Statistical Analysis Plan for the NOD Age-related Macular Degeneration (AMD) Audit

Second year of the prospective RCOphth NOD AMD Audit

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1 Abbreviations

Abbreviation	Description
AMD	Age-related Macular Degeneration
Anti-VEGF	Drug blocking the action of vascular endothelial growth factor
CDVA	Corrected distance visual acuity
CF	Count Fingers – a measure of visual acuity
COVID-19	Coronavirus Disease 2019
CQC	Care Quality Commission
EMR	Electronic Medical Record
ETDRS	Early Treatment Diabetic Retinopathy Study
HM	Hand movements - a measure of visual acuity
IMD	Index of Multiple Deprivation
IOI	Intraocular Inflammation
LogMAR	Logarithm of the Minimum Angle of Resolution – a measure of visual acuity
NHS	National Health Service
NOD	National Ophthalmology Database
NPL	No perception of light - a measure of visual acuity
PIE	Presumed Infectious Endophthalmitis
PHVA	Pin hole visual acuity - The pinhole is an eye shield with several small holes which allow light rays to reach the retina without the interference of optical problems of the eye. It is used to test visual acuity.
PL	Perception of light – a measure of visual acuity
RCOphth	The Royal College of Ophthalmologists
UDVA	Uncorrected distance visual acuity
UK	United Kingdom
VA	Visual acuity – This is traditionally measured by the ability to distinguish letters or numbers at a given distance according to a fixed standard. We have reported VA using ETDRS letters. A “normal” ETDRS letter visual acuity would be 85 ETDRS letters and the number increases as vision improves. 70 ETDRS letters would be at the boundary for driving a car and is described here as ‘good’ vision. 35 ETDRS letters would be at the level of registrable severe sight impairment.
VEGF	Vascular endothelial growth factor

2 Acknowledgment

We would like to acknowledge the support and guidance we have received from the RCOphth NOD AMD Audit Advisory Group members, the NOD Steering Group members, the RCOphth Executive Committee, Informatics and Audit Subcommittee and the Lay Advisory Group. Their guidance has helped us to ensure that the audit has relevance for not only the professional readership but also patients, their relatives and carers. We thank all the members for reviewing this report.

We also acknowledge the support of the organisations that are participating in the prospective audit and thank our medical and non-medical colleagues for the considerable time and effort devoted to conscientious electronic data collection as they go about caring for their patients. All participating centres are acknowledged on the RCOphth NOD audit website (www.nodaudit.org.uk).

It is with deep regret that we note the death of our friend and colleague Robert Johnston, who sadly died in September 2016. Without his inspirational vision, determination and career long commitment to quality improvement in ophthalmology this work would not have been possible.

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3 Introduction

The Royal College of Ophthalmologists (RCOphth) is the governing authority for the National Ophthalmology Database Audit (NOD) and conducts the UK AMD Audit on data relating to treatment for 'wet' or neovascular form of age-related macular degeneration. The audit is open to providers of both National Health Service (NHS) and privately funded AMD treatment in England, Guernsey, Scotland, Northern Ireland and Wales. The data is collected as part of routine clinical care on electronic medical record (EMR) systems and the analysis is performed by the RCOphth NOD Audit statisticians based in Cheltenham General Hospital. Centres without an EMR who can collect data on a bespoke system can participate after communication with the audit team about the volume and quality of data they could submit.

Results are published on the RCOphth NOD website (www.nodaudit.org.uk), produced for peer review journals and published in annual reports. This document concerns the statistical analysis plan for the prospective national AMD audit analysis.

The RCOphth NOD receives data collected on multiple systems that can have different ways to record the information. For this reason, the terminology used in this document is the wording used in the supplied information.

4 AMD Inclusion/Exclusion criteria

Eligibility for any AMD analysis

The definition of an eligible eye is an eye with a recorded diagnosis of wet or neovascular AMD starting anti-VEGF treatment in the relevant time period for the analysis.

Reasons for exclusion are listed below:

- Eyes with any prior treatment for wet AMD (before the relevant time period)
- Eyes receiving treatment from a clinical trial drug
- Eyes from patients aged <55 years at the start of treatment
- Eyes without a diagnosis or indication for surgery for wet AMD

National Ophthalmology Database AMD Audit specific criteria

For the RCOphth NOD National AMD Audit annual report further criteria apply, these are:

- For named centre results, at least 25 eligible eyes are required
- For visual acuity (VA) results, at least 25 eligible eyes with VA data at the relevant time points are required for a VA result at the relevant time point. This applies to baseline, one year and monthly time points. For change in VA at one year, both a baseline and a one-year VA are required for at least 25 eligible eyes for a result to be produced for a centre
- RCOphth NOD annual reports use the NHS year (01 April to 31 March) as the designated years that results are reported for
- For 24-month results, results are reported for eyes starting treatment in the previous year to the reported NHS year for 12-month results. Eligibility criteria remain the same.

