# 1 Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

| | Who | When | How | To Whom |
|---|---|---|---|---|
| **SAE** | Chief Investigator | -Report to Sponsor within 24 hours of learning of the event<br><br>-Report to the MREC within 15 days of learning of the event | SAE Report form for Non-CTIMPs, available from NRES website. | Sponsor and MREC |
| **Urgent Safety Measures** | Chief Investigator | Contact the Sponsor and MREC Immediately<br><br>Within 3 days | By phone<br><br>Substantial amendment form giving notice in writing setting out the reasons for the urgent safety measures and the plan for future action. | Main REC and Sponsor<br><br>Main REC with a copy also sent to the sponsor. The MREC will acknowledge this within 30 days of receipt. |

| | | | | |
|---|---|---|---|---|
| **Progress Reports** | Chief Investigator | Annually ( starting 12 months after the date of favourable opinion) | Annual Progress Report Form (non-CTIMPs) available from the NRES website | Main REC |
| **Declaration of the conclusion or early termination of the study** | Chief Investigator | Within 90 days (conclusion)<br><br>Within 15 days (early termination)<br><br>*The end of study should be defined in the protocol* | End of Study Declaration form available from the NRES website | Main REC with a copy to be sent to the sponsor |
| **Summary of final Report** | Chief Investigator | Within one year of conclusion of the Research | No Standard Format<br>However, the following Information should be included:-<br>Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants | Main REC with a copy to be sent to the sponsor |

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# 8 2 Appendix 2 – Form A, Inclusion criteria

| | Question | Required answer |
|---|---|---|
| | General Inclusion | |
| 1. | Is the patient over 18 years of age? | Yes |
| 2. | Does the patient have capacity to give informed consent? | Yes |
| 3. | Has the patient previously been enrolled in this study in regards to their other eye? | No |
| | General Health | |
| 4. | Does the patient have a formal diagnosis of Diabetes Mellitus? | Yes |
| 6. | Has the HbA1c test been performed within the past 2 months. | Yes |
| 7. | Is there a history of chronic renal failure requiring either dialysis or renal transplantation? | No |
| 8. | Has the patient suffered a major thromboembolic event within the past 6 months as (defined as TIA, Stroke, or MI) | No |
| 9. | Has the patient undergone major surgery within the past 6 months or is major surgery planned over the next 12 months defined as requiring GA or reduced mobilisation | No |
| 10. | Is there a documented allergy or a significant adverse event to anti-VEFG therapy in the past? | No |
| 11. | Is the current blood pressure over 180 systolic and/or 100 diastolic? | No |

| | | |
|---|---|---|
| 12 | Is the patient on pioglitazone | No |
| 13 | The patient has any other condition that in the opinion of the investigator would preclude participation in the study (such as unstable medical status or severe disease that would make it difficult for the patient to be able to complete the study) | No |
| 14 | The patient has very poor glycaemic control and has started intensive therapy within the previous 3 months. | No |
| 15 | The patient will use an investigational drug during the study | |

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| | Past Ocular History | |
|---|---|---|
| 16 | Has the eye received macular laser photocoagulation within 750 microns of the foveal centre at any point in the past? | No |
| 17 | Has the eye undergone vitrectomy at any point in the past? | No |
| 18 | Other than intravitreal Ranibizumab, Aflibercept therapy or cataract surgery has the eye undergone any other laser, surgical or injection therapy in the last 24 weeks | No |
| 19 | Was any cataract surgery performed at least three months prior to recruitment? | No |
| 20 | Besides diabetic maculopathy with or without associated vitreo-retinal interface abnormalities, does the eye suffer from any other underlying | No |

| | | |
|---|---|---|
| | ophthalmic diseases liable to impair visual acuity, including but not limited to: visually significant cataract, AMD, uveitis, vein occlusion, glaucoma, optic neuropathy, amblyopia? | |
| 21 | Has the patient had symptomatic visual loss attributable to diabetic macular edema for less than one year. | Yes |
| | Present Ocular Status | |
| 22 | Does the eye have either (i) active (untreated or partially-treated) proliferative diabetic retinopathy or (ii) very severe non-proliferative diabetic retinopathy? | No |
| 23 | Is the current BCVA better than 35 ETDRS letters? | Yes |
| 24 | Is the central sub field thickness greater than 349 microns? | Yes |
| 25 | Is there any Fresh, central axis-involving vitreous hemorrhage? | No |
| 26 | Presence of clinically significant cataract or media opacity | No |
| | Stratification criteria | Yes |
| 27 | Presence or absence of localized distortion of the inner retinal surface on the OCT scan due to epiretinal membrane or vitreomacular traction with associated retinal thickening that is contiguous with the central sub field thickening. | **Yes**: stratify to traction group<br>**No**: stratify to the no traction group |
| | | |

