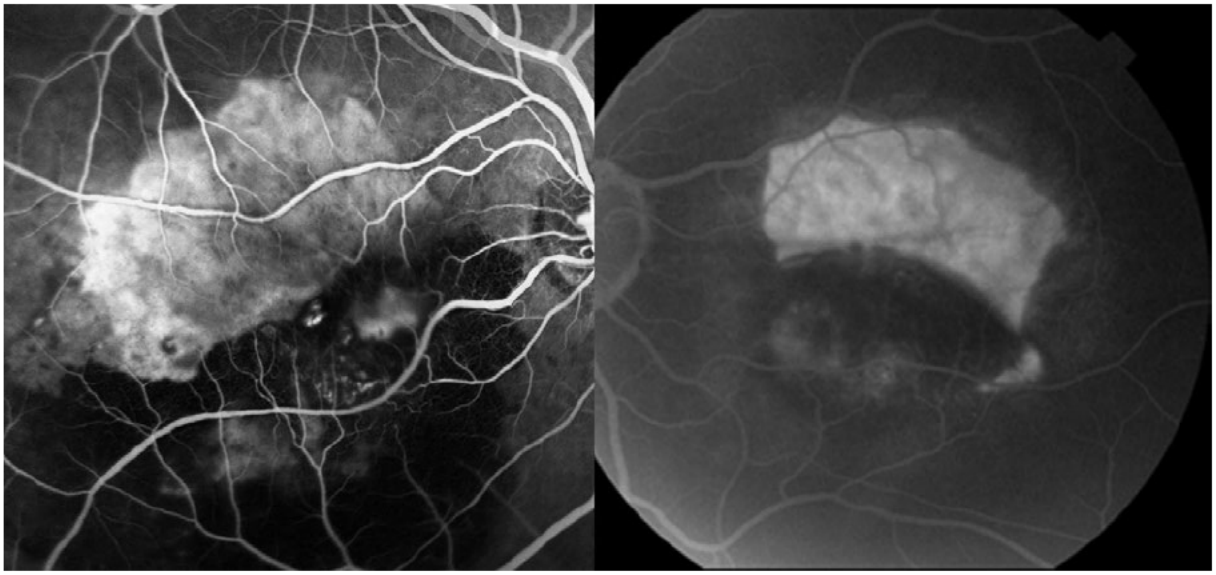

Fig 9. RPE Rip/Tear

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.5 Serous Pigment Epithelial Detachment (SPED)

Any SPED present within total lesion area should be measured. When an SPED is adjacent to CNV, it can obscure the boundaries making it impossible to judge how far the CNV extends.

SPEDs can be any size but tend to be between 500- 3000µm in diameter, occurring between the RPE and choroid. They demonstrate elevation and sharp definition, with a solid appearance. SPEDs are often oval, round or kidney shaped and are smooth, with a dome-like contour.

In FA images, a serous detachment of the RPE will appear as a uniform oval, circular or dome-shaped well-circumscribed elevation of RPE. The area will hyperfluoresce due to pooling of fluorescein dye and the contours of the dome will be smooth and homogeneous.

The hyperfluorescence occurs early or late and persists in the late phase of the angiogram. An SPED does not leak beyond its boundaries. In some cases, the central part of the SPED can show less hyperfluorescence than the remainder.

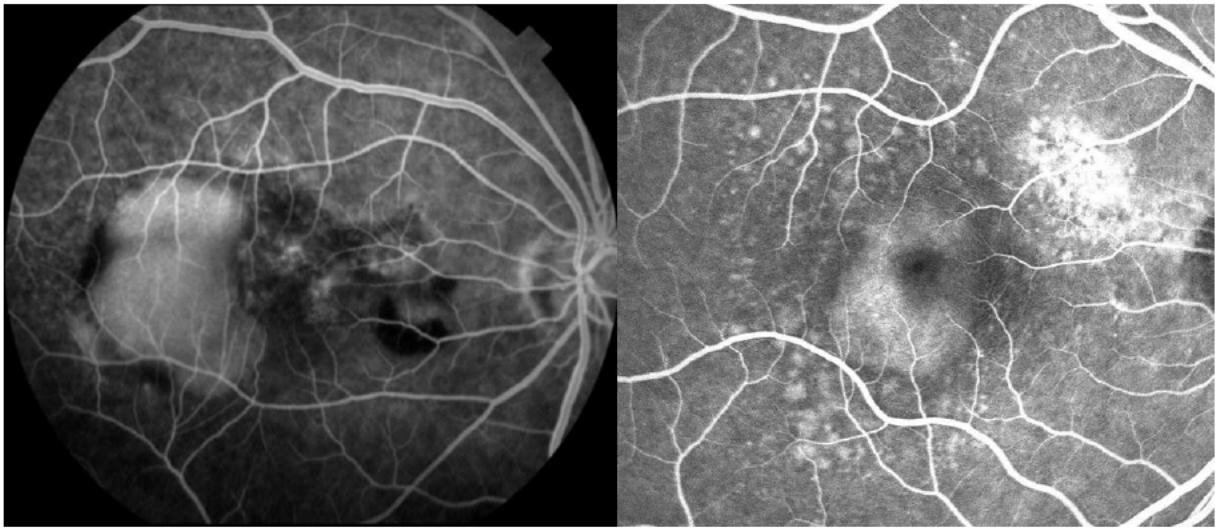

Fig 10. Serous Pigment Epithelium Detachment (SPED)

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm²
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.6 Fibrosis

In eyes with age-related macular degeneration, fibrosis is sheets or mounds of creamy white/yellow material under the neurosensory retina. These sheets consist of fibrous tissue that has proliferated in areas previously occupied by CNV. This dull-coloured fibrous tissue, is a scar, and involves the neural retina. It occurs as a consequence of the neovascular process and replaces the active membrane over time. Early in the development of such scars the creamy white/yellow material may sometimes be fibrin. If most of the serous fluid is resolved, there may only be a rim of fibrous scar left, some abnormal pigment and a large atrophic region.

In the early stages of FA, fibrosis tends to cause blockage of fluorescence. The shut-down net of choroidal vessels may be seen and these will hyper fluoresce. During the FA, different parts of fibrosis will take up stain at different rates but hyperfluorescence always stays within the boundary of fibrous tissue. By the late frames (around 10 minutes) the hyperfluorescence usually starts to fade.

Thicker areas and those areas closest to the new choroidal vessels take up stain more quickly and more intensely than thinner more distant areas from original new choroidal vessels.

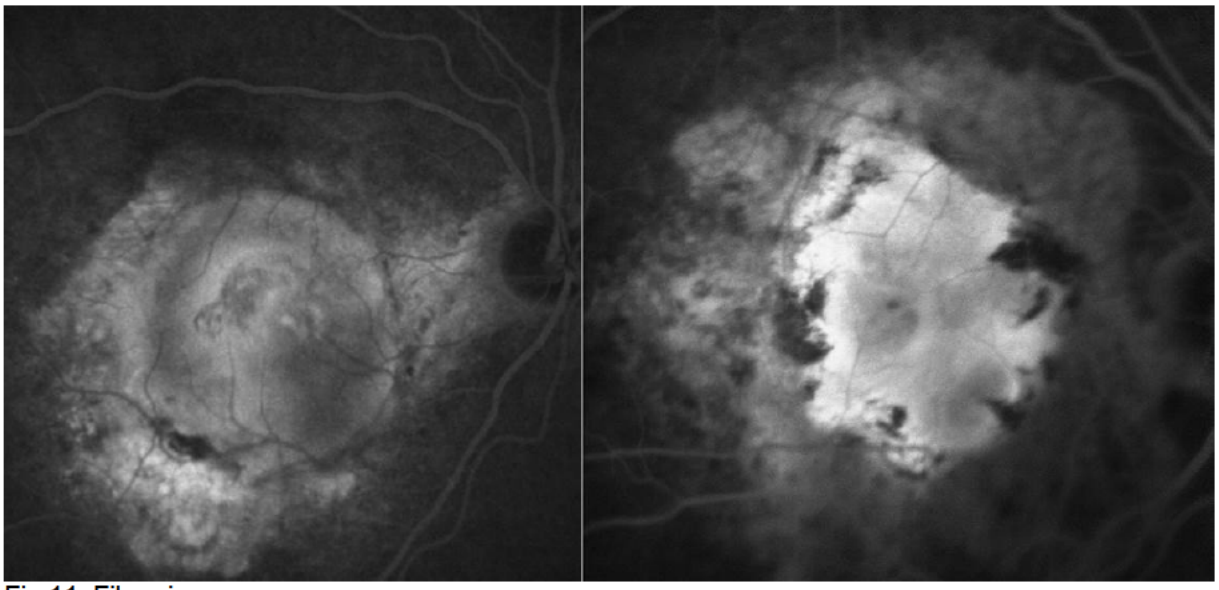

Fig 11. Fibrosis

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm^2
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.7 Atrophy within the Lesion:

An area of atrophy within the total lesion that is deemed to have once been an area of active lesion. This may be present beside active CNV or fibrosis. Atrophy within the lesion will typically hyperfluorescence early, will stay the same through the run and then will fade in the late images. Within the lesion this feature may be complicated by other overlying features such as fibrosis.

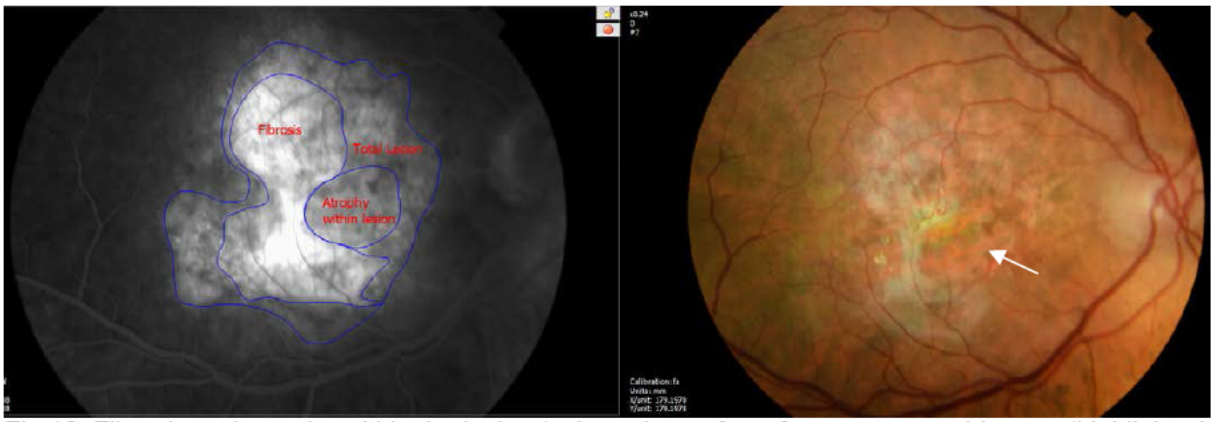

Fig 12. Fibrosis and atrophy within the lesion (colour picture for reference to atrophic area (highlighted with white arrow)

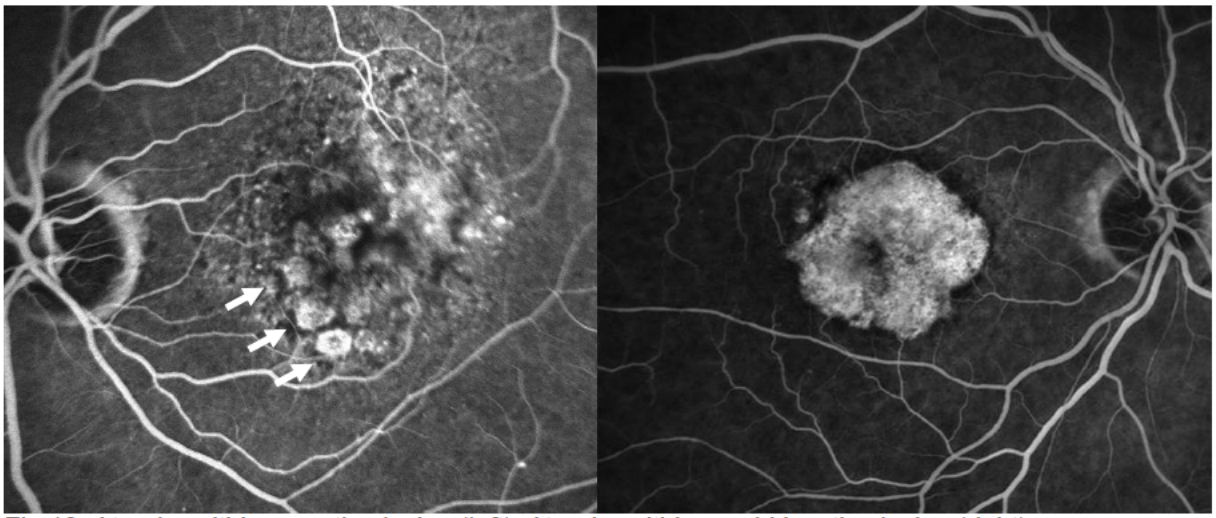

Fig 13. Atrophy within an active lesion (left). Atrophy within an old inactive lesion (right)

Grade Options			
Yes	If Yes:		
No	Area	*measurement of area/s*	mm²
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	

1.2.8 Total Lesion Size and GLD

On FA, this refers to the entire complex of abnormal features observed in the macular retina. It consists of the area of all CNV and all other components listed above. Areas of atrophy within the lesion, and fibrosis are included in the measurement of total lesion size. Areas are recorded in mm^2 using the freehand area tool available on the grading software.

Atrophy outside the lesion, SRF and RPE thinning are not included in 'total lesion' as these are not thought to mask any CNV.

Grade Options			
Total Lesion Size and GLD			
	Lesion Size	*measurement of area/s*	mm²
	GLD	*measurement of area/s*	mm

1.2.9 Total Active Lesion Size and GLD

On FA, this refers to the entire complex of active abnormal features. This includes CNV – Classic; CNV - Occult (FPED); CNV – Occult (LLIO) and RAP.

Blocked fluorescence (blood/other) should also be included in total active lesion if overlying or contiguous to the active components above. The reason for this is that areas of contiguous blocked

fluorescence may harbour areas of CNV or RAP. If the grader is unsure about including blocked fluorescence, they should select adjudication.

Record the greatest linear dimension of the total active lesion in mm. This can be found in the annotation statistics dialogue box after drawing is complete. Graders should ensure they record the GLD that corresponds to the Total Active Lesion.

Grade Options			
Total Active Lesion Size and GLD			
	Lesion Size	*measurement of area/s*	mm²
	GLD	*measurement of area/s*	mm

1.2.10 Atrophy outside the Lesion

Atrophy outside the lesion is a sharply defined drop-out of the RPE and choriocapillaris (which must be at least 175µm in diameter), exposing the underlying large choroidal vessels. Several patterns characterise the appearance of atrophy. For example, it can appear as one patch, with its size varying from meeting the minimum criteria, through to very large. Often, it begins as several smaller oval/round lesions surrounding the fovea.
If large atrophic areas are present, they often have scalloped edges (the scalloped edges are the last evidence that individual atrophic patches existed prior to fusion into one large patch).