5 Eligible “wet” AMD diagnosis and indication for treatment

An eligible eye must have at least one diagnosis of or indication for treatment for “wet” AMD. If no valid “wet” AMD diagnostic record or indication for treatment is recorded, then the eye is excluded. Diagnosis and indication for treatment can be recorded to indicate definitive “wet” AMD or can be recorded without specifying “wet” or neovascular AMD. For this reason, diagnosis and indication for treatment information is divided into definitive “wet” AMD and assumed “wet” AMD.

The following diagnoses and indications for treatment are considered to indicate the presence of definitive “wet” AMD:

- <50% of lesion is CNV
- >50% of lesion is CNV
- Age-related macular degeneration
- Age-related macular degeneration - peripapillary choroidal neovascular membrane
- Age-related macular degeneration with subretinal fluid / exudate / blood
- Classic choroidal neovascular membrane
- Clinically avascular PED
- Clinically avascular (serous) PED
- CNV outside posterior pole
- CNV (type not specified)
- Disciform scar
- Extrafoveal CNV
- Extramacular choroidal neovascular membrane
- Exudative age-related macular degeneration
- Exudative retinal detachment associated with age-related macular degeneration
- Fibrovascular PED
- Foveal intraretinal haemorrhage
- Foveal sub RPE haemorrhage
- Foveal subretinal haemorrhage
- Haemorrhagic detachment of retinal pigment epithelium
- Haemorrhagic PED
- Juxtafoveal CNV
- Macular pigment epithelial rip
- Multifocal CNV
- Neovascular age-related macular degeneration (mixed classic and occult CNV)
- Neovascular age-related macular degeneration (type 3 CNV - RAP lesion)
- Neovascular AMD (classic no occult CNV)
- Neovascular AMD (idiopathic polypoidal choroidal vasculopathy)
- Neovascular AMD (minimally classic CNV)
- Neovascular AMD (occult no classic CNV)
- Neovascular AMD (predominantly classic CNV)
- Neovascular AMD (retinal angiomatous proliferation)
- Neovascular AMD (subtype not specified)
- Occult choroidal neovascular membrane
- Occult neovascularisation of macular
- PED
- Peripapillary choroidal neovascular membrane
- Peripapillary CNV
- Peripheral CNV
- Prior treatment for CNV secondary to AMD
- Retinal Pigment Epithelial detachment with vascularisation
- Retinal Pigment Epithelial rip / tear
- Sub-foveal CNV

- Subretinal choroidal neovascular membrane
- Sub RPE haemorrhage
- Suspected neovascular AMD
- Turbid PED
- Vascularised (notched) PED
- Vitreous haemorrhage secondary to age-related macular degeneration
- Wet age-related macular degeneration

The following diagnoses and indications for treatment do not indicate that the eye has “wet” AMD. If any of these are recorded and the eye is receiving anti-VEGF injections, then the eye is assumed to have “wet” AMD:

- Age-related macular degeneration - non-confluent atrophy
- Age-related macular degeneration with hard drusen
- Age-related macular degeneration with soft drusen
- Atrophic macular change
- Basal laminar drusen
- Cuticular drusen
- Degenerative drusen
- Dominant basal laminar drusen
- Dominant drusen
- Drusen
- Drusen stage macular degeneration
- Drusenoid PED
- Early AMD
- End stage macular
- Extramacular drusen
- Few drusen
- Focal macular hyperpigmentation
- Focal macular hypopigmentation
- Foveal involving atrophy
- Large drusen
- Macular diffuse atrophy
- Macular drusen
- Medium drusen
- Nodular drusen
- Non-exudative age-related macular degeneration
- Non-foveal involving atrophy
- Non-geographic atrophy
- Numerous drusen
- Peripheral drusen
- Reticular pseudodrusen
- Reticular retinal degeneration
- Senile reticular retinal degeneration
- Small / hard drusen
- Widespread retinal pigment epithelium (RPE) atrophy

6 Ineligible AMD diagnosis and indication for treatment

If any of the following indications for surgery are recorded as the indication for the AMD treatment, then the eye is excluded from analysis. For the specified diagnosis, if any of these are recorded at any point prior to and including the day of first anti-VEGF injection, then the eye is excluded from analysis. When an ocular co-pathology is recorded as "other" and there is text to detail the condition, this information is treated as a diagnosis for exclusion purposes.