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# 3 Appendix 3: Schedule of assessments

| **Assessment** | **Week 0, Baseline** | **Week 0 – Week 8** | **Treat and Extend Follow up visits** | **Week 52 Final visit** |
|---|---|---|---|---|
| Informed Consent | **x** | | | |
| Demographics | **x** | | | |
| Ophthalmic History | **x** | | | |
| Medical History | **x** | | | |

| | | | | |
|---|---|---|---|---|
| Blood Pressure | x | | | |
| COMplog Visual Acuity | x | | x | x |
| Contrast Sensitivity (at participating centres) | x | | | x |
| ERG (at participating centres) | x | | | x |
| Slit lamp exam and Cataract Assessment | x | x | x | x |
| High Resolution Macular OCT<br>(sent to reading centre) | x | | | x |
| Macular OCT<br>(*not* sent to reading centre) | x | | x | x |
| Fundus Photographs and Retinopathy grading | x | | | x |
| Vitrectomy operation | | x | | |
| Ranibizumab or Aflibercept followed by Treat and Extend | x | x | x | x |
| VFQ-25 patient questionnaires[‡] | x | | | x |

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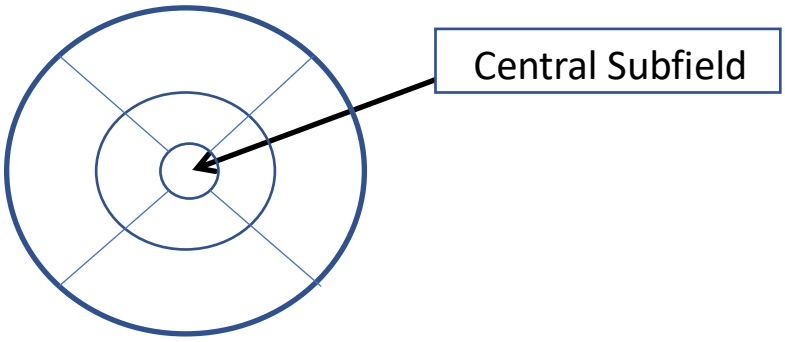
# 4 Appendix 4: Assessment of subfield thickness and OCT settings with EDI where possible

On the OCT result page, the following ETDRS grid is displayed for all machines. The central subfield thickness measurement is the value at the centre of the circle (arrow). Before recording the central subfield thickness please make sure that the grid is centred at the fovea and the segmentations errors are corrected.

Image 1: Central subfield in ETDRS grid




## *4.1 Settings*

Settings for OCT machines used other than Heidelberg.

High resolution scans are taken at baseline and final visit. Routine scans are taken at follow up visits. Enhanced Depth Imaging (EDI) may be used for where available for high-resolution images, however it is advised to check for image quality at the vitreo-macular interface. It may, therefore, be necessary to take scans with and without EDI.

Topcon for both eyes

High res scan = Raster Line scan,

Routine scan = 3D Scan, 6x6mm, 512x128

Cirrus for both eyes

High Res scan = 5 line HD Raster scan (length 9mm)

Routine Scan = Macular Cube 512x128

Spectralis for both eyes

High res scan = pre set 7 lines Raster scan

Routine scan = 31 sections, 30°x25°, ART 15, HS

## *4.2 Instructions*

1. Scan parameter e.g. Raster Line scan, or 3D Scan, 6x6mm, 512x128

2. Fixation set to Macula

3. Position patient, line the OCT on the pupil and drive the camera forward

4. Focus on the retina

5. Optimise the scan signal

6. Make sure the OCT image is centre on the screen

7. Press the button to capture the OCT scan

8. Click save, then check image quality

9. Repeat procedure for 2nd scan scan

10. Repeat procedure for both eyes

11. Export baseline and 12 month scan to central unit within 2 months of baseline test, and 1 month of final assessement.