An area of atrophy outside the lesion must be at least 175µm. In addition to size, if two of the three following characteristics of atrophy are present, definite atrophy outside the lesion can be graded:

- Visibility of choroidal vessels
- Well defined margins
- Scalloped edges

On FA, an area of atrophy outside the lesion will hyperfluoresce early, will stay the same through the run and then will fade in late frames.

1.2.11 Total Area of Atrophy Outside the Lesion

If atrophy outside the lesion is positively identified, the grader must also determine if the area is Unifocal (one area) or Multifocal (multiple areas), location of atrophy, this can be multiple locations so multiple options can be chosen, then draw all and add areas together to get one figure.

Grade Options			
Yes	If Yes:		
No	Is Atrophy	Unifocal / Multifocal	
	Location	Sub-foveal / Juxta-foveal /Extra-foveal	
	Area	*measurement of area/s*	mm²

2.0 Adjudication

This should be requested if the grader is unsure over important aspects of their grading. The grader must complete the grading to the best of their ability regardless, and the grading will then be queued for the senior grader. If the senior grader is unable to resolve the query, the grading will be queued for the Reading Centre Clinician to resolve.

Please add as much information as possible to your adjudication question, include image time (if available) and any landmarks

3.0 Grading Definitions (Glossary)

Drawing the components

Stereo Pair: Two images which have been specifically captured for the purpose of stereo-viewing. Using stereo-view, graders are required to draw the total lesion and the outline of the lesion components present on the early frame selected, and to enter these area values into the appropriate sections on the grading form.

The grader should use the best stereo images available at appropriate stage of the run for drawing lesion components for measurements, and should use their own discretion.

Location

- **Sub-foveal:** The area under the geometric centre of the foveal avascular zone (FAZ).
- **Juxta-foveal:** The posterior edge of the CNV lies between 1μm and 199μm from the geometric centre of the foveal area.
- **Extra-foveal:** The area just beyond the foveal avascular zone (FAZ). The boundaries of the FAZ are mapped by the tips of the retinal capillaries, which form an oval arcade encompassing an area of approximately 400μm in diameter. Lesions are said to be extra-foveal if its posterior

Fluorescein Angiographic Phases:

For grading purposes, these phases are defined according to the time from injection of fluorescein:

Phase Time from Injection

- **Early** ≤30 seconds
- **Mid** >30 seconds, & <5 minutes
- **Late** ≥ 5 minutes

Given the variability in injection rates and circulation times (especially in older patients), the boundary between early and mid-phases can be shifted somewhat in each direction based upon angiographic appearances.

Foveal Avascular Zone (FAZ): The centre of the macular retina which is composed almost entirely of cone photoreceptors. An average FAZ is approximately 400μm but can have a diameter

of up to 700µm. Within the FAZ there are no retinal vessels and histologically all the inner retinal layers are displaced laterally allowing as much light as possible to be focused with fine precision on the photoreceptors.

Clinically it is recognised by the presence of a dark foveal reflex in the young eye. In older people this reflex may be reduced.

The FAZ can be mapped by tracing the smallest retinal vessels to their termination. When all the vessels are mapped, their tips form a circle which encompasses the FAZ.

Grid Area: Area covered by the grading grid.

Hyperfluorescence: In FA images, this can be defined as an increased intensity of fluorescence from that of the normal choroidal flush, or an abnormal intensity of fluorescence at a given time in the fluorescein angiogram. Leakage, staining and pooling of fluorescein dye and transmission/window defects can cause hyperfluorescence.

Hypofluorescence: In FA images, this may be defined as a diminished intensity of fluorescence from that of the normal choroidal flush in a given area or at a given time.
It may occur as a result of blocked fluorescence or reduced perfusion.

Reverse Stereo: Where a grader would expect to see elevation instead lies posteriorly when stereo-viewing. Images have been in the opposite way by the photographer. This can be rectified by swapping the order of the stereo images.

5.0 Appendix A

The stages of RAP:

• Stage I: intra-retinal neovascularization (IRN) describes the capillary proliferation within the retina that originates from the deep capillary plexus in the paramacular region. This stage is often accompanied by intra-retinal hemorrhages and oedema *(See Figure 1).*

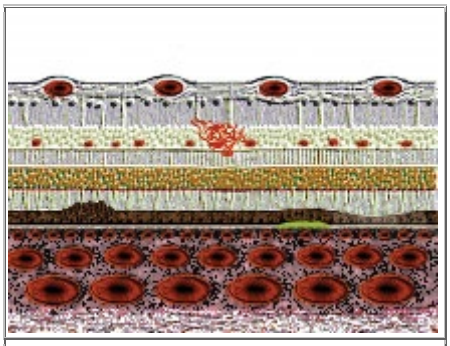

Figure 1: Retinal angiomatous proliferation (RAP) Stage I: intraretinal neovascularization.

• Stage II consists of sub-retinal neovascularization (SRN) that occurs when the IRN extends posteriorly, beyond the photoreceptor layer of the retina into the sub-retinal space. A localized, neurosensory retinal detachment develops with increasing intra-retinal edema, intra-retinal and pre-retinal hemorrhages, as well as an associated serous pigment epithelial detachment (serous-PED) *(See Figure 2)*.

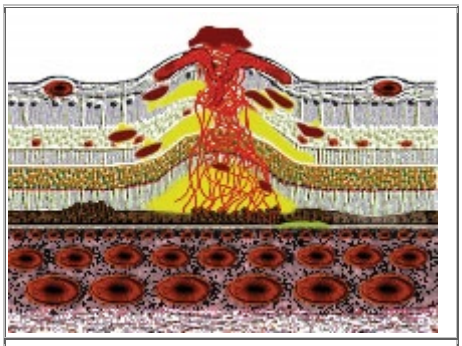

Figure 2: RAP Stage II: subretinal neovascularization with a retinal-retinal anastomosis.

• Stage III describes choroidal neovascularization seen clinically and angiographically, sometimes in association with a vascularized pigment epithelial detachment (vascularized-PED) *(See Figure 3).* During the evolution of this vascularized process, an axonal communication between the retinal and choroidal circulation forms a retinal-choroidal anastomosis (RCA) *(See Figure 4).*

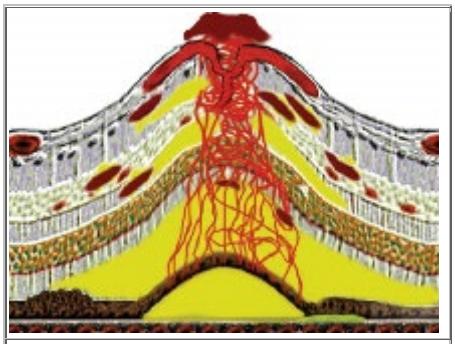

Figure 3: RAP Stage II: subretinal neovascularization with a serous pigment epithelial detachment.

Figure 4: RAP Stage III: Choroidal neovascularization with a vascularized pigment epithelial detachment and a retinal-retinal anastomosis.

Yannuzzi, L.A., Negrao, S., Lida, T., Carvalho, C., Rodriguez-Coleman, H., Slakter, J., Freund, K.B., Sorenson, J., Orlock, D., Borodoker, N. Retinal angiomatous proliferation in age-related macular degeneration. Retina 2001; 21(5):416-34.

Product Name: EDNA
Document Title: Supplement 4 – Fundus Autofluorescence (FAF) Grading Definitions and Rules

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Project Closure Report Version Control

Version	Date	Author	Change Description

Initials	Name	Title	Functional Role
DGP	David Parry	Mr	Senior Ophthalmic Image Grader

Revision History

Revision	Date	Author	Section	Reason for Change
1.0		DGP		Created Document
1.1	09/07/2020	CJ		EDNA only protocol

Contents

1.0 Fundus Autofluorescence (FAF)

With the introduction of fluorescein angiography decades ago, ophthalmologists observed that, even without the use of fluorescein, parts of the fundus showed areas of fluorescence in certain conditions. Although it was faint, autofluorescence (AF) was found to have potential as a diagnostic indicator and a tool for monitoring disease progression.

We now know that fundus autofluorescence imaging can provide information about the health and function not just of the central retina but of the periphery as well.

The retinal photoreceptors contain light-sensing molecules, a class of retinoids that are susceptible to damage and cross-linking. The photoreceptors shed their damaged outer segments, which the retinal pigment epithelium (RPE) ingests through phagocytosis. The molecules are stored in liposomes and form lipofuscin.
Over years, each RPE cell will eventually phagocytize 3,000,000,000 outer segments, and up to 25 percent of the cell volume will be occupied by lipofuscin. In addition to age, disease states and potentially increased oxidative damage can contribute to the build-up of lipofuscin in RPE cells.

Lipofuscin can be made to fluoresce by a broad range of wavelengths, about 500 to 800 nm[1]. After excitation, the molecule will spontaneously release a photon of light of a somewhat longer wavelength, efficiently recorded with a variety of imaging methods.

Areas of excess lipofuscin accumulation will appear hyperfluorescent. However, when RPE cells die or are absent, lipofuscin disappears, leading to hypofluorescence.
Fluorescence comes from other layers of the retina as well. With age and under certain pathologic conditions, this autofluorescence increases dramatically and adds to the signal produced by the lipofuscin in the RPE.

Fundus Autofluorescence (FAF) is a non-invasive imaging that detects increased and decreased fluorophores such as lipofuscin within the retina and retinal pigment epithelium (RPE). This test can help detect many types of eye disease involving the retina and RPE; these range from macular degeneration, dystrophies, inflammatory and infectious.

Lipofuscin is a dominant fluorophore in the macula that absorbs blue light.

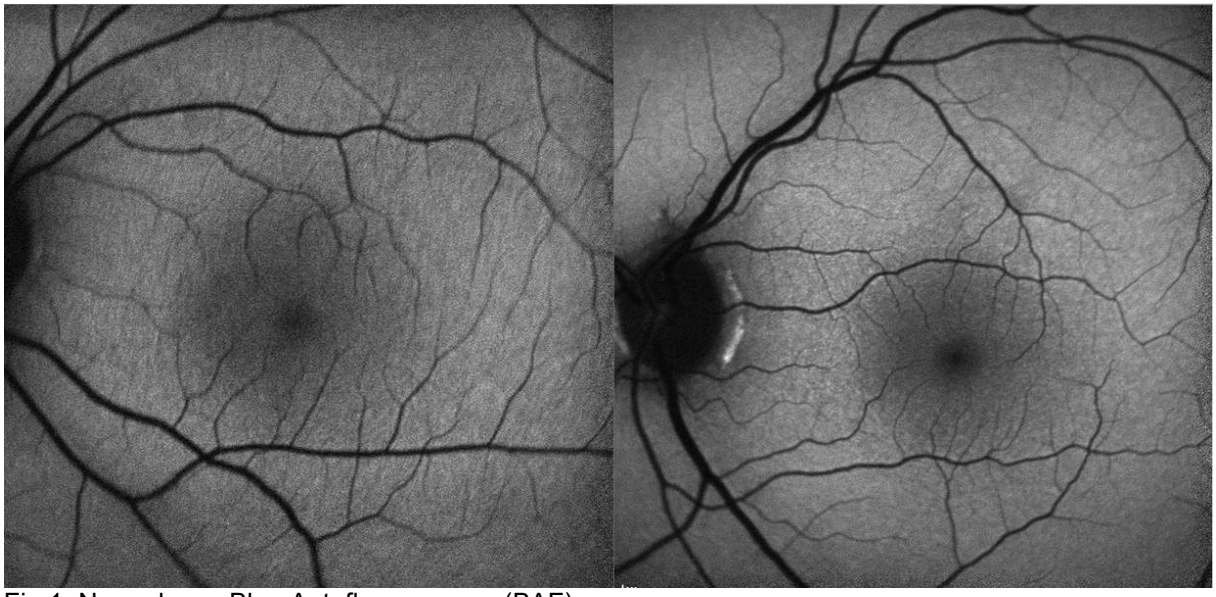

Fig 1. Normal eye. Blue Autofluorescence (BAF)

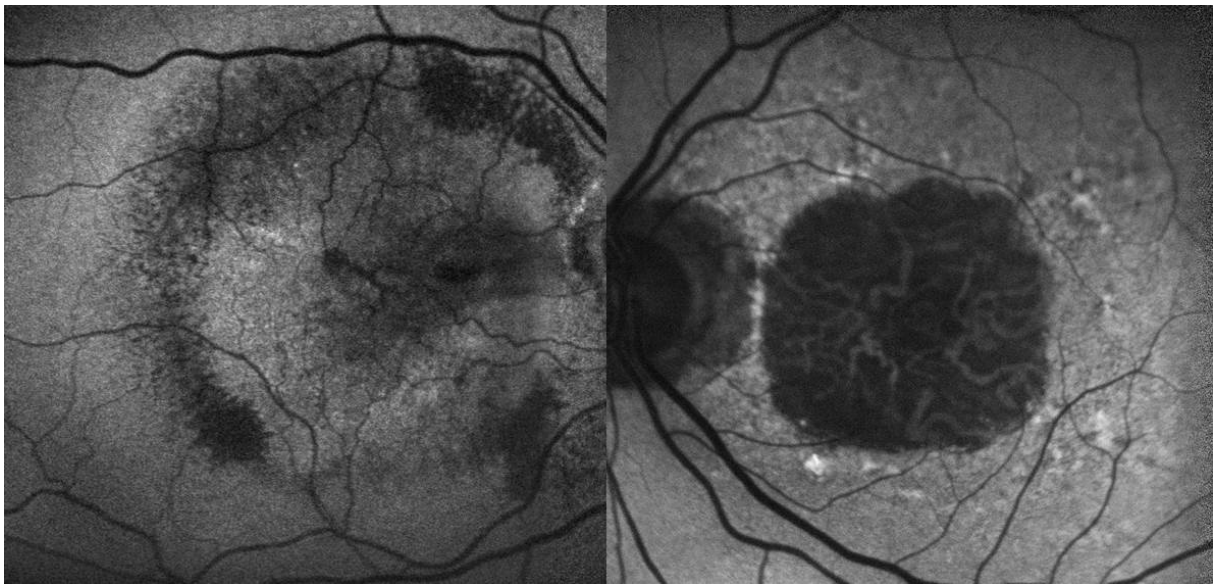

Fig 2 Abnormal - nvAMD (left) and Geographic Atrophy (right) BAF

2.0 Auto Fluorescence pattern

The normal FAF pattern is dark in the parafoveal area and increases toward the periphery. AF is very dark at the fovea due partially to absorption of the short wavelength light by melanin and luteal pigment and partly due to decreased lipofuscin content in that area. There is an absence of auto fluorescence at the optic disc due to the absence of RPE, and at blood vessels due to the masking of the RPE by the overlying blood column.

Drusen can have a hyper or hypo-autofluorescent appearance on AF images depending on the composition of the drusen. Graders should confirm drusen presence on other image modalities if identified on AF.

Exudative AMD lesions can also have a hypo-autofluorescent appearance on AF images. SRF, blood, pigment and fibrosis lying over the RPE can block the auto-fluorescence from the RPE giving the appearance of hypo-autofluorescence.

2.1 Hypo-autofluorescence

Hypo-autofluorescence is caused by areas of decreased lipofuscin. This may be due to exudative AMD lesion, atrophy and/or drusen.

Graders will be asked to determine if the hyper-autofluorescence is due to drusen. Options available are 'YES', 'NO', or 'CG'.