The following indications for surgery from the available data are classified as ineligible "wet" AMD indications for surgery:

- 1-2 disc areas of geographic atrophy
- 1/2 disc area of geographic atrophy
- 1 disc area of geographic atrophy
- ≥ 2 disc areas of geographic atrophy
- Atrophy (non-geographic atrophy)
- Dry age-related macular degeneration
- Geographic atrophy

7 Anti-VEGF therapy

Anti-VEGF medications that indicate they was treated for "wet" AMD are as follows:

- Aflibercept (Eylea)
- Faricimab (Vabysmo)
- Bevacizumab (Avastin)
- Brolucizumab (Beovu)
- Ranibizumab (Lucentis)
- Ranibizumab biosimilar (Such as Ongavia, Byooviz or Ximluci)

Not all of the above medications were recorded for eyes in the submitted data

8 Diabetes mellitus status

The patient's diabetic status can be recorded on the participating centres EMR systems or inferred from diagnosis, indication for treatment and ocular co-pathology data. For ocular co-pathology the inferable record is when diabetic retinopathy is recorded.

It is possible for patients to develop diabetes mellitus between the time of their first and second eye starting treatment, thus the establishment of the patient's diabetic status can be different for each eye and is allocated as follows:

For single eye treated patients:

- if the eye has a record indicating the patient has diabetes mellitus, then the patient can be considered to have diabetes mellitus.

For both eye treated patients:

- If the first treated eye has a record indicating the patient has diabetes mellitus, then the patient can be considered as having diabetes mellitus for both eyes
- If the first treated eye has no record indicating the patient has diabetes mellitus, and the second treated eye does, the patient can be considered as having diabetes mellitus for the second treated eye

9 Index of multiple deprivation

The Index of Multiple Deprivations (IMD) score, national ranks and national deciles are calculated during the data extraction using separate indices for each of the four nations that centres are located in:

- For centres located in England, the English Indices of Deprivation 2019 are use (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019)
- For centres located in Northern Ireland the Northern Ireland Multiple Deprivation Measure 2017 are used (https://www.nisra.gov.uk/statistics/deprivation/northern-ireland-multiple-deprivation-measure-2017-nimdm2017)
- For patients treated in centres located in Scotland the Scottish Index for Multiple Deprivation 2020 are used (https://simd.scot/)
- For centres located in Wales the Welsh Index of Multiple Deprivation 2019 are used (https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation)

Reasons for missing IMD data are the non-recording of a patient's postcode on the hospital admission system, a patient's postcode not recognisable in the IMD conversions or no matching to deprivation data during data extraction.

For the first and second prospective AMD Audit years, the RCOphth NOD received IMD data from centres using the Medisoft EMR and one centre using an in-house database. For the 3rd round of data extractions, the Open Eyes EMR now includes matching to IMD data during data extraction, and centres using Open Eyes can submit this data once they upgrade the version they use.

If the RCOphth NOD is granted section 251 exemption, then future data extractions could include the patients full post code and the matching to social deprivation data would be possible for all centres from regions where social deprivation data can be matched to a postcode.

10 Visual Acuity criteria

Visual Acuity (VA) abbreviations

- Corrected distance visual acuity = CDVA
- Uncorrected distance visual acuity = UDVA
- Pin hole visual acuity = PHVA
- Count fingers = CF
- Hand movements = HM
- Perception of light = PL
- No perception of light = NPL
- ETDRS = Early Treatment Diabetic Retinopathy Study
- LogMAR = Logarithm of the Minimum Angle or Resolution

Visual Acuity can be measured using CDVA, UDVA or PHVA and it is possible for more than one of these types of methods to be used in the same assessment. On any day if more than one type of VA measurement is recorded, the best of these measurements is used. In audit results VA is reporting using the ETDRS numbers and/or the LogMAR scales.

Baseline VA

- Uses the VA measurement closest to the date of first injection, including the day of first injection and within 28 days prior to treatment.

VA at monthly intervals

- Uses VA measurements closest to four-week intervals from the first injection and within a 14-day period either side of this date.

VA at one year

- Uses VA measurements closest to one year from the first injection and within a –28 to +84 day period either side of this date.

VA at two years

- Uses VA measurements closest to two years from the first injection and within a –28 to +84 day period either side of this date.

For estimates of visual acuity for a contributing centre (i.e., the median preoperative VA), at least 25 eligible operations with VA measurements are required.

Adjusted VA

For the second year of the AMD audit, two risk factor models were developed and used to report adjusted visual acuity estimates for centres. The two models are for:

- Achieving ‘good’ VA at one year - assessed by the percentage of eyes with VA ≥70 ETDRS letters at the end of the first year of treatment
- A decrease of ≥10 ETDRS letters at one year - assessed by the percentage of eyes with a decrease of ≥10 ETDRS letters between baseline and the end of the first year of treatment.