# 5 Appendix 5: Visual Tests, Assessment of visual acuity and contrast sensitivity

Refracted best corrected visual acuity (BCVA) is performed at baseline and final visit in all subjects in both eyes. The better of habitual refraction and pinhole acuity is recorded in both eyes at follow up visits. VA is always measured in the study eye first, then the fellow eye.

**Initial VA Measurement**:

At the baseline visit, initial VA is measured, whilst the subject is wearing his/her own distance glasses or unaided (if subject doesn't have distance glasses), using COMplog visual acuity software. At all follow-up visits refraction found during the previous study refraction will be used. The fellow eye is lightly patched with a tissue. If the initial acuity is less than 20/200 refraction should occur at 1 metre.

**Subjective Refraction**

Subjective refraction should be carried out according to the methods routinely employed by the Optometry Department at host site. The subjective refraction is performed at 4m using the COMPlog ETDRS chart in standard room lighting.

**Final VA Measurement**

VA in the study eye first is always measured first, then the fellow eye. The subject is instructed that the chart contains letters only and no numbers. If the subject forgets this during the course of the examination, they should be reminded that the chart contains no numbers and asked for a letter instead of the number. The subject is advised that there are 5 letters on each line, and that they should attempt to read the line from left to right. The examiner must not point at any letters or read any letters out loud during the test. It is acceptable to briefly point at a line, should the subject have difficulty finding the next line. The subject should be instructed to read the letters slowly, about one letter per second. The subject should be encouraged to guess any letters that are difficult to read, and be instructed to make a definite decision. If the subject is unable to identify a certain letter they should tell the examiner that they are moving on to the next letter along the line. If the subject incorrectly identifies a letter and then proceeds to read the next letter, s/he cannot go back and correct the mistake later. It is permissible to allow correction as long as the subject has not started to read the next letter aloud. The subject should be asked (and encouraged) to move on to the next line, as long as they manage to correctly identify at least one letter on the previous line.

With the subject wearing the best correction in the trial frame, the eye not being tested is occluded with a standard occluder in the trial frame, or with a tissue/patch behind the frame, if the subject moves his/her head a lot to use eccentric fixation.

Following refraction the best VA's are measured at 3m using COMPlog with a 24 inch secondary monitor. COMPlog will be set for 5 letters per line with termination criteria of 5 letters wrong per line. COMPlog will be calibrated for viewing distance and screen resolution prior to each testing session. Measurements will be performed in number of ETDRS letters. Room lighting is on during COMPlog measurements.

**ETDRS Score**

**Testing for Count Fingers**

If the subject's VA is so poor that s/he cannot correctly identify any letters on the COMPlog secondary monitor, then test for Count Fingers. The eye not being tested should be completely occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner holds the hand two feet in front of the subject's face and presents an arbitrary number of fingers in random order and repeated 5 times. Eccentric fixation, if present, should be encouraged. If the subject correctly identifies 3 of the 5 presentations, then count fingers vision is noted. If not, then the subject must be tested for hand movements.

**Testing for Hand Movements**

The eye not being tested is occluded with a patch. A light must be shone from behind the subject's head at the examiner's hand. The examiner's hand should be moved two feet in front of the subject with all fingers spread out. The hand should be moved either horizontally or vertically at a constant speed of approx. one back and forth movement per second. The subject is asked to watch the examiner's hand and respond to the question "in which direction is my hand moving?" The examiner should not explain that it will be moving either from side to side or up and down! Correct answers at four out of five presentations suggest that hand movement vision is present. If not, then light perception should be tested for.

**Testing for Light Perception**

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The indirect ophthalmoscope should be focused at 1meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the eye at least four times, and the subject should be asked to respond when they see the light. If the examiner is convinced that the subject perceives light,

vision should be recorded as “Light Perception”. If not, vision should be recorded as “No Light Perception”.

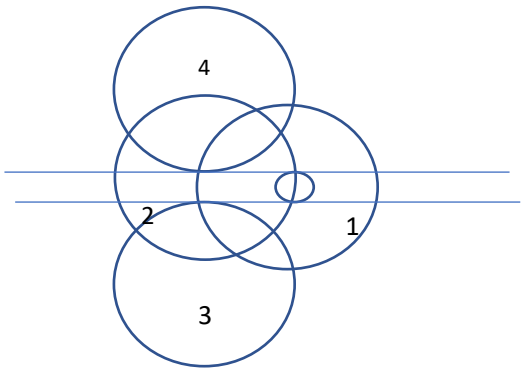
# 6 Appendix 7: Fundus photography and EDTRS grading of retinopathy

Retinopathy is graded in all subjects at baseline and visit at 52 weeks. 4 stereo photographs must be obtained or a single Optos wide field fundus photograph.