Hypo-AF	
Due to drusen	Yes / No / CG

2.2 Hyper-autofluorescence

Hyper-autofluorescence is caused by areas of increased lipofuscin. This may be due to exudative AMD lesion and/or drusen.

Graders will be asked to determine if the hyper-autofluorescence is due to drusen. Options available are 'YES', 'NO', or 'CG'.

Hyper-AF	
Due to drusen	Yes / No / CG

2.3 Reticular Drusen

Reticular drusen have a distinct pattern on AF which can be likened to a "starry-sky" or "leopard-spots" they tend to be in a densely packed arrangement, with less hypo/hyper-autofluorescence than that of atrophy. Reticular drusen also have a distinctive bright hyper AF halo around hypo AF spots.

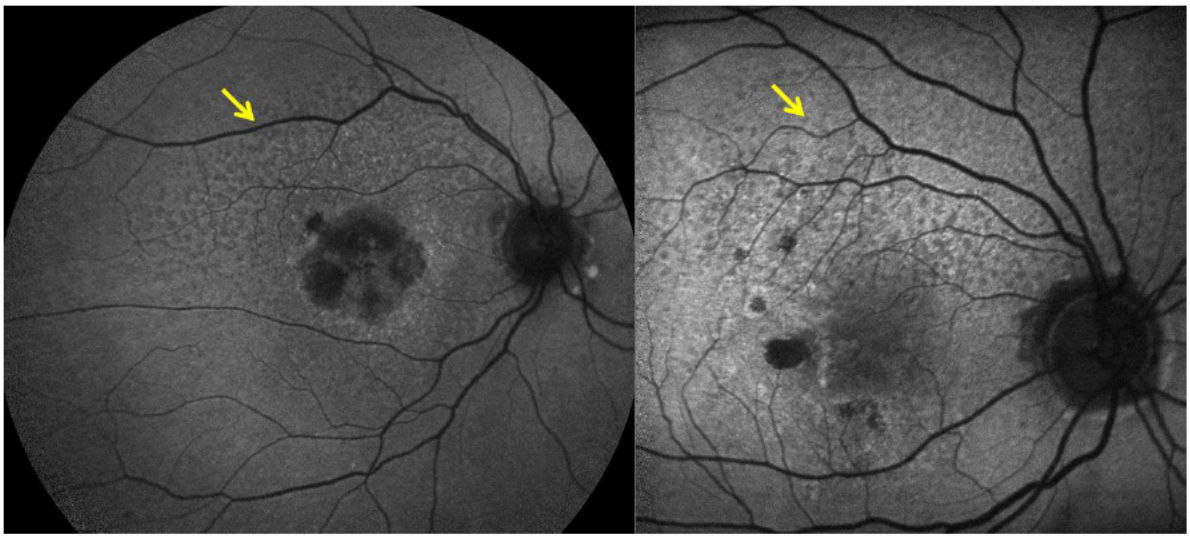

Fig 3. Reticular drusen superiorly

Presence of Reticular Drusen	
Yes	If pattern is similar to Fig. 8
No	
CG	

3.0 Other

This section has been included for information only. Graders are not required to grade the presence of other pathologies on AF; however, this info may help the grading of other features.

3.1 RPE Tear/RIP

RPE tears appear as a well demarcated area of hypo-autofluorescence fig.10 highlighted by the yellow arrows in the two samples below, with an adjoining area/s of hyper-autofluorescence which highlight the areas of rolled up RPE/CNV.

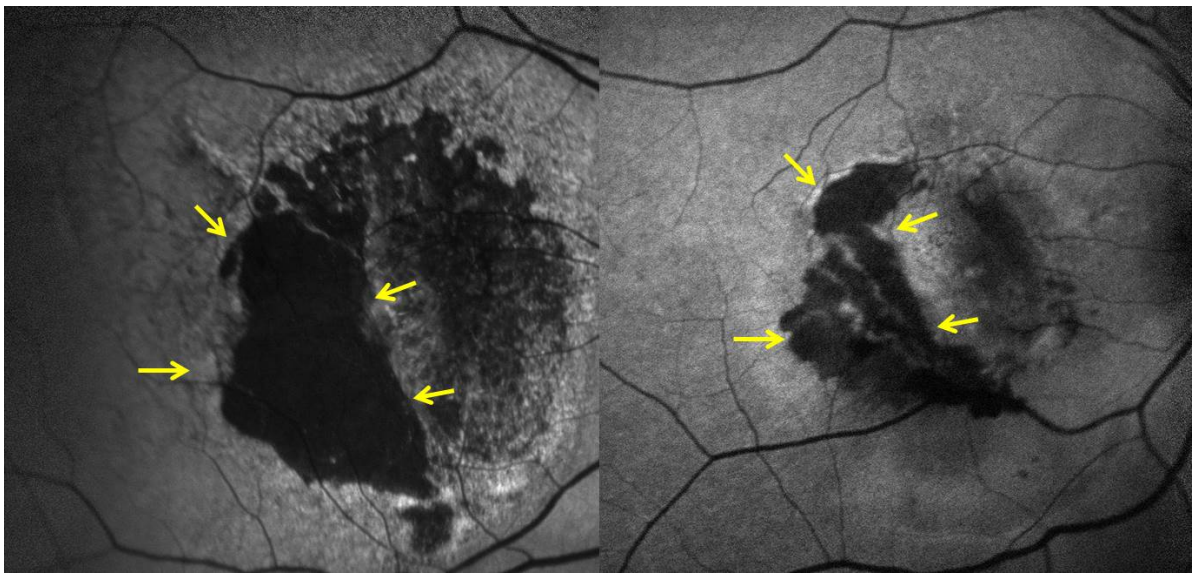

Fig 9. Areas of laser scars

3.2 Laser Scars

Laser scars, while having a hypo-autofluorescent well demarcated area, do generally not follow the same patterning of hyper-autofluorescent boarders as GA and can also be distinguished by the orderly multiple close peripheral pattern.

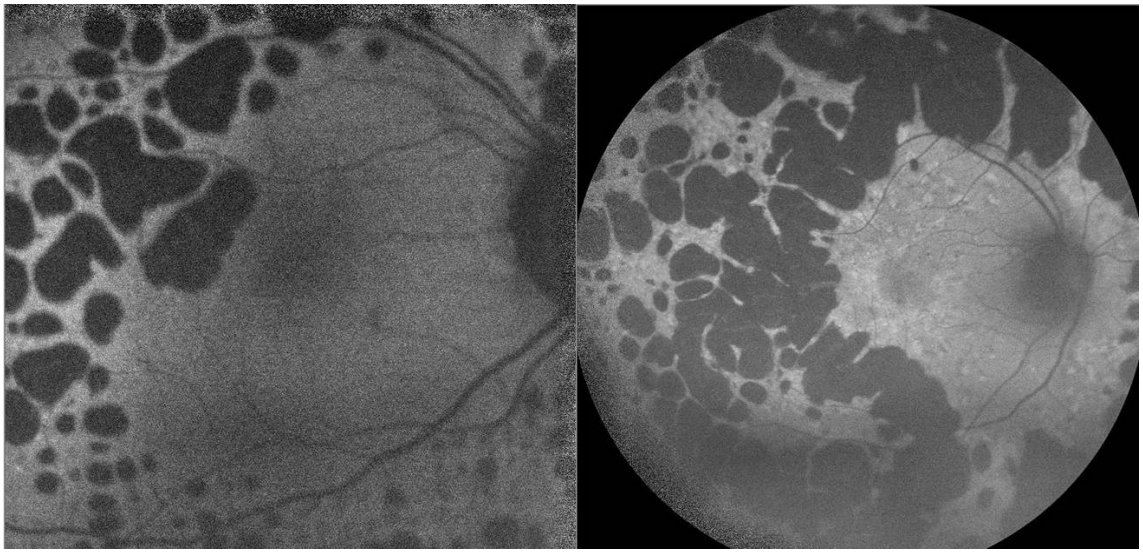

Fig 10. Areas of laser scars

3.3 CSCR

CSCR can look very similar to nAMD which will make it difficult to distinguish between the two. As there can be blocking from SRF; CSCR can show on FAF in a granular hyper-autofluorescent way, with (in some cases) a granular hyper/hypo-autofluorescent downward track (Fig.11, right image). One other thing to note is that in many cases of CSCR there are no drusen, due to the typically lower age of patients.

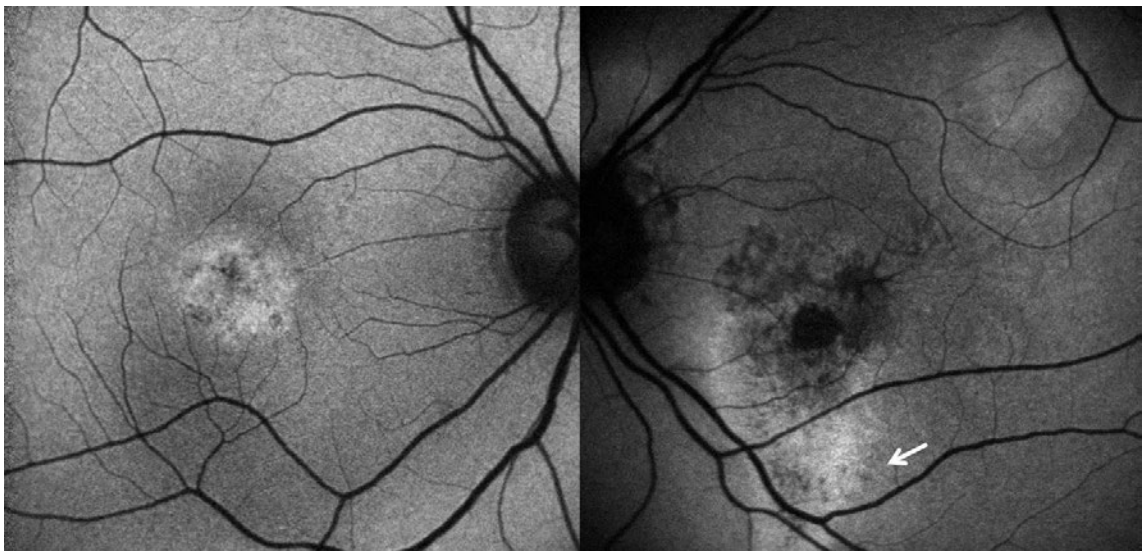

Fig 11. CSCR in both images with right having a typical appearance of the fluid track present (tear drop)

3.4 Vitelliform lesions

These types of lesions tend to show up as a bright central hyper-autofluorescent area with generally well-demarcated boarders, these lesions can develop nAMD so take care to note any changes.

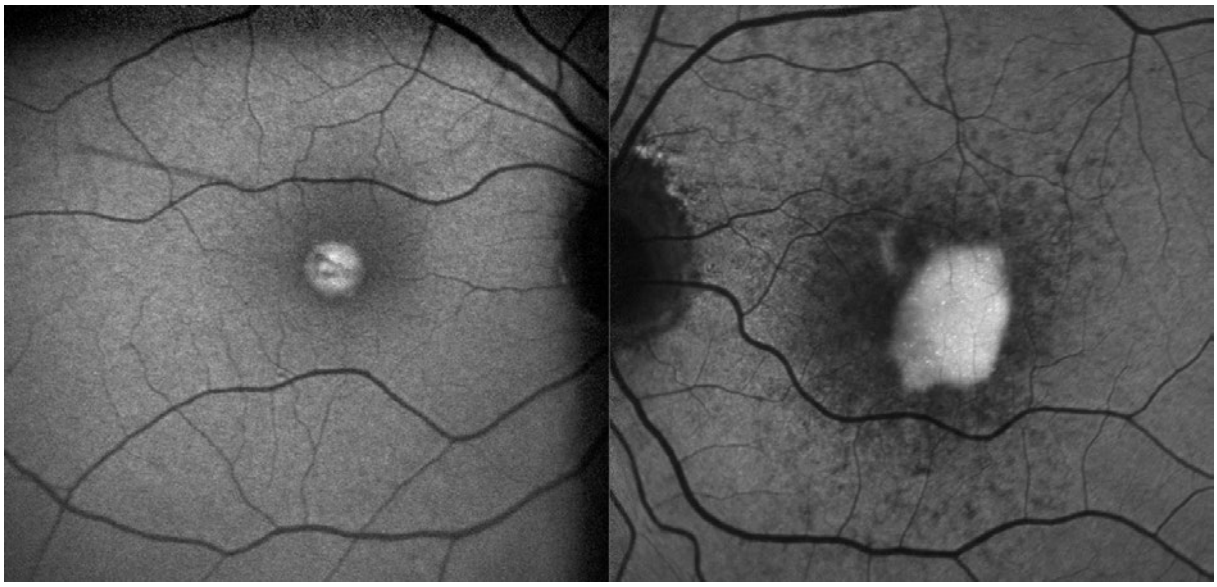

Fig 12. Vitelliform type lesions

4.0 Adjudication

If a grader has any unresolved issues relating to the FAF grading, adjudication should be selected and a detailed comment added to describe the query.

Study Name: EDNA
Document Title: Supplement 5– Optical Coherence Tomography (OCT) - Grading Definitions and Rules

Prepared By

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Approved By

Document Approver (s)	Project/Organization Role	Signed	Date
Prof Tunde Peto	Director of CARF	[redacted]	01MAY2017

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DGP	David Parry	Mr	Senior Ophthalmic Image Grader

Revision History

Revision	Date	Author	Section	Page	Reason for Change
1.0		DGP	-	-	Created document
1.1	05FEB2018	BH	3.10/3.11	19/21	Increased detail of retinal layer definition. Figure 20 updated.
			5.3	38	Specific scan inserted for CFT and TMV.
1.2	15FEB2018	BH	6.0	42	HRM note added
1.3	09/07/2020	CJ	All	All	EDNA protocol only

Contents

1.0 General Notes for OCT Image Grading

Spectral domain OCT will be utilised to assess sub-retinal fluid, intra-retinal thickening, abnormalities within the retinal layers and neovascular lesion components at each visit.

It has been agreed that all imaging modalities should be used to determine a final grading. This is important for the production of coherent grading data for the imaging modalities being graded or assessed in the case of the colour images.

You are permitted to go back to the colour, FA and ICG and change grading data if you realise that you have graded incorrectly.

It is very important to remember however, that you can **only grade what you see**. For example, if a certain lesion characteristic is identified in the colour image but cannot be identified on any of the OCT images then that feature should not be graded as present on the OCT grading form. If, however, a grader suspects SRF on colour but confidence level is less than 90%, and the OCT confirms the presence of SRF, the grader can modify the colour section of the grading form.

2.0 OCT grading

2.1 What is the overall scan quality?

An overall assessment of the scans provided should be made and described as below.

<u>Good</u>

Excellent or good discrimination of retinal layers and sub-retinal layers (particularly External Limiting Membrane (ELM), Ellipsoid Zone (EZ) and RPE/Bruch's Complex (R/BC)) throughout the majority of the scans supplied, especially in sub-foveal region.

<u>Fair</u>

Discrimination of retinal layers and sub-retinal layers (particularly External Limiting Membrane, Ellipsoid Zone and RPE/Bruch's Complex) may be less distinct than 'Good' –

above, but still of suitable quality for acquisition of reliable data. This should be the case throughout the majority of the scans supplied especially in sub-foveal region.