Full information for these two models can be found in a model development explanatory document on the audit website (https://nodaudit.org.uk/healthcare-professionals/resources)

11 Ocular co-pathology / known risk factor

The RCOphth NOD audits use diagnosis, treatment, indication for surgery and medication data to infer the presence of concomitant ocular diseases or conditions which are classified as ocular co-pathology / known risk factor. The same inferring methodology applies to both the National Cataract Audit and the National AMD Audit for any of the concomitant ocular diseases or conditions that are reported in the respective audits. Full details on the inferring methodology can be found on the audit website (https://nodaudit.org.uk/healthcare-professionals/resources).

12 Complications of treatment

The two main complications of intravitreal therapy reported in the RCOphth NOD AMD Audit are Intraocular Inflammation (IOI) and Presumed Infectious Endophthalmitis (PIE), where each is identified as follows:

Intraocular Inflammation
Intraocular inflammation (IOI) was defined if any of the following occurred within 42 days of an anti-VEGF injection:

- a post-injection record of IOI as a complication of prior intra-vitreal injection
- a post-injection record of IOI as a new diagnosis

This approach is required as recording the presence or absence of IOI as a postoperative treatment complication may not be mandatory within the EMR.

Presumed Infectious Endophthalmitis
Presumed infectious endophthalmitis (PIE) was defined if any of the following occurred within 42 days of an anti-VEGF injection:

- a post-injection record of PIE as a complication of prior intra-vitreal injection
- a post-injection record of PIE as a new diagnosis or indication for surgery
- a surgical record of vitreous biopsy and/or anterior chamber tap
- an injection of intravitreal ceftazidime and/or vancomycin.

This approach is required as recording the presence or absence of PIE as a postoperative treatment complication may not be mandatory within the EMR.

Complications of treatment would only be ascribed to a centre when the complication was identified, and the prior injection was administered in the same centre.

13 Profession of the staff administering the injection

The profession of the staff administering the injection was categorised as follows:

- **Doctors:** When the recorded grade of profession was any of the following: Consultants, Locum Consultants, Associate Specialists, Staff Grade, Trust Doctor, Fellows, Registrars, Specialty Trainees (years 1 to 7), foundation year 1 and 2 doctors, Senior House Officer and General Practitioners with a special interest in ophthalmology.
- **Nurses:** When the recorded grade of profession was any of the following: Clinical Nurse Specialists, Nurse and Health Care Assistants.
- **Other Healthcare Professionals:** When the recorded grade of profession was any of the following: Orthoptist, Optometrist, Surgical Care an Operating Department Practitioner, Clinical Assistant and Ophthalmic Technician.
- **Profession Unknown:** When the recorded grade of profession was not recorded or recorded as Administration Staff or Other.

In case of the multiple professions assigned to the same injection record, the profession was assumed using a hierarchy process where Doctor supersedes Nurses and Other Healthcare Professionals, and Nurses supersede Other Healthcare Professionals.

14 Loss to follow up

Loss to follow up was defined based on the last clinical date available for the eye. If this date was less than one year +84 days from starting treatment and the eye had no visual acuity measurement at one year, the eye was considered lost to follow up at one year. All eyes with visual acuity data at one year were considered not lost to follow up at one year, even if their last clinical date was before one year.

The same logic applies for loss to follow up at two years, based on the last clinical data available two years plus 84 days from starting treatment and the eye had no visual acuity measurement at two years, the eye was considered lost to follow up at two years. All eyes with visual acuity data at two years were considered not lost to follow up, even if their last clinical date was before two years.

15 Audit reporting destinations

Reporting destinations

The prospective National AMD Audit results are published in annual reports available on the RCOphth NOD website. On the completion of an audit year, audit results are sent to Getting It Right First Time (GIRFT) programme and a data set is uploaded to www.data.gov.uk. Results could be sent to the Care Quality Commission (CQC) if the CQC confirms interest in receiving this information.

Annual reports – Data quality and VA results are provided for all eyes treated in a centre. A minimum of 25 eligible eyes per centre is required for inclusion. For results of VA measurements, at least 25 eligible operations with a VA measurement are required.

For the RCOphth NOD website (www.nodaudit.org.uk):

Behind the secure log-in – Results for data completeness and visual acuity are available behind a secure log-in for access by relevant staff in participating centres. Date searching functionality is available when the data covers a period longer than the official prospective audit period.

Public facing – The RCOphth NOD website has a public facing section where selected results for centres concerning the most recent audit period could be available once resources permit.

For the CQC – At the time of writing, the CQC have confirmed that at present they are not able to receive data from the AMD audit for participating organisations.

For GIRFT – Once the annual report is published, results for participating English organisations can be sent to the GIRFT programme.

For data.gov.uk – Once the annual report is published, a data set for audit results is uploaded to www.data.gov.uk.