4 stereo photographs

1. 4 stereo photographs: Centred on the disc with the temporal border on the macula
2. Centred on the macula with the nasal border over the centre of the disc.
3. Directly inferior to the macula with the inferior border in line with the superior edge of the disc.
4. Directly superior to the macula with the superior border in line with the inferior edge of the disc.

Image 2: 4 retinal stereo photographs




Optos: Imaging should be performed in a dimly lit room. Before beginning, check the amount of air in the eye pillow and set it so that when the pillow is touched, you can feel the scan head.

Patient should be sitting straight ahead with knees facing the device. Have the patient move close to the instrument. Observe that they are sitting up straight and tall with the chair close to the unit. Hand the patient

the hand switch button and explain that when instructed to do so, they will click the button to capture an image.

Position the instrument using the up and down switch so that the patient’s pupil is in the centre of the image aperture. Patients will lean forward if the table height is too low, causing lash and lid on the image. Leaning into the instrument will prevent the eye from getting closer to the eye pillow.

While the patient is about 2 inches away from the eyehole, position the patient’s right/left eye by rotating the head to a 45° angle; and ensure that their nose is outside the pillow

Adjust their position until the green light is in the centre of their view (see example 3). Tell the patient to move in slowly, keeping the green ball in view, until they see a thin red ring, (see example 4). Support the patient’s head to help guide the patient. The iris should fill the alignment ring.

Ask the patient to open both eyes wide and not to blink during the flash. Have the patient click the hand switch button. You may control the hand switch button if necessary. While the patient is still against the eye pillow, review the image quality. Particularly note the optic disk saturation and adjust if necessary and re-image.

When the iris aligns with the eye camera ring, the patient should be looking directly at the green dot and see a full fine red halo in their peripheral vision

In some patients, images may be obscured by the patient's lids and lashes. You should follow your practice procedures to minimize lids and lashes in images.

In some cases the amount of lid and lash can be minimized by gently lifting the patient's eyebrow. With clean

hands, place your thumb below the patient's eye and your forefinger on the brow line. Gently open the eye a little further. Just lifting the upper lid may pull the lower lid further into the image.

# 7 Appendix 8: COMPlog visual acuity software

COMPlog is a computerised visual acuity measurement system consisting of a laptop PC capable of running Micrsoft Windows XP®, a 24 inch 1920X1080 resolution LCD flat panel secondary monitor and a software programme running within the Microsoft dotnet® framework. The examiner controls the test through a series of sequential control screens presented on the laptop monitor (fig 1): these enable collection of demographic data, control of various aspects of the testing algorithm (see below), response recording, and presentation of results in one of two logMAR formats (decimal logMAR and number of ETDRS letters) and one of three Snellen equivalent format scores (Decimal Snellen, UK Snellen and US Snellen).

Image 3: COMPlog set-up


The COMPlog testing algorithm consists of two phases, “range finding” and “thresholding”, both of which require forced choice responses from the subject and input of the response to each letter as correct or incorrect by a technician. Range finding aims to roughly identify threshold and consists of presentation of sequentially smaller single crowded Sloan letter steps starting from 0.8 logMAR, with a step size of 0.2 logMAR. If the 0.8 logMAR letter cannot be correctly identified, then sequentially larger letters are presented. The thresholding phase commences 0.4 logMAR larger than the range finding result, unless this exceeds 1.2 logMAR in which case it commences at 1.6 logMAR. The thresholding phase consists of presentation of sequential lines of randomly chosen Sloan letters surrounded by a crowding box. No letters are repeated on any line. The line size increment employed in the thesholding phase is set at 0.1 log units. The other aspects of the test are however user-controllable: these include letter spacing, the presence or absence of crowding bars, the number of letters per line, number of letters per line incorrectly identified to terminate the test and number of tests upon which the score is based. In this study, five letters per line spaced half a letter width apart and surrounded at the same separation by a crowding box of one stroke width thickness (fig 1) were employed. The termination criterion is set at all five letters on one line. In the event of letters being incorrectly identified on the first thresholding line sequentially larger lines are presented until an entire line is correctly read, with the programme then descending to threshold, but only presenting lines of each size of letters once. If all five letters