Poor

Discrimination of retinal layers and sub-retinal layers (particularly External Limiting Membrane, Ellipsoid Zone and RPE/Bruch's Complex) is not distinct. Some information may still be discerned but no reliable measurements could be taken. This should be the case throughout the majority of the scans supplied especially in sub-foveal region.

Ungradable

Discrimination of retinal layers and sub-retinal layers (particularly External Limiting Membrane, Ellipsoid Zone and RPE/Bruch's Complex) is not of suitable quality for acquisition of reliable data. This should be the case throughout the majority of the scans supplied especially in sub-foveal region.

Details and reference images can be found in Supplement 1 – Image Quality.

2.3 Is exudative AMD present?

The presence of exudative AMD is based on the presence of any of the following features:

- Fibrovascular pigment epithelial detachment (FPED)
- Serous pigment epithelial detachment (SPED)
- Haemorrhagic/pigmented PED
- Serous retinal fluid (SRF). See section 2.7

2.3.1 Fibro-vascular Pigment Epithelial Detachment (FPED)

FPED demonstrates well-defined irregular and relatively shallow elevation of the R/BC with a deeper area of mild backscattering corresponding to fibrous proliferation.

There is moderate reflectivity throughout entire sub-RPE (sub-R/BC) space. Fibrovascular proliferation does not scatter as much light compared to blood and therefore allows for penetration of light through entire lesion down to the level of choroid, where attenuation of choroidal reflection is typically noted.

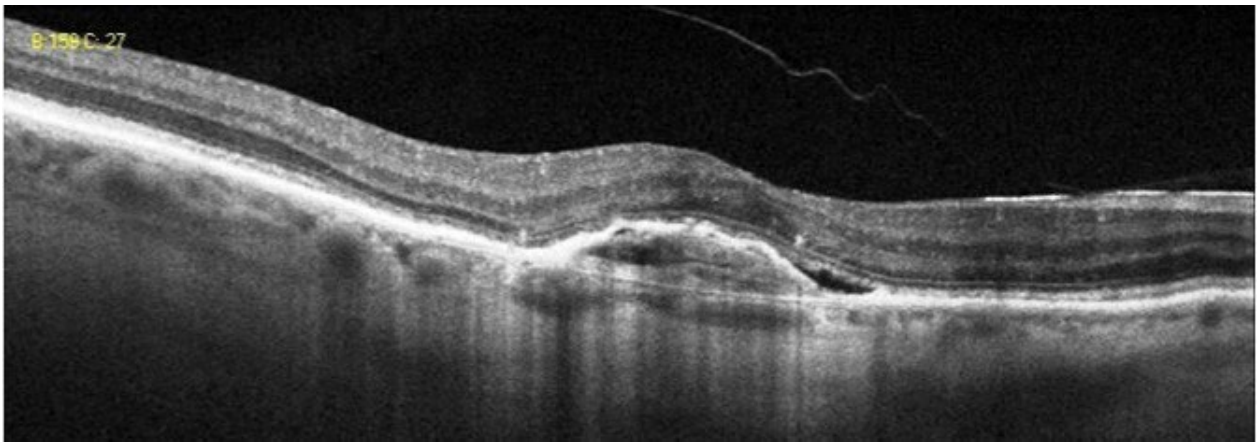

Fig 1. OCT shows elevation of the outer margin of the R/BC (FPED) with an area of increased backscattering below corresponding to fibrovascular material

2.3.2 Serous Pigment Epithelial Detachment (SPED)

On OCT an SPED appears as focal elevation of the R/BC over an optically clear space with sharp margins. The detached RPE is slightly more reflective than normal (possibly due to morphological changes in detached RPE). Increased reflectivity of the R/BC reduces reflection from the underlying choroid. The amount of shadow will depend on the amount of sub-RPE fluid present and the height of the SPED. The angle at the edge of the detachment is typically acute, probably because of the tight adherence of RPE cells to Bruch's membrane at the edge of the detachment.

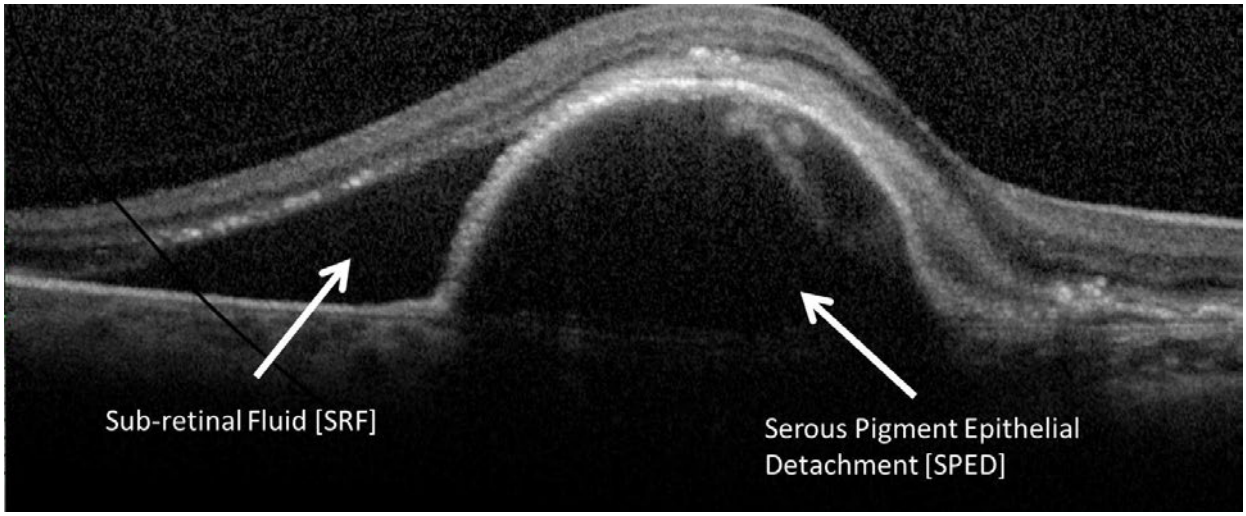
Sub-retinal Fluid [SRF]
Serous Pigment Epithelial Detachment [SPED]

Fig 2. SPED

2.3.3 Haemorrhagic / Pigmented PED

These two types of PED can be distinguished from other PEDs by the presence of a thin, moderately reflective layer directly beneath the detached/elevated R/BC. Blood directly underneath the RPE is only moderately reflective because of attenuation of probe light through detached RPE. Likewise, pigment only allows a certain amount of penetration of the OCT probe light.

Penetration through blood is usually less than 100µm. Reflections from deeper portions of blood and choroid are severely attenuated when either blood or heavily pigmented scarring is present.

Loss of choroidal details correlates with thickness of the blood/pigment. It is extremely difficult to differentiate between blood and pigment on OCT, so a heavily pigmented and elevated scar will have similar OCT appearances to a densely haemorrhagic PED.

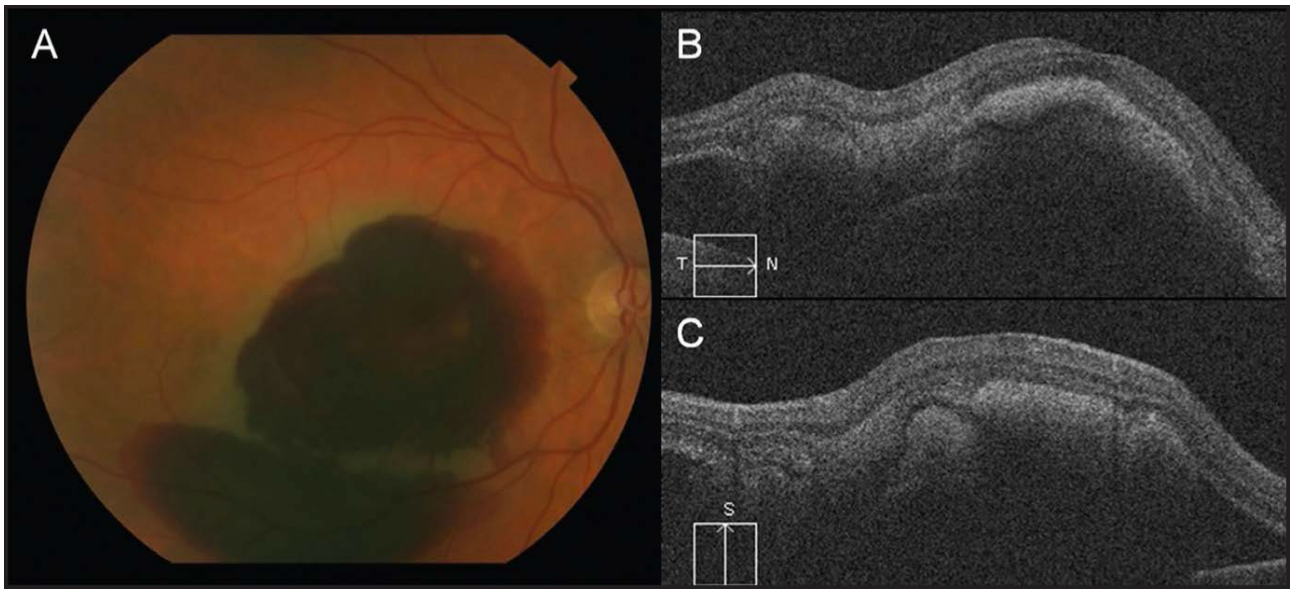

Fig 3. OCT and corresponding colour image showing haemorrhagic PED

Is exudative AMD present	
Yes	If Yes:
No	Continue with the questions below
CG	

2.4 Is there disruption of the External Limiting Membrane (ELM)?

The ELM appears on the OCT scan as a very thin hyper-reflective band between the Outer Nuclear Layer and Myoid Zone and is situated around the inner segments of the photoreceptors. Dependent on pathology found in the OCT the beginning of the disruption of the ELM can be difficult to locate, so start where you can see the ELM clearly and work your way along until you notice the ELM missing. Grade as 'No' if disruption is caused by shadowing.

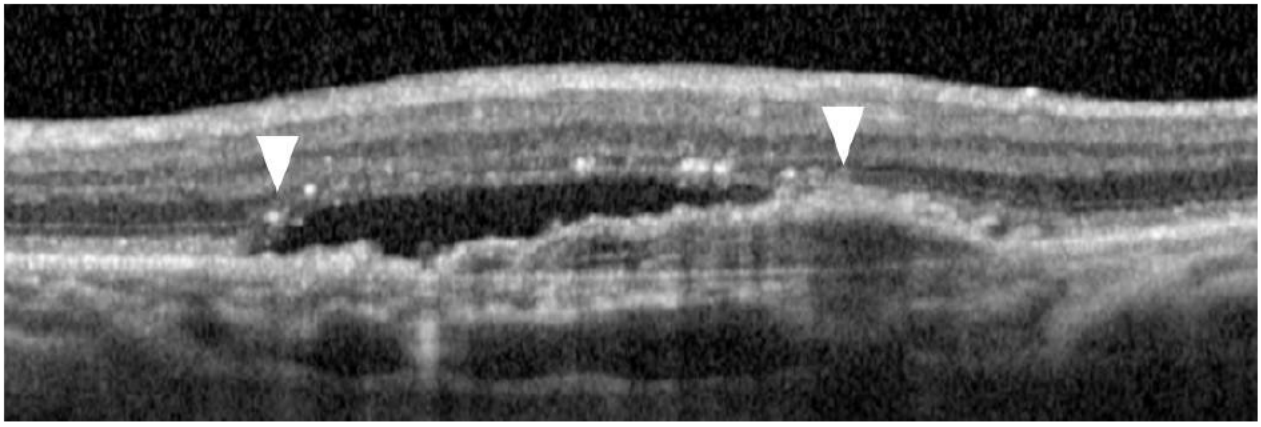

Fig 4. The edges where the ELM is lost are highlighted with white arrow

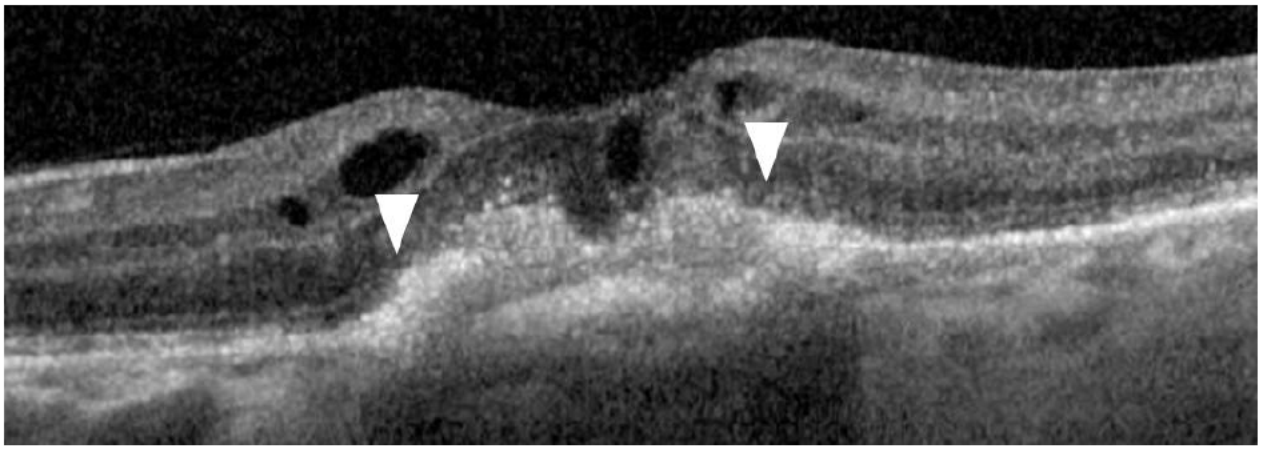

Fig 5. The edges where the ELM is lost are highlighted with white arrow

Is there ELM Disruption	
Yes	If Yes: Continue with the questions below
No	
CG	

2.5 Disruption of the Ellipsoid Zone

Graders should assess all scans available to determine if the ellipsoid zone is disrupted (non-continuous). Theoretically, it should be possible to follow the ellipsoid zone along the scan starting from an area of normal ellipsoid zone. By doing so, it should be possible to tell whether the ellipsoid zone is disrupted or intact. If disruption can be identified on any scan, the grader should select 'Yes'. Graders should then assess the foveal scans and determine if the disruption involves the fovea.