cannot be fitted simultaneously on to the secondary monitor, the line is broken up into fractions with as many letters as possible of each size being presented. Letters larger than 1.6 logMAR are not presented, if a patient is unable to correctly identify any letters of 1.6 logMAR size, the programme invites scoring on a count fingers, hand movements, perception of light and no perception of light scale. In this way, with a 21 inch monitor and a single viewing distance of 3 m, an acuity range of up to 1.68 logMAR (one ETDRS letter, 1.5/71 UK Snellen or 20/957 US Snellen) may be measured without moving the patient.

Once the termination criterion has been met, the test automatically terminates with calculation and presentation of a fully interpolated logMAR acuity score and its Snellen equivalent in the selected formats, along with the total test time

# 8 Appendix 9: Exporting data

Topcon

Export Procedure

You have two options when exporting the FDS file. Option one is a simple copy and paste of the file while option 2 uses the Data Management option in the Topcon software.

Option 1

In the Topcon software find the patient you want to export. Click on the scan you wish to export i.e. Radial Scan RE and the same visit for the LE. Make a note of the encounter ID's for both eyes, circled in blue in the screenshot below. Locate the matching FDS files in the Data folder of the Topcon installation. This will vary from site to site but is typically Z:\3DOCT_DATABASE\DATA. The Z can be any drive letter.

Once you have found the appropriate FDS files that match the encounter ID's as noted in the step above, right click and choose copy, then paste the files into the folder you created earlier.

Option 2

You can also use the Data Management option in the Topcon software. Open up the patient's visits and select the scans you want to export. In the dropdown box next to "Copy To:" choose "Export" and click "Copy To:" This will export both scans to a predefined folder on your system. This will vary from site to site but is typically Z:\Export. The FDS files can them be moved from the Export folder to the patient folder created earlier.

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Anonymize the FDS/FDA

The FDS file is the Topcon native export file (OCT1000) which can be opened on the Topcon review software. The file will contain whatever patient information was input on patient registration. If the coded data protocol was used then there is no need to anonymize it. If however actual patient names were used at registration then you must anonymize the FDS file which is now in the patient folder.

DO NOT ANONYMIZE THE FDS FILE IN THE TOPCON DATA FOLDER.

To anonymize the FDS file you need a small application called "OCTPatientInfoRemover" (see icon below) All sites should have this application.

IMPORTANT NOTE:

If you are using a newer system which exports .fda files, the "OCTPatientInfoRemover" program will not find the .fda file. Simply rename this to .fds and it will work.

Cirrus

- Create a new folder on the Desktop by clicking the new folder icon and name it

  "studyname_subjectID_dateofscan"

- Go to the main patient database
- Click "records/export"
- Search for the patient you wish to export
- Click browse in the "Export to" box and browse to the folder created in step 1 above
- Select the scans you wish to export
- Click export and save to this new folder

Spectralis

Before exporting any scans, create a folder on the Desktop to where you will export the images. Use the following naming protocol:

"CentreID_PatientID_VisitNumber_DateOfVisit" eg "20_1234_week4_26 April218" Please use month name rather than number.

- Search for patient to be exported
- Double click on patient name in the left panel of the window to load into the right panel
- In order to export only the visit required, you must open the scans in the viewer by double clicking on the

patient name in the right panel

- Select the visit required from the tabs across the top of the screen
- If scans are separated into eyes (Re & LE), click on the “No Split” icon to merge all scans
- Highlight all scans
- Right click on the scans and select “Export/asE2E” (dialog box as below)
- Set the destination to the folder created as above
- Leave the rest as default as patient data should be anonymised when entered and click ok
- You should now have one E2E file in the destination folder

# 9 Appendix 10: Castor database

The Castor database is a secure online database that permits entry of non-identifiable patient data pertaining to the VIDEO trial.

Sites will be provided with a username and password upon registration.