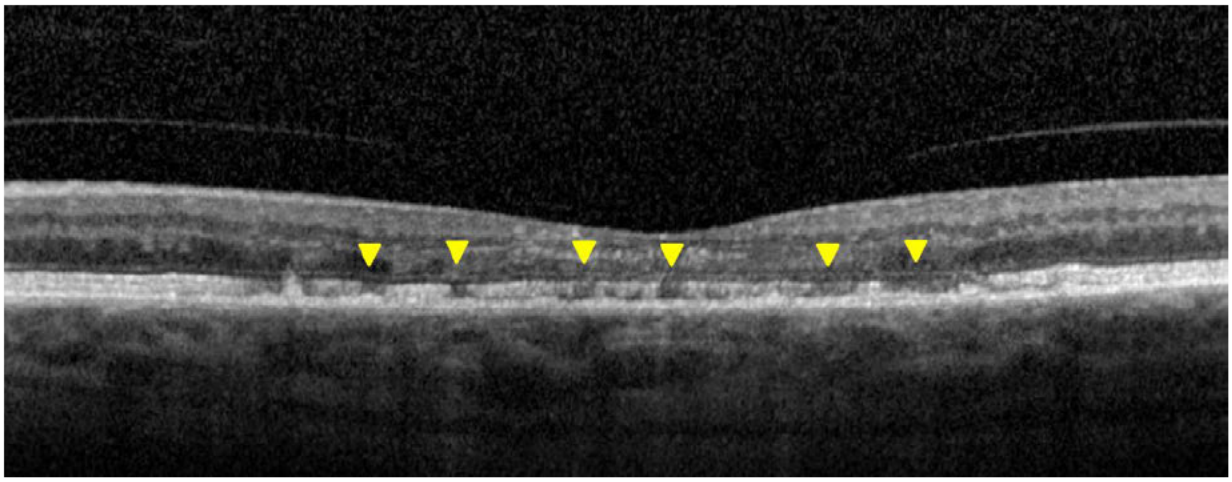

Fig 6. Multiple areas of disrupted ellipsoid zone

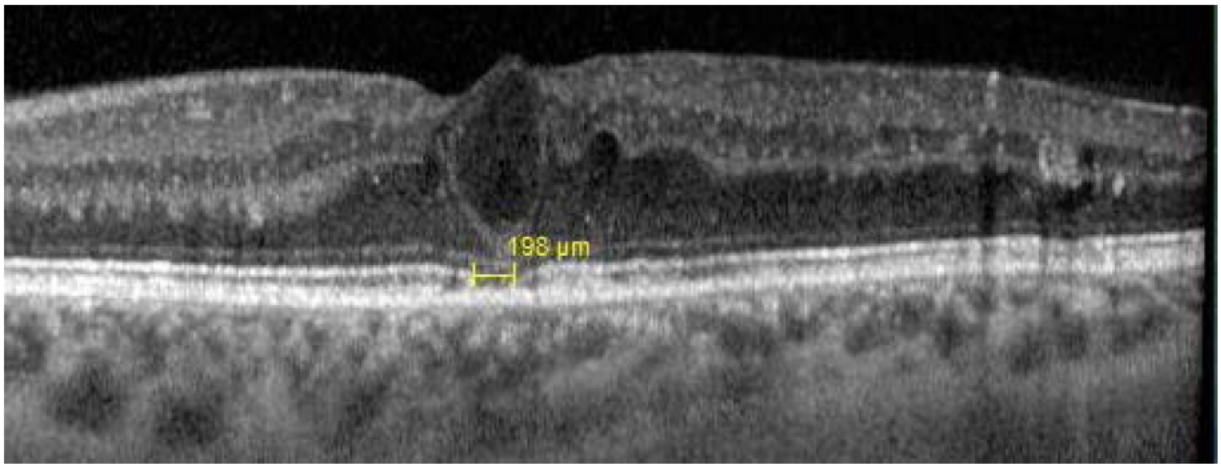

Fig 7. Ellipsoid zone focally disrupted with sub-foveal involvement shown above

Is there disruption of the Ellipsoid Zone (EZ)	
Yes	If Yes:
No	Continue with the questions below

CG	

2.6 Hypo-reflective spaces within the neurosensory retina

Macular oedema presents on OCT as optically clear spaces in the intra-retinal layers and can be focal or diffuse. It can be easily missed on interpretation of FA alone (due to overwhelming fluorescence arising from CNV).

On OCT, cystoid macular oedema (CMO) is visualised as intra-retinal, hypo-reflective spaces with no reflectivity (appear black) due to the presence of intra-retinal fluid. Hypo-reflective spaces are typically separated from each other by reflective septa.

Hypo-reflective spaces are typically round/oval in shape and must have a minimum height of at least 50µm. Small hypo-reflective spaces are generally confined to the outer retinal layers while larger hypo-reflective spaces can span nearly the entire thickness of the retina. CMO may present as one hypo-reflective space only or as multiple hypo-reflective spaces.

Breakdown of the reflective septa causes disruption of the normal retinal architecture and enlargement and coalescence of the hypo-reflective spaces. This is more likely to occur if CMO becomes chronic and longstanding and this disruption to the architecture then becomes permanent.

Diffuse oedema cannot be easily seen or measured.

If any areas of focal or diffuse hypo-reflective spaces are present, grade presence as ‘Yes’.

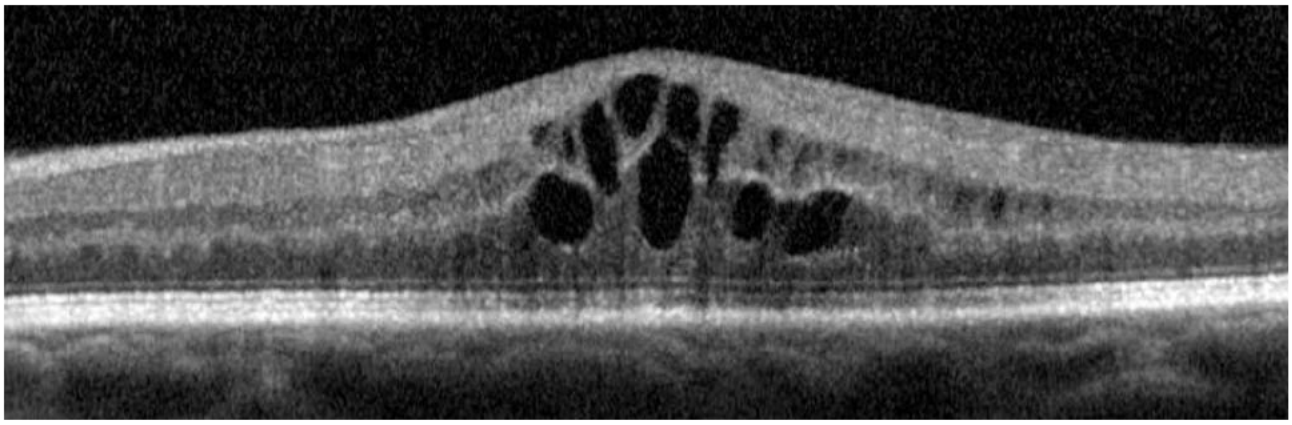

Fig 8. Cystoid

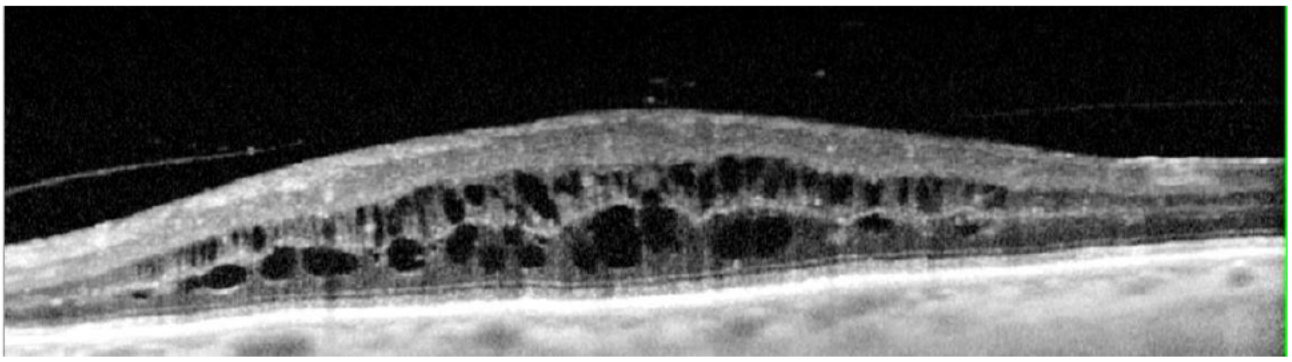

Fig 9. Diffuse

Hypo-reflective spaces within the neurosensory retina		
Yes	If Yes:	
No	Location	Outer Layers / Mid Layers / Inner Layers
CG		

2.7 Hypo-reflectivity separating neurosensory retina from R/BC (SRF)

Areas of non-reflectivity or moderate reflectivity between the neurosensory retina and R/BC are identified in this section.

Non-reflective Fluid

An optically clear space anterior to the R/BC. The space represents a collection of fluid that can be evaluated quantitatively. Sub-retinal fluid (SRF) is identified when a non-reflective space between the posterior boundary of neurosensory retina and the R/BC is present. The R/BC is undisrupted and follows the contour of globe (in distinction to intra-retinal oedema the non-reflective area of SRF is not present within neurosensory retina, nor is it typically round). SRF non-reflective space is typically semi-circular with tapered lateral extensions. Numerous variations may present due to the presence of other abnormalities such as CNV or PEDs.

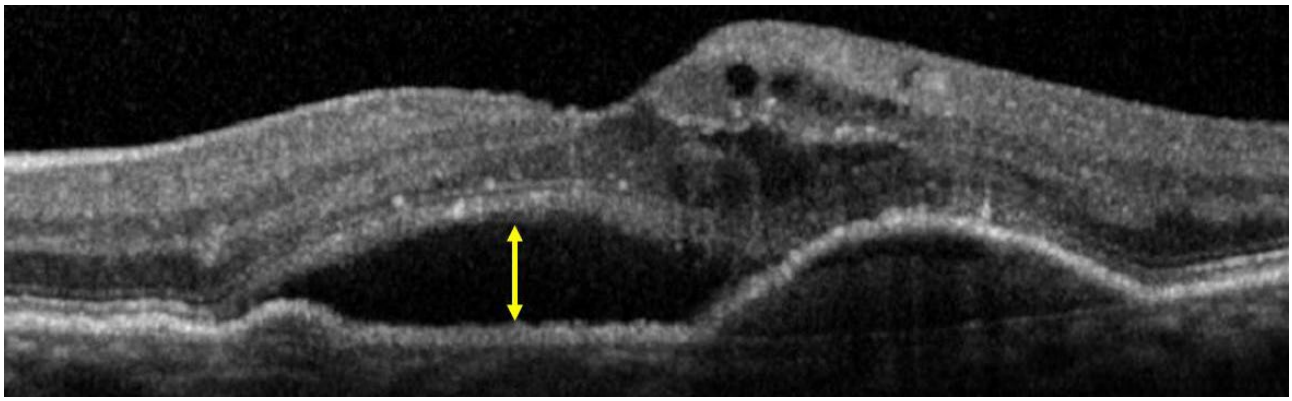

Fig 10. Non-reflective sub-retinal fluid

Moderately reflective Fluid

Areas of moderate hypo-reflectivity should also be recorded. These may be due to blood or turbid fluid. They will not usually be as hypo-reflective as sub-retinal fluid (some evidence of reflectance will be present) but will be present in the space between the neurosensory retina and R/BC.

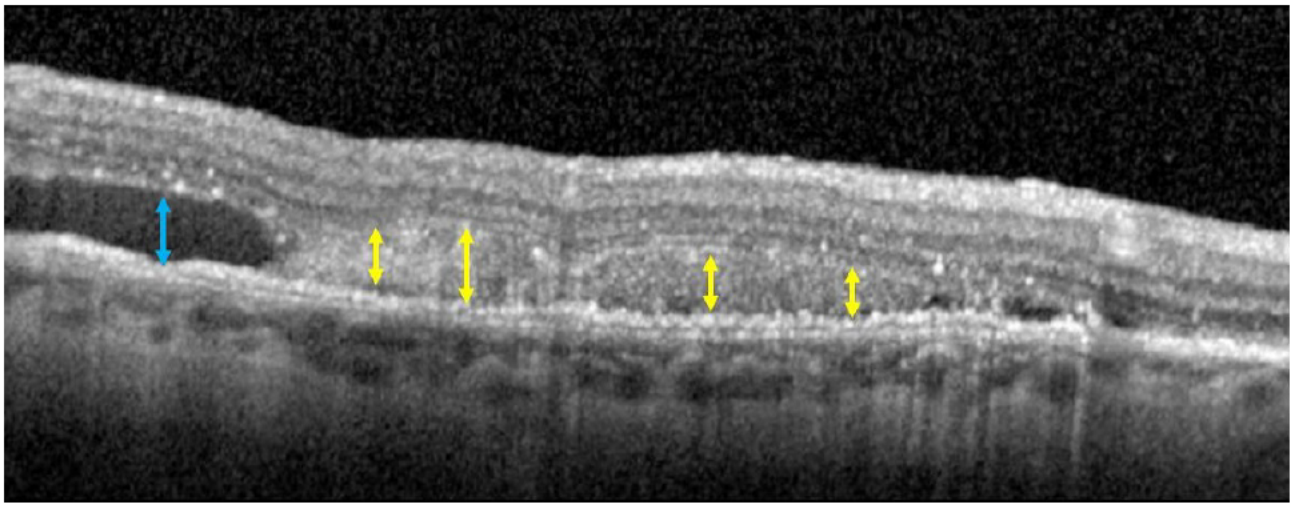

Fig 11. Moderately reflective sub-retinal fluid highlighted in yellow with an area of non-reflective fluid highlighted in blue

If an area of hypo-reflectivity between the posterior boundary of neurosensory retina and R/BC is present, grade as 'Yes'. If 'Yes' a location based question will be presented. If the area of hypo-reflectivity between the posterior boundary of the neurosensory retina and R/BC is present sub-foveally, grade as 'Yes'.

<table>
<tr><th colspan="3">Hypo-reflectivity separating neurosensory retina from R/BC (SRF)</th></tr>
<tr><td>Yes</td><td colspan="2">If Yes:</td></tr>
<tr><td>No</td><td rowspan="2">Location Sub-foveal</td><td rowspan="2">Yes / No</td></tr>
<tr><td>CG</td></tr>
</table>

2.8 Drusen

The grader should assess the OCT for the appearance of drusen and record their presence or absence as well as type of drusen. Also see NICOLA study OCT protocol and samples for more examples. Drusen definition being clear evidence of elevation of the RPE layer by discrete deposits.

On OCT, drusen appear as RPE deformation or thickening that may form irregularities and undulations.

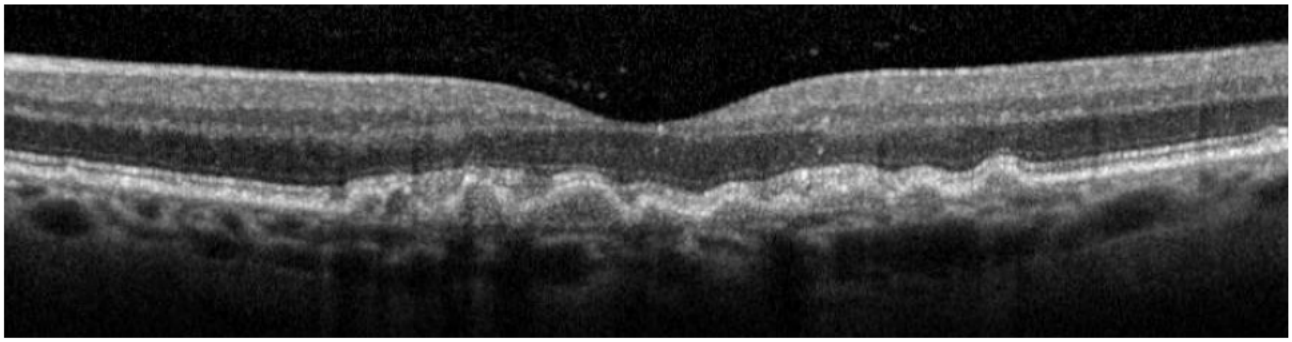

Fig 12. Nodular type drusen

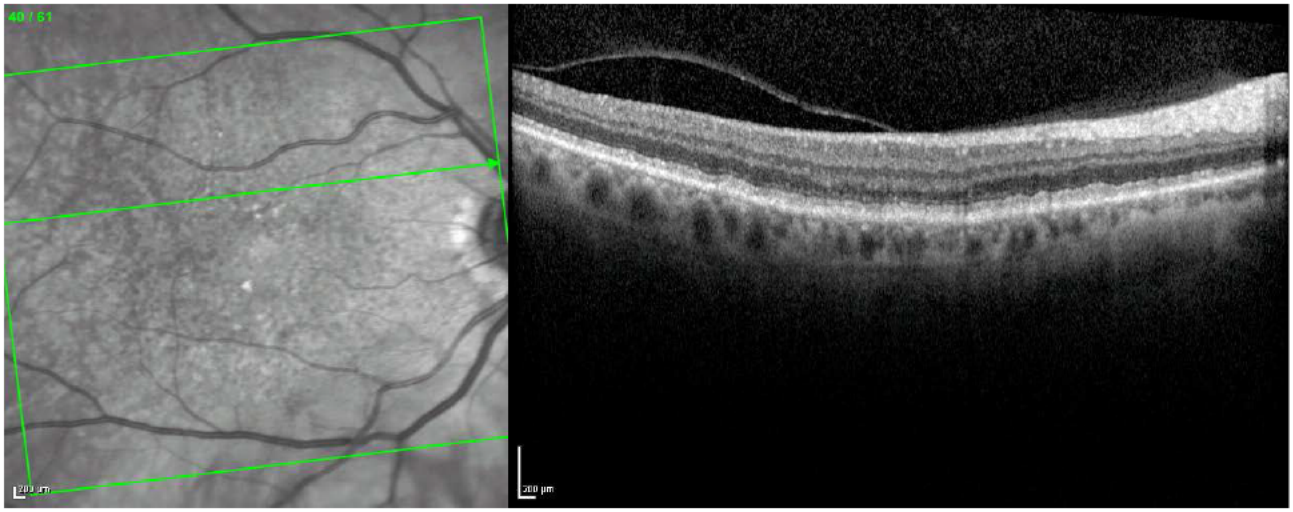

Fig 13. Reticular type drusen

Are There Drusen Present		
Yes	If Yes:	
No	Location	Nodular / Reticular / Both
CG		

2.9 Sub-retinal Drusenoid Deposits (SRDD)

Sub-retinal drusenoid deposit (SRDD) is membranous debris, the principal component of soft drusen and basal linear deposit, which is found in the sub-retinal space.

Curcio *et al*. demonstrated that these sub-retinal materials shared partial molecular commonality with drusen. Sub-retinal drusenoid deposits were proposed as the correlate to pseudodrusen by these authors because the size, distribution and prevalence of the material observed in a series of 22 donor eyes corresponded so closely to pseudodrusen imaged clinically by several methods.

The grader should look for the presence of sub-retinal drusenoid deposits, and if present they should be categorised into ‘discrete’, ‘diffuse’ or ‘both’ for the type present.

Discrete:

Sub-retinal accumulation of material, typically forming sharp peaks.

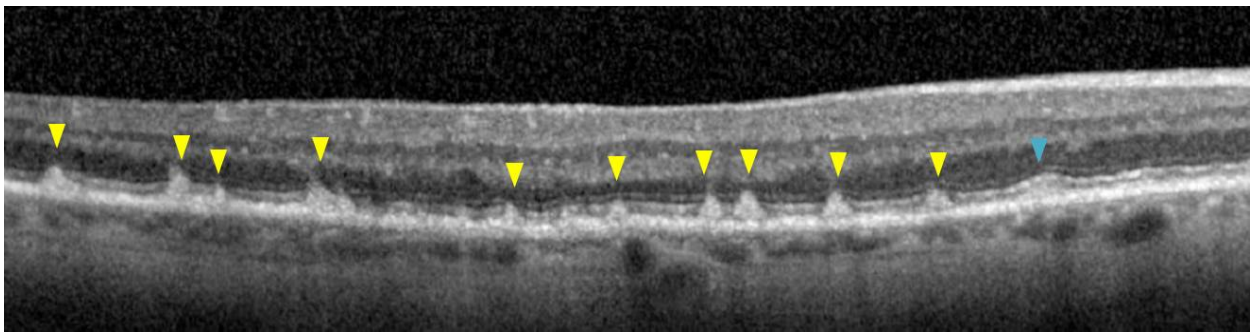

Fig 14. Discrete SRDD with the typical peaks highlighted in yellow. A single Diffuse SRDD is highlighted in blue

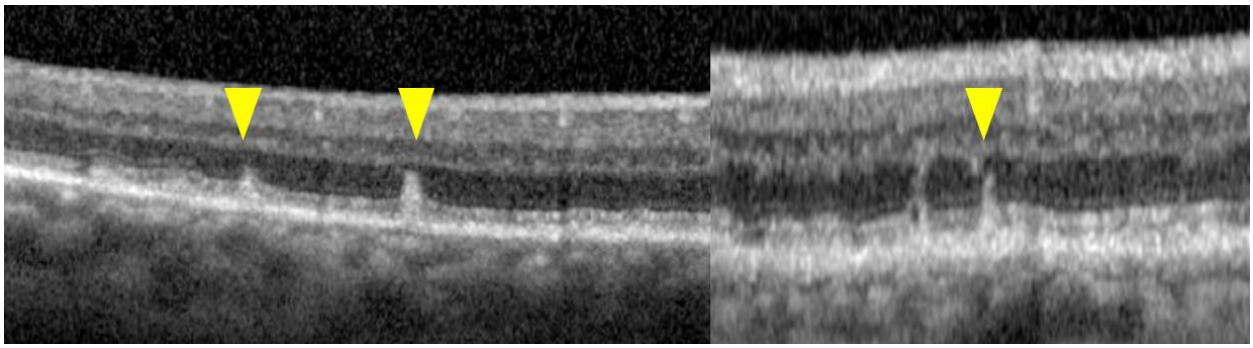

Fig 15. Discrete sub-retinal druse with the typical peaks

Diffuse:

Sub-retinal accumulation of material, typically forming broad, rounded elevations.

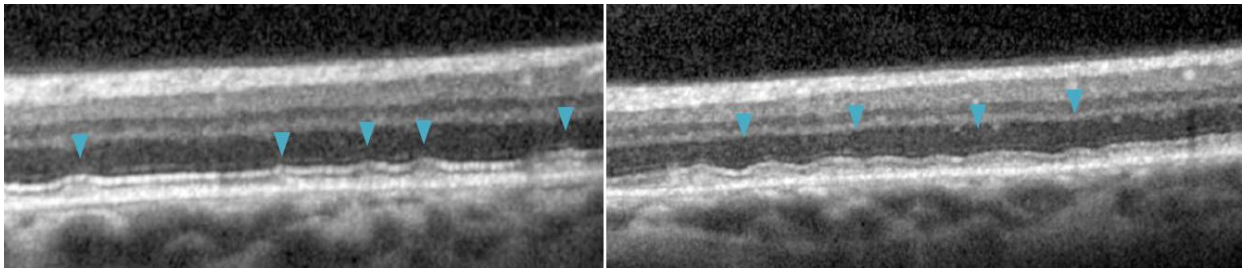

Fig 16. Diffuse SSRD highlighted in blue

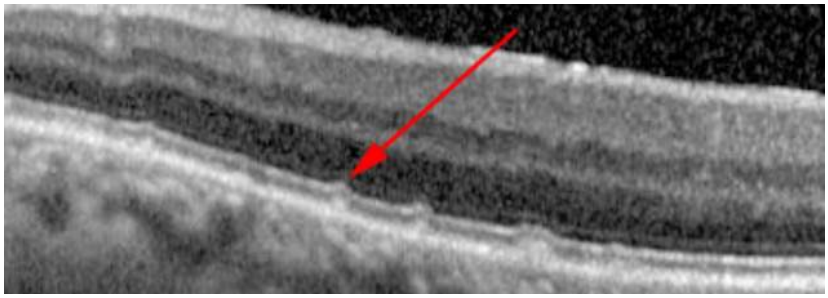

Fig 17. Minimum size required to grade as Diffuse SRDD

Grade Options		
Yes	If Yes:	
No	Options	Discrete / Diffuse / Both
CG		

3.0 Focal Atrophy

The grader should assess the OCT for the presence of focal atrophy.

This is deemed present if there is:

- Increased signal transmission through the RPE/Bruch's complex
- RPE band thinning or missing
- Outer nuclear layer thinning, missing or dropping

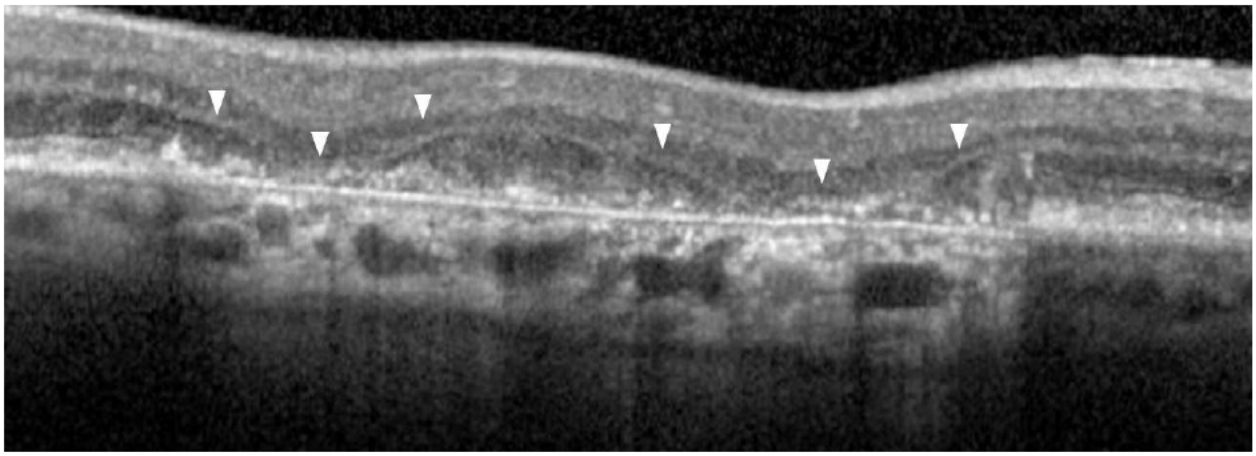

Fig 18. White arrows highlighting the start of the outer nuclear layer dropping and centre point

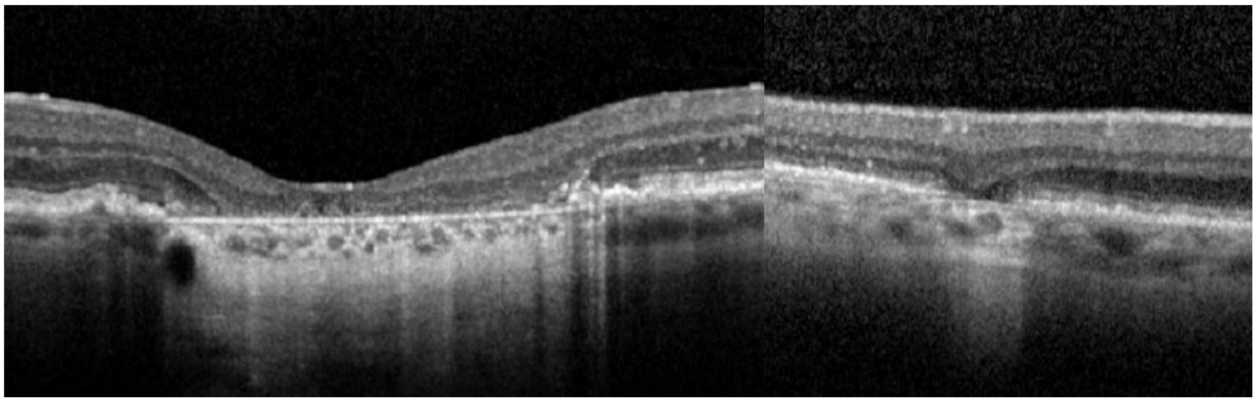

Fig 19. The above are samples of dropping of the outer nuclear layer

Is There Any Focal Atrophy Present		
Yes	If Yes:	
No	Evidence of inner nuclear subsidence	Yes / No
CG	Transmission Defect	Yes / No

3.1 Choroid Thickness

The grader should determine if the choroid is thin, normal or thick. This should be based on comparison with the size guide and images shown below, the measurement should be taken around the area of the fovea or presumed fovea if not visible due to pathology

Guide to choroid height:

- ≤ 200µm = Thin
- 201 - 400 µm = Normal
- ≥ 401 = Thick

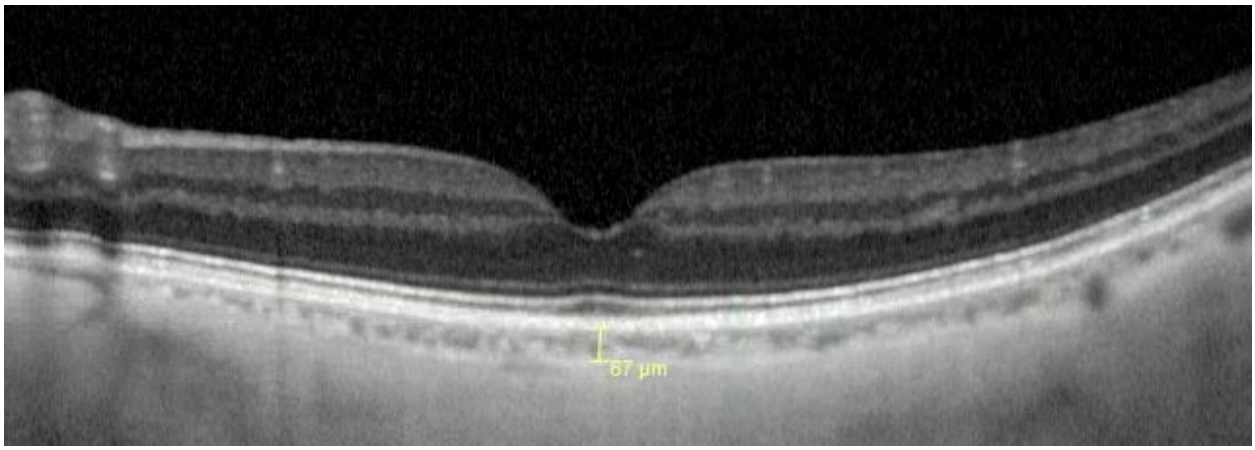

Fig 20. Thin choroid

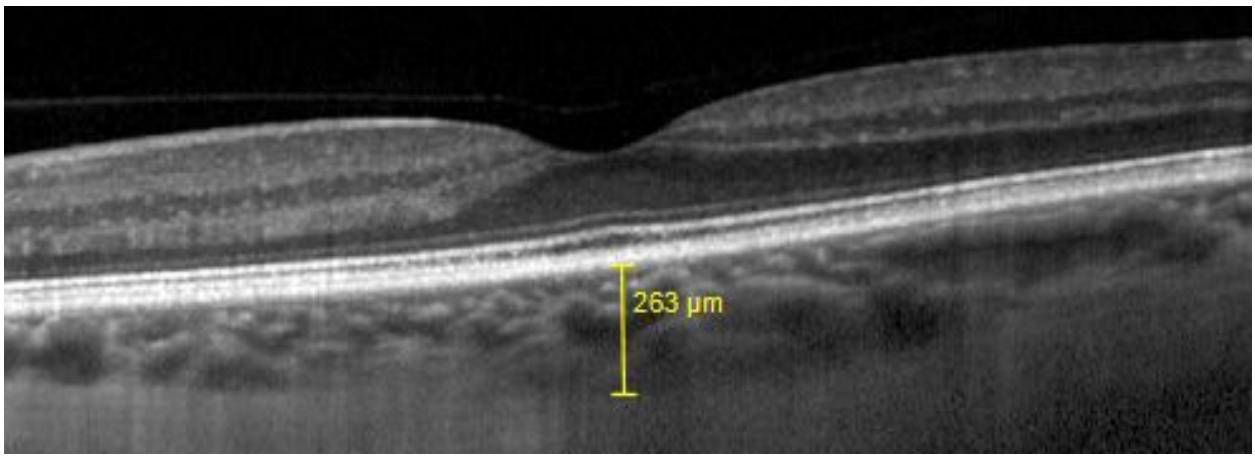

Fig 21. Normal choroidal thickness

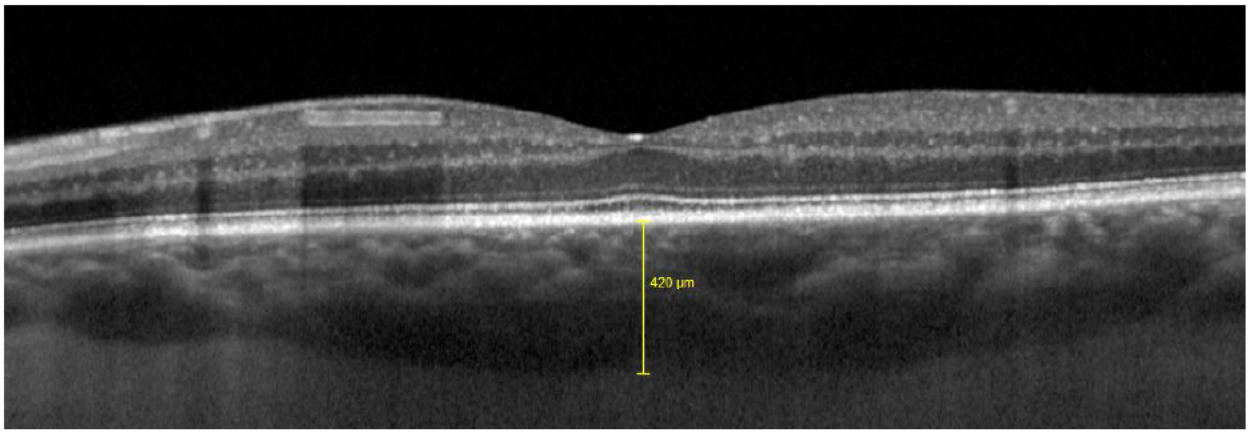

Fig 22. Thick choroid

Choroid Thickness	
Is the choroid	Thin / Normal / Thick

3.2 Epiretinal Membrane (ERM)

ERM typically appears as a highly reflective layer visible on the inner retinal surface. Essentially an ERM is demonstrated by a thickening of the normally thin highly reflective layer on the surface of the retina. This represents the nerve fibre layer in the normal eye, and it is thicker on the side next to the disc than it is temporal to the fovea. In ERM this highly reflective band is abnormally thickened. There are different types of ERM, depending on the degree of attachment or separation of the abnormally thickened band, which basically represents fibrous tissue running along the surface of the retina. This can then become detached from the surface of the retina in places, causing a separation. Also the fibrotic band can contract causing surface wrinkling of the inner highly reflective band.

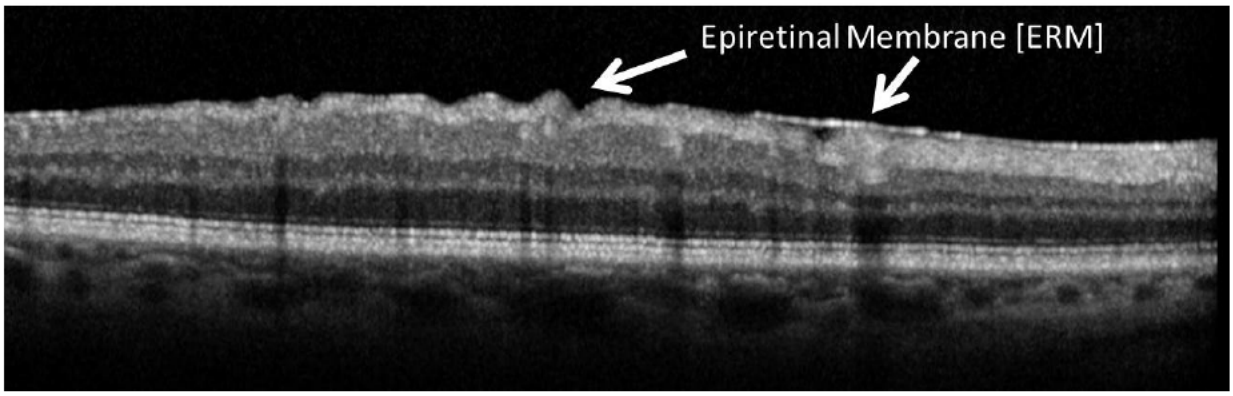

Fig 23. ERM

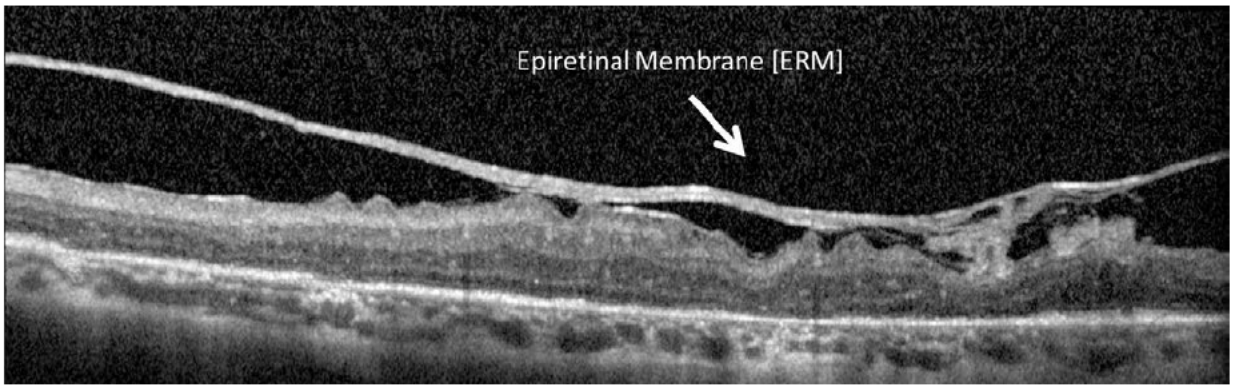

Fig 24. ERM with detachment

Epiretinal Membrane (ERM)		
Yes	If Yes:	
No	Was it seen on Colour Fundus Imaging	Yes / No

3.19 Evidence of Vitreal Attachment

Vitreal attachment is defined as an incomplete separation of posterior hyaloid with focal attachment at the macula/fovea. This is only demonstrable if the correct slice through the

precise point of attachment is taken, any OCT slice or section taken which is outside of this point will miss it totally. The posterior hyaloid face, if apparent at all, is only visible if there has been some separation or detachment of the vitreous from the retinal surface. It appears as a thin, highly-reflective line within the vitreous and is usually just above and parallel to the inner surface of the retina on the OCT scan. In some disease states, for example diabetes, this posterior hyaloid face becomes thickened and more prominent on the OCT.

Grade as present only if the point of attachment between the posterior hyaloid face and macula is visible on any OCT scan.

The options for grading are:

- **Attached with Traction:** This should be selected if a vitreal attachment at the macula is evident with traction

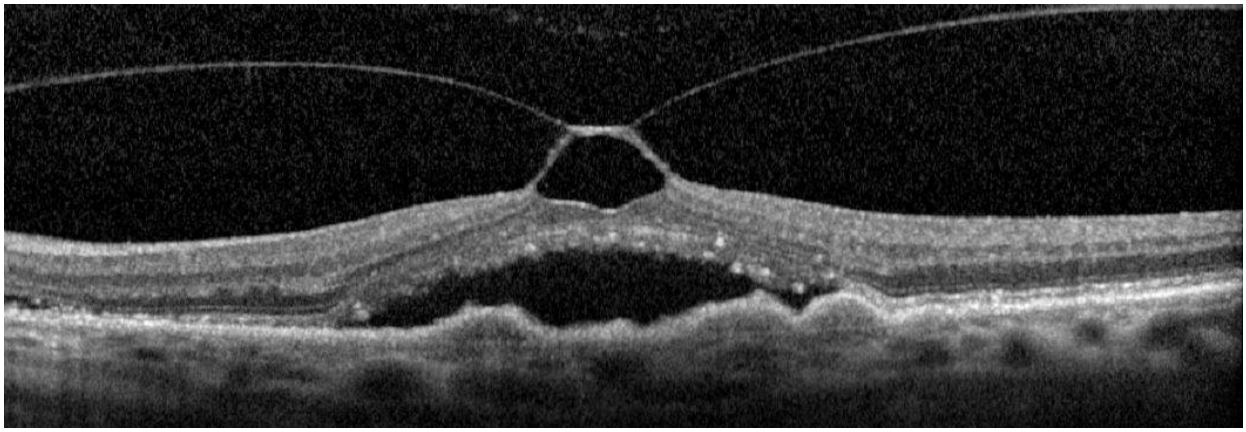

Fig 25. Vitreous attached at macula with traction

- **Attached without Traction:** This should be selected if a vitreal attachment at the macula is evident but no traction is evident i.e. there is no distortion of the inner retinal surface

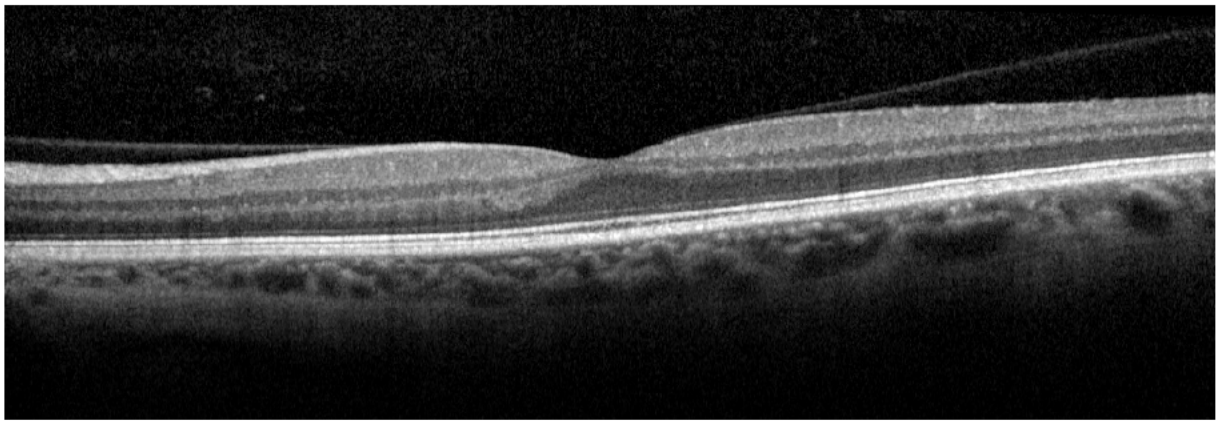

Fig 26. Vitreous attached at macula without traction

- **Definitely Detached:** The vitreous face is visible but not attached on any scans present

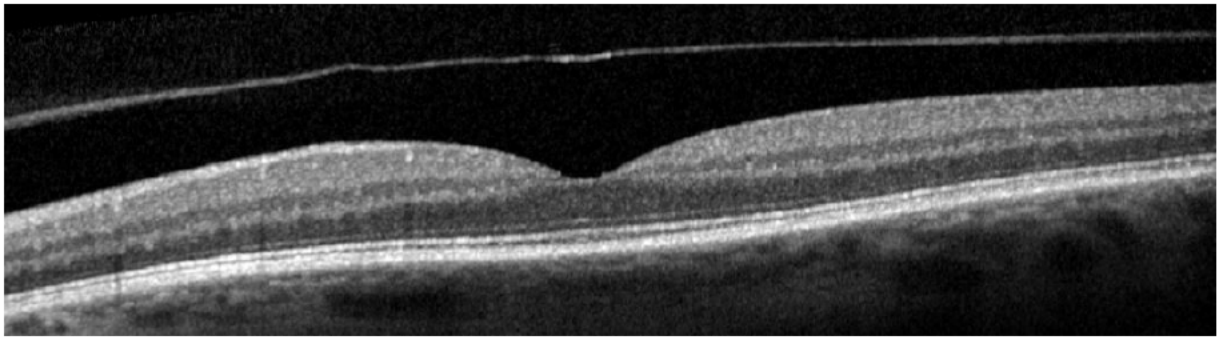

Fig 27. Vitreous definitely detached at the fovea

- **Not known:** Either fully detached and beyond range of scan or fully attached and therefore not visible

- **CG:** Where image quality is graded as CG this should be selected

Evidence of Vitreal Attachment		
Yes	If Yes:	
No	Choose Option	Attached at Macula with Traction

		Attached at Macula without Traction
		Definitely Detached
		Not Known
		CG

4.0 Central Foveal Thickness (CFT)

The grader should select the thickness map or equivalent on the OCT software, and identify the Central Foveal Thickness.

****Grader must select the standard IR & OCT scan to identify and record Central foveal thickness** (EDI IR&OCT to be used as secondary option if standard scan not available)**

Please take great care when recording measurements from the imaging software onto the grading forms; it is important that all data is accurate. Ensure that you copy the values directly from the software onto the grading form and double check that you have recorded the correct value. If the volume/cube scan is not supplied, this will be recorded in the scan profile question at the beginning of the OCT grading form and the question will not be required.

Example images of the location of CFT for each software application are shown below.

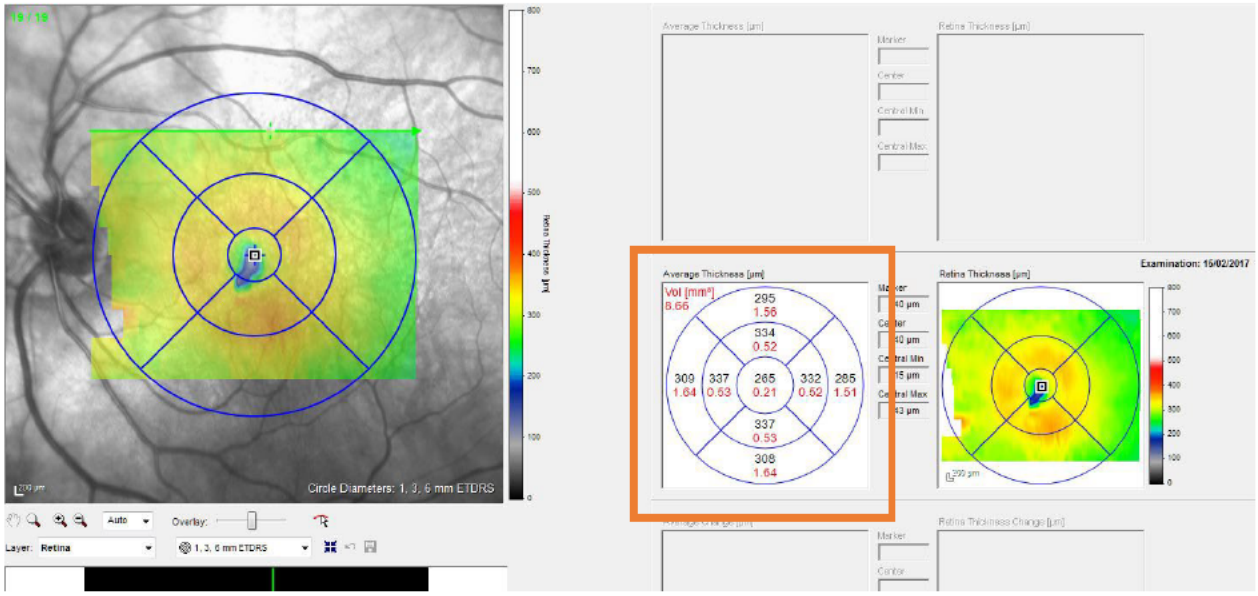

Fig 28. CFT Location for Heidelberg Spectralis SD OCT

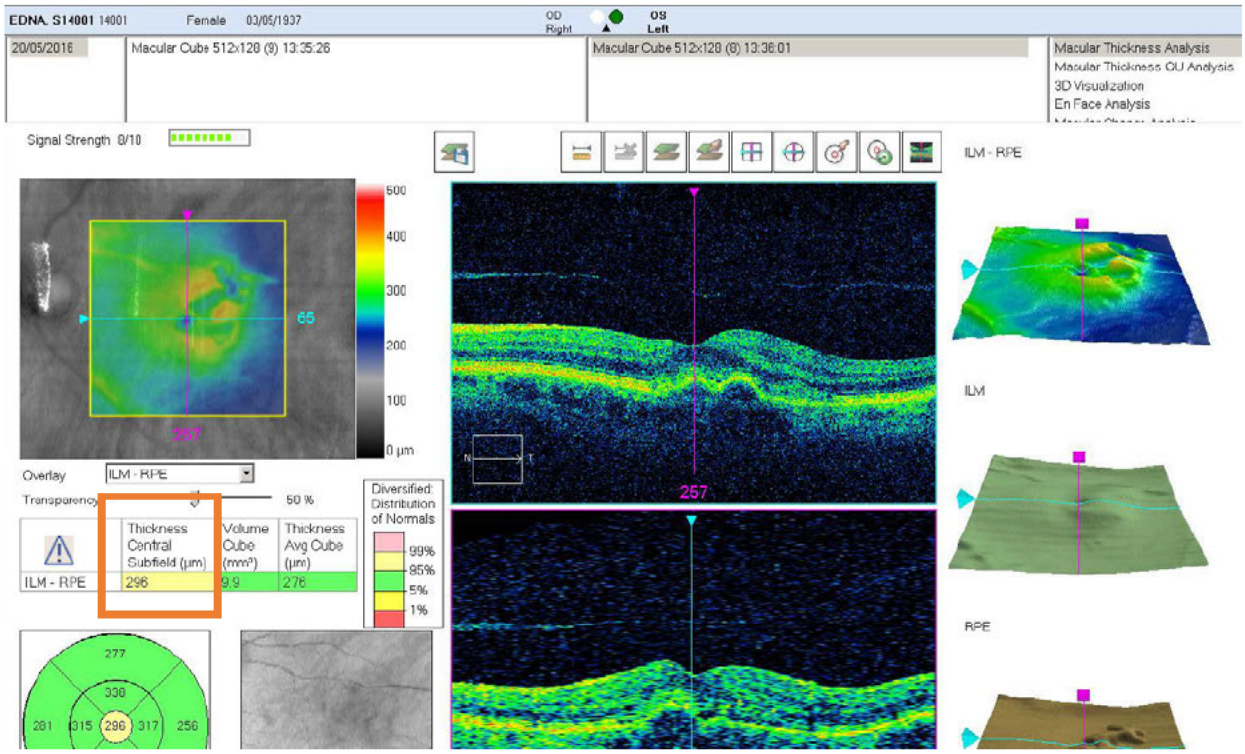

Fig 29. CFT Location for Zeiss Cirrus FD OCT

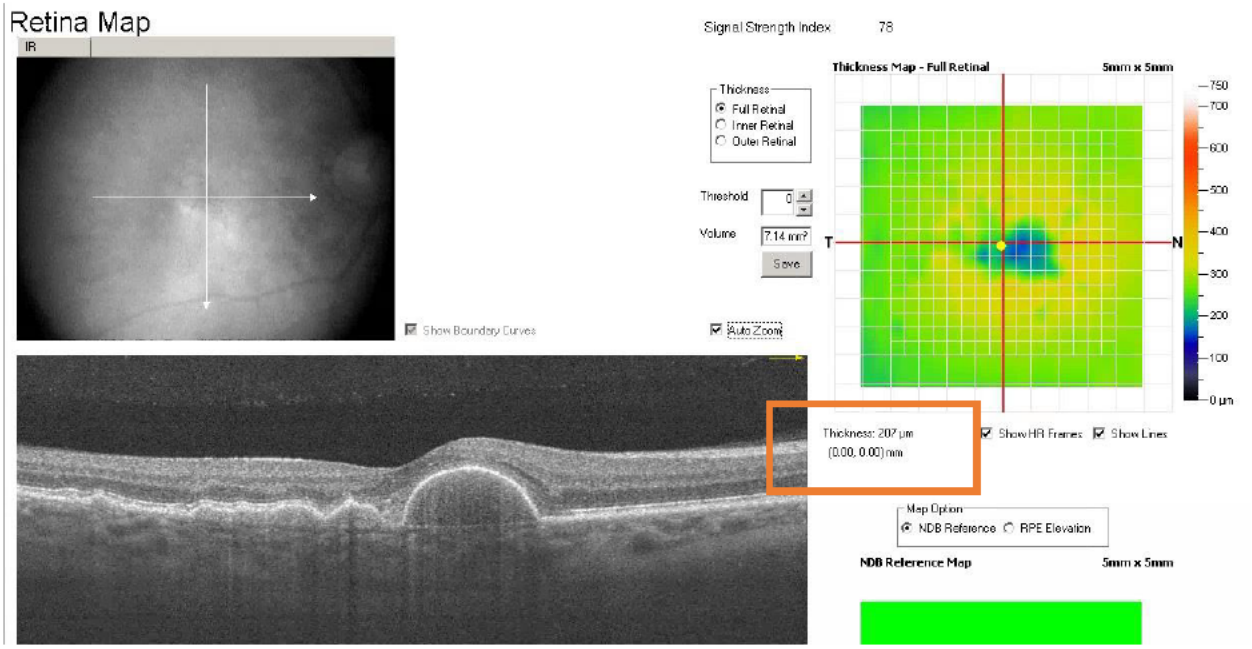

Fig 30. CFT location for RTVue D OCT: Ensure full thickness is selected

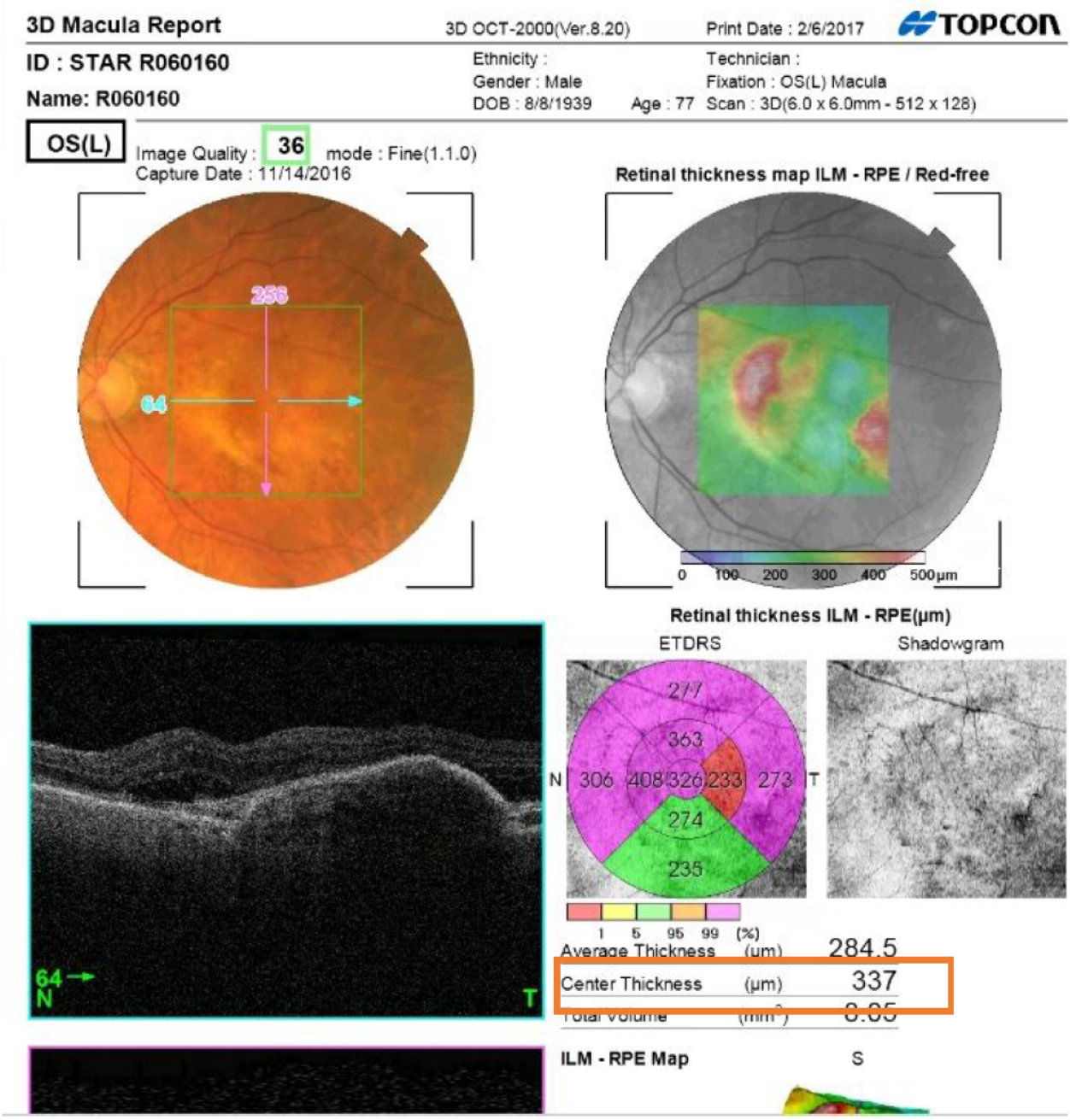

Fig 31. CFT Location for Topcon 1000 & 2000 FD OCT

Central Foveal Thickness ungradable	
Yes	

No	If No: record value

5.0 OCT Layers

The reference image below shows annotations of the various layers of the retina that can be seen in a normal eye OCT image. In eyes with pathology, abnormalities may be seen in some of these layers.

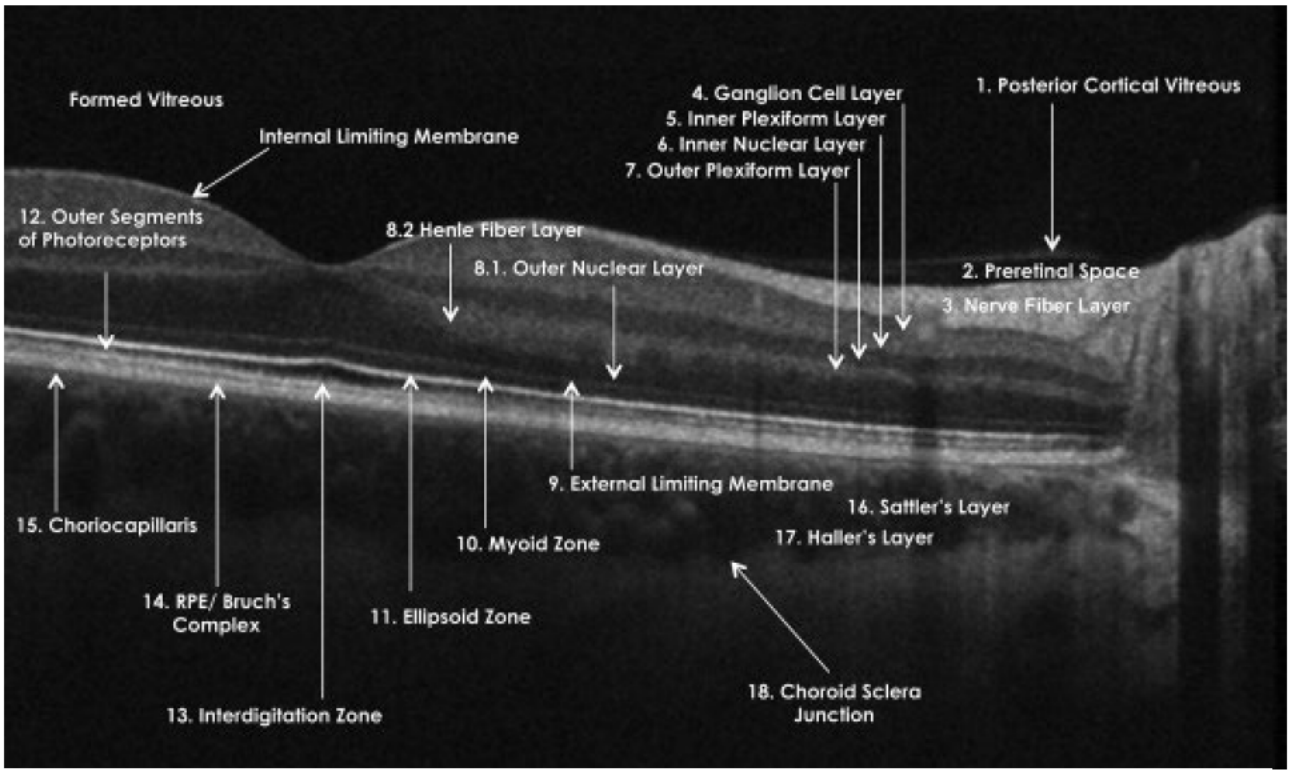

Fig 32. Proposed Lexicon for Anatomic Landmarks in Normal Posterior Segment Spectral-Domain Optical Coherence Tomography

6.0 Adjudication

If a grader has any unresolved issues relating to the OCT grading, adjudication should be selected and a comment added to describe the query.

I.