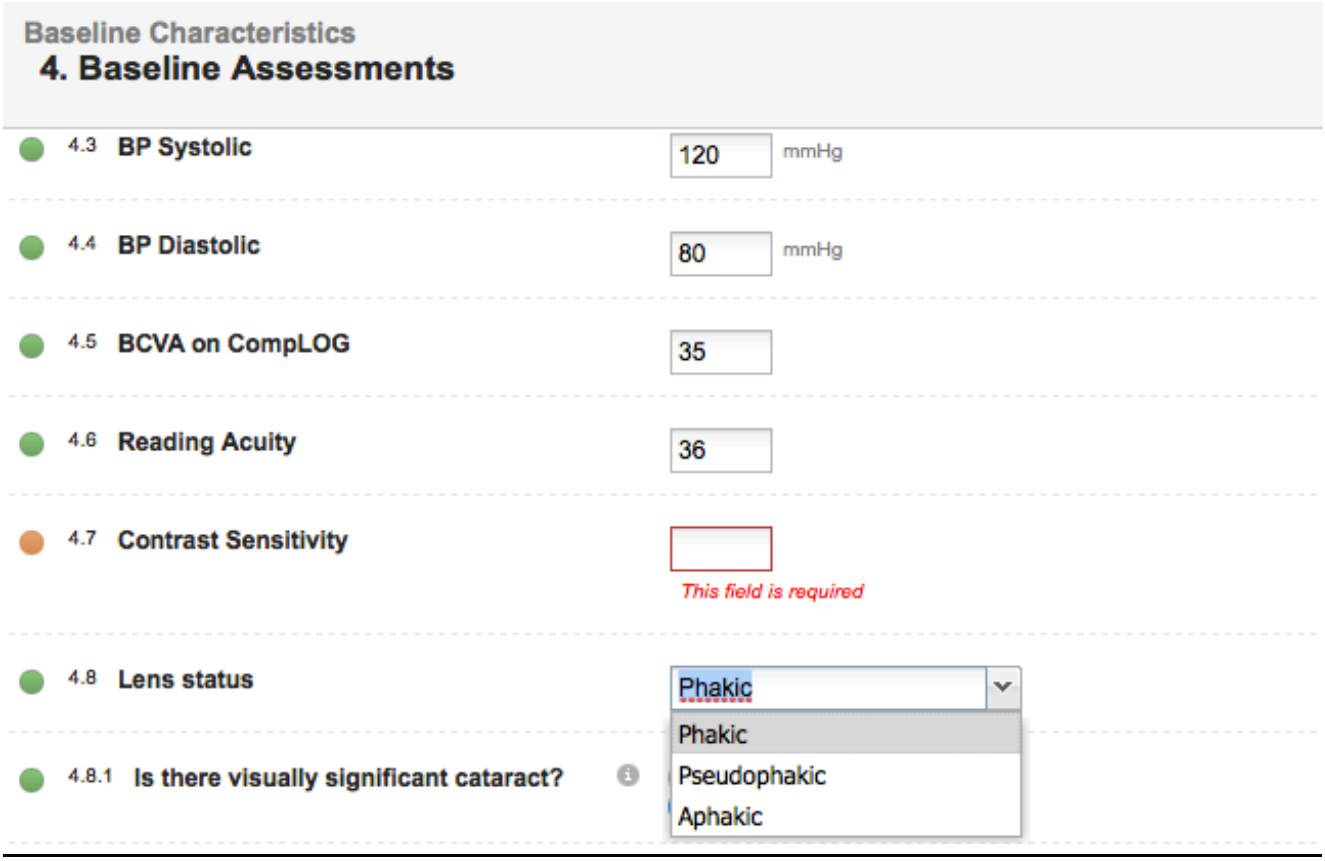
Users will be required to enter baseline information at week 0 and follow the instructions to randomise the patient to treatment or control group.

Data is entered at each numbered follow-up appointment and at the final week 52 visit. Data is entered as numbers, free text, or multiple-choice selection via radio buttons or drop down menus.

It has been designed to be easy to use, safe and to facilitate compliance with good clinical practice guidelines .

A screenshot of the interface is shown below.

Image 4: Castor database




# 10 Appendix 11: Data monitoring and Ethics Committee Charter

A DMEC will be appointed for this study, the aim of which is protect the interests of the patients in the trial and will authority to terminate the trial in the event of harm to either group.

Every 3 months all patients with SAE or losing 3 and 6 lines of vision compared to baseline will be reported to the DMC

Where vision loss has occurred, other cause will be determined from the clinical record

The DMEC have the right to stop the trial in the event being advise by the statistician of a statistical probability of harm occurring to patients in either arm.

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram