OPT1038: Qualitative OCT Image Grading Study Comparing the P200TE and the P200TxE in Glaucoma Patients

NCT03912584

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CLINICAL INVESTIGATION PLAN

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Product Name	P200TxE
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Protocol Signature Page
For
OPT1038 - Qualitative OCT Image Grading Study Comparing the P200TE and the P200TxE in Glaucoma Patients

I have read the attached document, concur that it contains all information necessary to conduct the study, and agree to abide by all provisions set forth therein.

I agree to conduct this study in accordance with 21CFR Parts 11, 50, 54, 56 and 812, and with consideration of the provision in ISO 14155-1,-2 (2011) Clinical Investigation of Medical Devices for Human Subjects, ICH Good Clinical Practices, and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board/Ethics Committee and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent (and, if applicable, assent for children) from each study subject prior to performing any study specific screening procedures.
I understand that my signature on a case report form indicates that the data therein has been reviewed and accepted by the signatory.

I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality and/or Clinical Research Agreement. I agree to protect the confidentiality of my patients when allowing the Sponsor of this clinical trial, and/or relevant regulatory authorities, and IRBs, direct access to my medical records for study subjects.

_____

Principal Investigator, Printed Name

_____

Principal Investigator, Signature and Date

Table of Contents

List of Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
HD	High Density
IRB	Institutional Review Board
ICD	International Classification of Disease
OCT	Optical Coherence Tomography
ONH	Optical Nerve Head
RNFL	Retinal Nerve Fibre Layer
SADE	Serious Adverse Device Effect
SLO	Scanning Laser Ophthalmoscope
UWF	Ultra-widefield

Definitions

Clinical utility - means is there structural information present in the image that is helpful to aid in clinical decisions such as diagnosing or managing ocular diseases in the eye.

Image quality - means does the image have sufficient quality to clearly view the relevant structures within the eye.

CLINICAL INVESTIGATION SUMMARY

Objectives

The primary objective of this study is to collect OCT scans to compare the qualitative B scan images produced by the Optos P200TxE to the FDA cleared Optos P200TE (K173707) in glaucoma patients. Qualitative imaging grading assessment of the scan types captured from the investigative P200TxE device and the cleared P200TE will be used to compare and determine whether the P200TxE scans are equivalent or better than the P200TE. The qualitative evaluation will be based on the clinical utility and image quality of the B scans captured on glaucoma patients.

Endpoints

The primary endpoint will be the qualitative assessment of the B scans from each device based on pre-specified grading criteria from three independent masked and qualified graders. The secondary endpoint will be an analysis of safety through assessment of any adverse event associated with the P200TxE.

Trial Population

The subject population will consist of a minimum of 10 glaucoma patients. Glaucoma patients will cover a wide range of disease severity as determined by ICD-10 classification.

Trial Design

This study is a prospective comparative, randomized, single centre study to gather clinical performance data.

Inclusion / Exclusion Criteria

Inclusion Criteria

1. Male or female subjects 22 years of age or older who have full legal capacity to volunteer on the date the informed consent is signed;
2. Subjects who can follow the instructions by the clinical staff at the clinical site,
3. Subjects who agree to participate in the study;
4. Subjects who have been diagnosed with glaucoma in the study eye as confirmed by the investigator;

Exclusion Criteria

1. Subjects unable to tolerate ophthalmic imaging;
2. Subjects with ocular media not sufficiently clear to obtain acceptable OCT images;
3. Subjects with any clinically significant ocular pathology except glaucoma, as determined by self-report and/or investigator assessment on the day of the study visit;
4. Subjects who are not reliably tested with at least one Humphrey Field Analyzer (HFA) visual field (24-2 or 30-2, white on white) measured on the day of the study visit or within the previous year from the study visit, defined as fixation losses > 20% or false positives > 33%, or false negatives > 33%;
5. Subjects with history of dementia or multiple sclerosis

Scan Types

Optomap Plus UWF SLO images and the following OCT scans will be captured on both devices.

- Line scan – averaged scan 14mm (P200TxE) and 12mm (P200TE)
- Retina Topography – 9 mm x 9 mm, 111 B scans (P200TxE) and 8.8mm x 8.8mm, 97 B scans (P200TE)
- Optic Nerve Head (ONH) Topography – 6 mm x 6 mm, 111 B scans (P200TxE) and 5.28mm x 5.28mm, 97 B scans (P200TE)

- Raster scan – 14 mm x 9 mm, 121 B scans (P200TxE) and 12mm x 9mm, 65 B scans (P200TE)

In addition, the following OCT scan types will be captured for the P200TxE only (not available in P200TE)

- Ultra-widefield Line – averaged scan 6 mm
- Ultra-widefield Extended Line – averaged scan 23mm
- Ultra-widefield volume – 6mm x 6mm, 121 B scans
- Ultra-widefield HD volume scan – 6mm x 3mm, 121 B scans

A direct comparison of grader scores will be made between similar scans from the two devices, including: Line scans, Raster scans, Retina Topography scans, and ONH scans. An analysis of grader's scores for the 4 scan types available in the P200TxE but not the P200TE will also be made. These scan types included: Ultra-widefield line scan, Ultra-widefield extended line scan, ultra-widefield volume scan, and ultra-widefield HD volume scan.

Image grading procedure

B scan images will be assessed for clinical utility and image quality by an independent Reading Center after the data collection phase is completed. The results will be compared between the predicate device and the investigational device.

All scans will be reviewed for image acceptance based on generally accepted industry standards, and scans that do not pass will be excluded (e.g., scans with blinks, eye movements, clipping,etc, are considered to be artifacts are not typically used clinically or in research). Scans will be reviewed based on specific image characteristics described in Appendix A. Excluded scans will not be graded. The operator will evaluate the scans for quality at the time of image acquisition. Unacceptable scans will be re-captured until an acceptable scan is obtained [up to three attempts to capture an acceptable scan].

For scans containing multiple B scans such as 3D cube or volume scans (e.g., Retinal topography scan), the entire set of B scans will be reviewed and graded as a whole (one grade for entire B scan series within a single 3D volume). All scans will be reviewed for grading using a Dicom viewer from Optos called OA (Optos Advance). This viewing software will not provide any information about which device the scan came from or any other identifiable information. Scans will be in a randomized order and numbered sequentially. Graders will not compare scores and will perform all grading independently of each other.

Three independent graders will assess the B scans for each scan type from each subject and grade them for clinical utility and image quality. Graders will evaluate a single B scan at a time and will be masked to which device the B scan came from.

Images will be graded based on both clinical utility and image quality. Clinical utility means is there structural information present in the image that is helpful to aid in clinical decisions such as diagnosing or managing ocular diseases in the eye. Image quality means does the image have sufficient quality to clearly view the relevant structures within the eye.

Statistics Summary

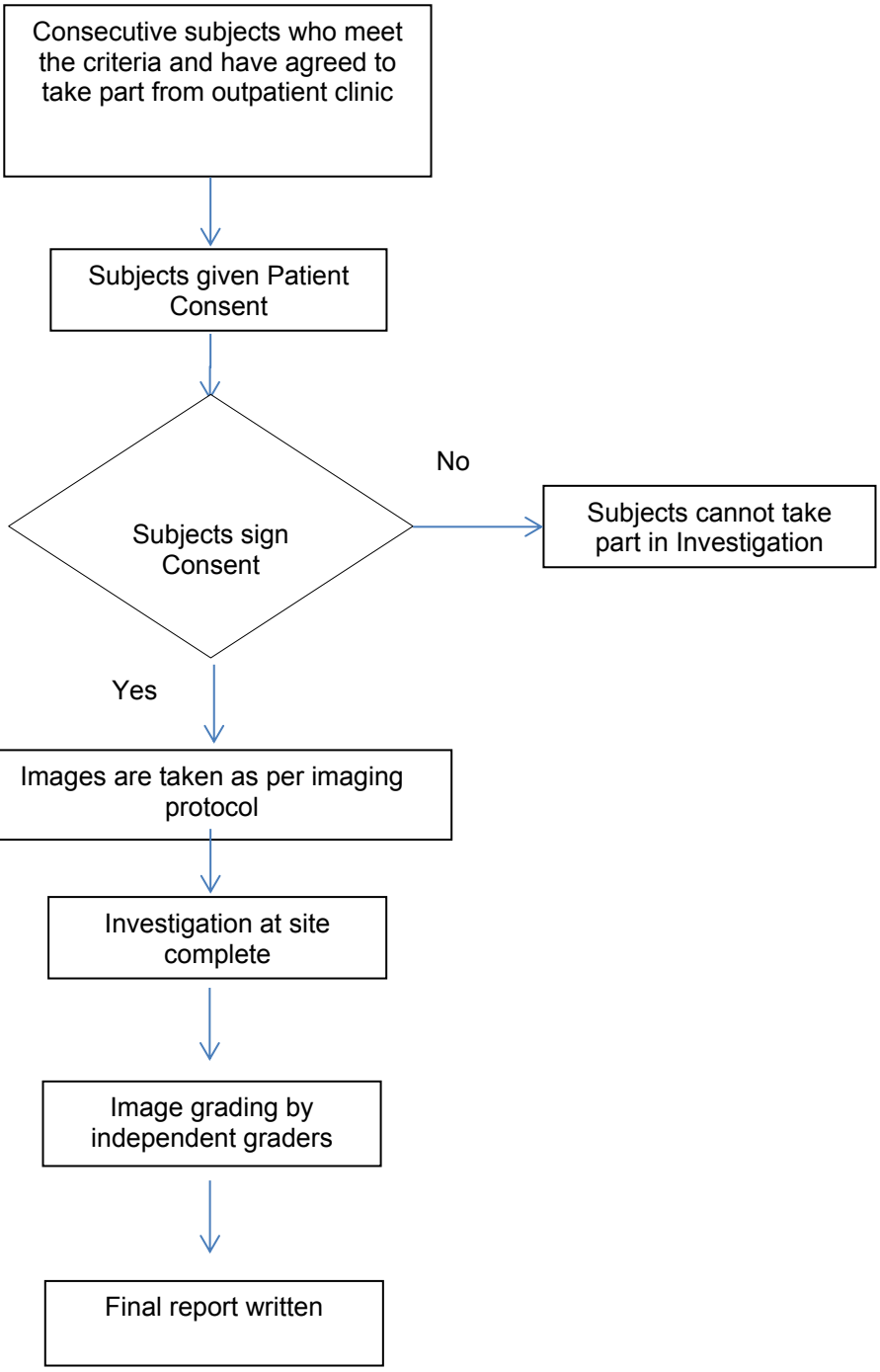
In general, descriptive statistics (mean and standard deviation) will be used to summarize the data by grader and device. Results for the clinical utility questions and the image quality questions will be presented separately.

The total number of scans taken and the total number of evaluable scans will be summarized by scan type and device.

A kappa analysis will be performed to determine the level of agreement between the graders and between devices.

These performance results will be reviewed to determine whether the investigational device's images are similar or better than the predicate device.

CLINICAL INVESTIGATION FLOW CHART



1 PRELIMINARY INVESTIGATIONS AND JUSTIFICATION FOR THE TRIAL

1.1 Introduction

The P200TxE is a non-contact scanning laser ophthalmoscope and optical coherence tomographer intended for in-vivo digital imaging of posterior ocular structures, including the vitro-retinal interface, retina, retinal layers, optic disc, choroid and choroido-scleral interface. It is indicated for producing high-resolution, wide field, en-face reflectance images, auto fluorescence images, fluorescein angiography images, indocyanine green angiography images, and axial cross-sectional images of the posterior ocular structures.

The system shall enable practitioners to capture multi-modal images in support of detection, investigation and monitoring of retinal conditions.

The P200TxE instrument uses red and green laser illumination for reflectance imaging, enabling it to image pathology throughout the layers of the retina, from the sensory retina and nerve fiber layer, through the retinal pigment epithelium (RPE) and down to the choroid. The image can be separated to present the distinct retinal sub-structures associated with the individual imaging wavelengths.

The P200TxE instrument uses green laser illumination to excite autofluorescence (AF) emission from the naturally occurring lipofuscin in the human fundus.

The P200TxE instrument uses infrared laser illumination for reflectance imaging simultaneously with OCT imaging. Infra-red reflectance images are used to track eye position during OCT imaging and are not available to the user. The P200TxE instrument uses infrared swept-source laser illumination for optical coherence tomography allowing a depth profile of the reflectance of the human fundus to be recorded.

The P200TxE images the eye via two ellipsoidal mirrors arranged so that a focal point of one of the mirrors coincides with a focal point of the other mirror; a mirrored scanner is also located at this common focal point. The pupil of the subject's eye is placed at one of the other focal points. A second mirrored scanner is located at the remaining focal point; a laser reflected off this scanner is relayed onto the second scanner by the first ellipsoidal mirror and from there is reflected through the pupil and into the eye by the second ellipsoidal mirror. The second scanning element is different for OCT and SLO imaging. The energy reflected back from the retina, or emitted by fluorophores returns through the same path to the detectors; the images are generated from the captured detector data.

The P200TxE refers to the scanhead component of the system, together with touchscreen and hand controller. It is supported by an image server, which delivers patient management and image storage, as well as interfacing with the business systems and hospital Electronic Medical Record systems. The images are captured by the scan head under operator control and then automatically saved to the image server that uses a database structure to hold the images and patient information. For subsequent image review, a number of viewing PC's are connected remotely or via a local area network to the image server. The patient records and images are then accessible in a distributed format suited to the physical layout of the eye-care practice.

Images can be reviewed through OptosAdvance review software (K162039) either on the image server, or on individual review stations, or other DICOM compliant PACS viewers.

1.2 Literature Review

OCT has been used clinically for over 20 years and has proven to be a powerful and indispensable tool. Numerous studies have shown it provides useful clinical information on various retinal structures useful to aid doctors in the diagnosis and management of many ocular pathologies[5,6,7]. In addition to the useful cross sectional B scans, thickness measurements provide accurate and repeatable measurements of various retinal layers that can also be used clinically to help diagnose and manage eye disease.

OCT has greatly improved over the years since it was first introduced. The early OCT devices operated in what is called 'Time Domain' and scanned at speeds of 400 A scans per second with a depth resolution of 10 microns (e.g., Stratus OCT). Time Domain methodology utilized a moving reference arm to get structural information at different retinal depths. More recently, a new methodology was developed called Fourier Domain or Spectral Domain OCT (e.g., P200TE). This method uses a stationary reference arm and employs a spectrometer and a Fourier transform to obtain structural information. This allowed scan speeds to increase between 25,000-70,000 A scans per second and depth resolution was also improved to five microns due to the use of a broad-band light source. Currently, the new investigational device (P200TxE) utilizes a third generation method called Swept Source OCT and can san at speeds of 100,000 A scans per second.

1.3 Device Risk Analysis and Risk Assessment

The sponsor believes that the "Comparative Qualitative OCT Image Grading Study of the Optos P200TE and the P200TxE in Glaucoma Patients" is a Nonsignificant Risk study because the Optos P200TxE device:

- is not intended as an implant;
- is not purported or represented to be for use supporting or sustaining human life;
- is not of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; and
- does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Both the investigational and predicate devices also comply with ISO 15004-2 for the requirements for optical radiation safety for ophthalmic instruments that direct optical radiation into or at the eye.

1.4 Rationale for Trial

The rationale for the trial is to collect data on a cohort of consecutively enrolled adult participants with and without a range of relevant ocular pathologies to evaluate and compare the P200TxE images to the predicate, P200TE, to support clearance of the P200TxE device.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to collect OCT scans to compare the qualitative images produced by the Optos P200TxE to the FDA cleared Optos P200TE (K173707) in glaucoma patients. Qualitative imaging grading assessment of the scan types captured from the investigative P200TxE device and the cleared P200TE will be used to compare and determine whether the P200TxE scans are equivalent or better than the P200TE. The qualitative evaluation will be based on the clinical utility and image quality of the B scans.

2.2 Primary Endpoint

The primary endpoint will be the qualitative assessment of the B scans from each device based on pre-specified grading criteria from three independent masked and qualified graders.

2.3 Secondary Objective

The secondary objective will be an assessment of safety through assessment of any adverse event associated with Optos P200TxE.

2.4 Secondary Endpoint

The secondary endpoint will be an analysis of safety through assessment of adverse events.

3. TRIAL POPULATION

The subject populations will consist of a minimum of 10 glaucoma patients. Glaucoma patients will cover a wide range of disease severity as determined by ICD-10 classification.

4 CRITERIA FOR SUBJECT SELECTION

4.1 Inclusion / Exclusion Criteria

Subjects must fulfil all of the following inclusion/exclusion criteria:

Inclusion Criteria

1. Male or female subjects 22 years of age or older who have full legal capacity to volunteer on the date the informed consent is signed;
2. Subjects who can follow the instructions by the clinical staff at the clinical site,
3. Subjects who agree to participate in the study;
4. Subjects who have been diagnosed with glaucoma in the study eye as confirmed by the investigator;

Exclusion Criteria

1. Subjects unable to tolerate ophthalmic imaging;
2. Subjects with ocular media not sufficiently clear to obtain acceptable OCT images;
3. Subjects with any clinically significant ocular pathology except glaucoma, as determined by self-report and/or investigator assessment on the day of the study visit;
4. Subjects who are not reliably tested with at least one Humphrey Field Analyzer (HFA) visual field (24-2 or 30-2, white on white) measured on the day of the study visit or within the previous year from the study visit, defined as fixation losses > 20% or false positives > 33%, or false negatives > 33%;
5. Subjects with history of dementia or multiple sclerosis

4.2 Randomisation Criteria

Subjects who agree to participate in the study will be consecutively enrolled within the study population if they meet the inclusion and exclusion criteria. One eye of qualified subjects will be enrolled into the study. The order of device testing will be randomized. If both eyes qualify for enrolment, one eye will be randomly chosen as the study eye. Randomization will be performed using a pre-specified randomization table for device order and eye enrolled.

4.3 Withdrawal Criteria

Subjects may be withdrawn from the study if they do not meet all the inclusion and exclusion criteria after enrolling in the study, or if the subject decides to discontinue participation in the clinical study. A subject may be withdrawn from the study at the discretion of the investigators or at the subject's request, at any time. If a subject is withdrawn from the study, data collected to the point of withdrawal will remain in the subject's source document. In the case of withdrawal, a Subject Withdrawal Form will be filled out to specify the reason.

Participation in this study is strictly voluntary and subjects may choose not to participate in the study for any reason simply by telling the clinical personnel. Patients may be withdrawn from the study for the following reasons:

- Intercurrent illness.
- Adverse event.
- Non-compliance with study procedures.
- Protocol violation.
- Administrative or other reasons.

4.4 CIP Violations and Deviations

A violation is defined when the procedures stated in this Clinical Investigation Plan (CIP) are not followed and the consequences could jeopardise the scientific validity of the data, e.g. inclusion criteria not fulfilled. A deviation is defined when the procedures stated in the CIP are not followed, but the consequences do not jeopardise the scientific validity of the data, e.g. trial visit a day outside permitted visit window. The Investigator must immediately inform the Sponsor of any CIP violations. All violations and deviations must be documented in the Case Report Form (CRF).

5 METHODOLOGY

5.1 Clinical Investigation Design

Subjects from a routine outpatient clinic appointment will be evaluated initially for suitability as a candidate for this study. Subjects that are candidates for enrolment will be asked their willingness to participate in this study and will undergo the required screening for the confirmation of inclusion criteria and exclusion criteria.

Eye examinations from the prior two months are allowed to be used if the investigator feels the patient is not likely to have changed significantly (eye is considered relatively stable and not progressing quickly).

Informed consent must be obtained from each subject prior to any study-specific image capture not routinely performed.

This is a prospective, comparative clinical study where the data collection will be conducted at one clinical site located in the United States. One Optos P200TxE device and one Optos P200TE will be required for this study. One device operator will be assigned to perform the imaging on all subjects. The operator will be trained and certified by the Sponsor. A backup operator will also be trained in case the first operator is no longer available to complete the study.

Subjects must meet all inclusion and exclusion criteria in order to be enrolled in the study. If both eyes qualify for enrolment, one eye will be randomly chosen as the study eye. Randomization will be determined using a pre-existing randomization sheet for both eye and device. The Optos P200TE and the Optos P200TxE will be used in accordance with this clinical protocol and each device's User Manual.

Lubricating eye drops (artificial tears) may be used at the discretion or request of the subject as desired.

5.2 Clinical Investigation Duration

The study will last approximately 2-4 weeks.

5.3 Clinical Investigation Visit(s)

The study will comprise of a single visit and will last approximately 30 mins

5.4 Informed Consent

Subjects attending their routine outpatient appointment at the clinic will be offered participation in the study. The Informed Consent will be presented to the subjects for review this explains the study, its risk and benefits, in detail. Subsequently to their review, a verbal explanation of the study risk and benefits will also be presented to the subject and if all questions are satisfactorily resolved, the informed consent form will be signed by all parties and witnessed.

5.5 Confidentiality of Data

A unique subject identifier will be assigned to the consented subjects. The date of birth will be listed as Jan 01, year of birth. No identifiable information will be provided to the sponsor or any third party. The investigator will keep a record matching the study ID number to the actual patient enrolled. No subject data which will identify the individual will be published or in any way disclosed to the sponsor or any third parties in accordance with the Health Insurance portability & Accountability Act of 1996.

5.6 Operator Training and Certification

One operator will be trained and certified by Optos personnel to conduct testing on study subjects. A backup operator will also be trained and certified in case the first operator is no longer available to complete the study. Operators will receive on-site training with the devices. Optos trainers will train the operators on device use, study procedures and image quality. Operators will be certified after successful completion of the training to ensure competency. Data quality will be assessed by Optos personnel to determine if this site is eligible to perform the testing. If data quality is poor, then a device re-training plan will be put in place until the site can successfully perform data acquisition.

6 CLINICAL INVESTIGATION

6.1 Scan Types

Optomap Plus UWF SLO images and the following OCT scans will be captured on both devices.

- Line scan – averaged scan 14mm (P200TxE) and 12mm (P200TE)
- Retina Topography – 9 mm x 9 mm, 111 B scans (P200TxE) and 8.8mm x 8.8mm, 97 B scans (P200TE)
- Optic Nerve Head (ONH) Topography – 6 mm x 6 mm, 111 B scans (P200TxE) and 5.28mm x 5.28mm, 97 B scans (P200TE)
- Raster scan – 14 mm x 9 mm, 121 B scans (P200TxE) and 12mm x 9mm, 65 B scans (P200TE)

In addition, the following OCT scan types will be captured for the P200TxE only (not available in P200TE)

- Ultra-widefield Line – averaged scan 6 mm
- Ultra-widefield Extended Line – averaged scan 23mm
- Ultra-widefield volume – 6mm x 6mm, 121 B scans
- Ultra-widefield HD volume scan – 6mm x 3mm, 121 B scans

A direct comparison of grader scores will be made between similar scans from the two devices, including: Line scans, Raster scans, Retina Topography scans, and ONH scans. An analysis of grader's scores for the 4 scan types available in the P200TxE but not the P200TE will also be made. These scan types included: Ultra-widefield line scan, Ultra-widefield extended line scan, ultra-widefield volume scan, and ultra-widefield HD volume scan.

The operator will review the scan at the time of acquisisiton and scans of poor quality will be retaken in accordance with normal, routine clinical practice as described in the User Manual and Appendix A (e.g., if the patient blinks, has eye-movements, there is clipping, etc). Up to three attempts are allowed to get an acceptable scan. All scans will be saved. If more than one scan is captured, the first acceptable scan that passes the scan review process will be used. This will be noted by the

operator at the time of acquisition. The sponsor will not arbitrarily pick which scan will be used by the image graders.

6.2 Investigational Medical Device

6.2.1 Optos P200TxE

The Optos P200TxE Ophthalmoscope encompasses a widefield Scanning Laser Ophthalmoscope (SLO) and an Optical Coherence Tomographer (OCT), allowing this one device to capture-high resolution images of the peripheral retina as well as its central structures. Widefield Scanning Laser Ophthalmoscope (SLO) fundus imaging is achieved using scanning red and green lasers. These laser wavelengths penetrate the retinal structures to different depths, each wavelength providing information for interpretation. In autofluorescence (AF) mode, the device captures optomap af images using the green laser to illuminate the eye. This allows an image of the natural fluorescence of the eye to be captured. In addition to AF, the P200TxE can also capture FA and ICGA. OCT imaging uses swept source OCT methodology to construct axial and cross-sectional scans.

The P200TxE is a non-contact scanning laser ophthalmoscope and optical coherence tomographer intended for in-vivo digital imaging of posterior ocular structures, including the vitro-retinal interface, retina, retinal layers, optic disc, choroid and choroido-scleral interface. It is indicated for producing high-resolution, wide field, en-face reflectance images, auto fluorescence images, fluorescein angiography images, indocyanine green angiography images, and axial cross-sectional images of the posterior ocular structures.

The system shall enable practitioners to capture multi-modal images in support of detection, investigation and monitoring of retinal conditions.

6.2.2 P200TE (predicate device)

The Optos P200TE Ophthalmoscope (K173707) encompasses a widefield Scanning Laser Ophthalmoscope (SLO) and an Optical Coherence Tomographer (OCT), allowing this one device to capture-high resolution images of the peripheral retina as well as its central structures. Widefield Scanning Laser Ophthalmoscope (SLO) fundus imaging is achieved using scanning red and green lasers. These laser wavelengths penetrate the retinal structures to different depths, each wavelength providing information for interpretation. In autofluorescence (AF) mode, the device captures optomap af images using the green laser to illuminate the eye. This allows an image of the natural fluorescence of the eye to be captured. OCT imaging is achieved using an infrared broadband Super Luminescent Diode (SLD) source and spectral domain OCT methodology to construct axial and cross-sectional scans.

The P200TE is indicated for use as a non-contact, scanning laser ophthalmoscope and optical coherence tomographer intended for in vivo viewing and digital imaging of posterior ocular structures, including the retina, retinal nerve fibre layer, and optic disc. It is indicated for producing high-resolution, widefield, en face reflectance images, autofluorescence images, and axial cross-sectional images of posterior ocular structures. There are no known contraindications for the Optos P200TE

6.3 Concomitant Medications

Concomitant medications will not be recorded for this study, however if any adverse events described in section 8 occur during the trial, the medications will be recorded.

7 ASSESSMENT OF IMAGES

B scan images will be assessed for clinical utility and quality. The results will be compared for the predicate device and the investigational device. Performance results that are similar or better for the investigational device's images will provide clinical evidence for substancial equivalence of the images.

All images will be reviewed in OA software and the images will be in a randomized order for grading and no identifiable features will be present to indicate which device each image comes from.

7.1 Image Grading

B scan images will be assessed for clinical utility and image quality by an independent Reading Center after the data collection phase is completed. The results will be compared between the predicate device and the investigational device.

All scans will be reviewed for image acceptance based on generally accepted industry standards, and scans that do not pass will be excluded (e.g., scans with blinks, eye movements, clipping,etc, are considered to be artifacts are not typically used clinically or in research). Scans will be reviewed based on specific image characteristics described in Appendix A. Excluded scans will not be graded. The operator will evaluate the scans for quality at the time of image acquisition. Unacceptable scans will be re-captured until an acceptable scan is obtained [up to three attempts to capture an acceptable scan].

For scans containing multiple B scans such as 3D cube or volume scans (e.g., Retinal topography scan), the entire set of B scans will be reviewed and graded as a whole (one grade for entire B scan series within a single 3D volume). All scans will be reviewed for grading using a Dicom viewer from Optos called OA (Optos Advance). This viewing software will not provide any information about which device the scan came from or any other identifiable information. Scans will be in a randomized order and numbered sequentially. Graders will not compare scores and will perform all grading independently of each other.

Three independent graders will assess the B scans for each scan type from each subject and grade them for clinical utility and image quality. Graders will evaluate a single B scan at a time and will be masked to which device the B scan came from.

Images will be graded based on both clinical utility and image quality. Clinical utility means is there structural information present in the image that is helpful to aid in clinical decisions such as diagnosing or managing ocular diseases in the eye. Image quality means does the image have sufficient quality to clearly view the relevant structures within the eye.

For clinical utility, the graders will assess specific structures and features in each B scan including: 1) the RNFL, 2) inner and outer retinal layers, 3) RPE complex, and 4) choroid. Note, the RPE complex is defined as the region in between the photoreceptor IS/OS boundary down to Bruch's membrane which includes the RPE layer proper. Each structure will be graded on a 4 point scale (0-3) described below.

For image quality, the graders will assess the B scan as a whole (not specific features or structures). As a whole, the image will be graded on a 4 point scale (0-3) described below.

The four point grading scale is defined as follows:

A score of 0 indicates the scan is a failure, and contains no clinically useful information. No relevant structures are visible in the scan.

A score of 1 indicates the condition of the structure or feature being assessed is **poor**, and it contains very limited clinical utility. Only limited structural information is available in the scan and the feature being evaluated is difficult to assess. This type of scan provides only very limited clinical information and is not very helpful for making clinical decisions. The clinical utility is low or poor.

A score of 2 indicates the condition of the structure or feature being assessed is **fair** or average. It contains some useful clinical information and therefore provides adequate clinical utility. Relevant structures are generally visible in the scan and the scan contains useful information to help guide clinical decisions. The clinical utility of this scan is acceptable or average for a typical B scan.

A score of 3 indicates the condition of the structure or feature being assessed is **good**. It contains useful clinical information. Relevant structures are clearly visible and it is helpful to guide clinical decisions. The clinical utility is high or good.

For 3D cube or volumetric scans, all B scans will be reviewed and grading will be performed on the entire image set as a whole (all B scans graded together as a whole).

The grading report form is shown in Appendix B. A grading guideline document was used to define the grading scale and provide several examples of each category and is provided in Appendix C. These examples of each grade category were reviewed and agreed to by a retina specialist.

8 ASSESSMENT OF SAFETY

8.1 Safety Assessments

Safety will be assessed by reviewing any adverse events associated with either the Optos P200TE or the Optos P200TxE.

8.2 Adverse Events and Adverse Device Effects

Consideration of Adverse Events will hereafter consist of Adverse Events and Adverse Device Effects, including Anticipated Adverse Device Effects and Unanticipated Adverse Device Effects.

An adverse event (AE) is any untoward medical occurrence (including intercurrent illness) experienced by a subject during their participation in a clinical trial. The adverse event may not necessarily have a causal relationship with trial treatment or device, but does have a temporal relationship with trial treatment or device.

An adverse device effect (ADE) is any untoward or unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition also includes any event that is a result of user error. An exacerbation of a pre-existing condition is an adverse event.

Adverse events (AEs) and adverse device effects (ADEs) will be recorded as they are reported whether spontaneously volunteered or in response to questioning about well-being at trial visits. The questioning about AEs and ADEs will cover the current visit as well as the period of time between the previous and the current visit.

All AEs and ADEs will be documented in the subject's medical records and CRF. All AEs and ADEs must be followed until resolution, or for at least 30 days after discontinuation in use of the device, whichever comes first.

The investigator will assess causal relationship of the AE or ADE to the investigational device according to the following classification:

- None: No relationship with investigational device. Other factor(s) certainly or probably causative.
- Unlikely: Time relationship non-existent or doubtful and/or other factor(s) certainly or probably causative.
- Possible: Time relationship exists. Reasonable possibility that the event was caused by the device. Other possible causative factor(s) may exist.
- Probable/Definite: Time relationship exists. The event was certainly or probably caused by the device. Other possible causative factor(s) may exist. A specific laboratory investigation (if performed) has confirmed the relationship.

The following definitions for rating severity of AEs and ADEs may be used:

- Mild: Awareness of signs or symptoms, but these are easily tolerated and are transient mildly irritating only. There is no loss of time from normal activities and symptoms do not require medication or a medical evaluation.
- Moderate: Discomfort enough to cause interference with usual activities or require therapeutic intervention e.g. concomitant medication.
- Severe: Incapacity with inability to do work or do usual activities.

8.3 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any adverse event, the specificity or severity of which is not consistent with the current protocol.

Any serious adverse effects on health or safety or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the protocol or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of Subjects. The occurrence of any Unanticipated Adverse Device Effect must be reported to the Sponsor within 2 business days.

8.3.1 UADE Reporting

All unanticipated adverse device effects must be reported within 24 hours from the point in time the investigator becomes aware of the event to the Sponsor. Refer to the Project Contact List for contact numbers.

It is the responsibility of the investigator to promptly notify the IRB of SAEs per the IRB reporting requirements. Investigators must report the occurrence of UADEs to their reviewing IRB as soon as possible, but no later than 10 working days after first learning of the event. All UADEs will be documented in the subject's medical records and CRF. All UADEs must be followed until resolution, or for at least 30 days after discontinuation of device use, whichever comes first.
Within 24 hours of the sponsor receiving and initial Serious Adverse Event (SAE) & Unatcipated Adverse Device Effect (UADE) Reporting Form, The Sponsor will conduct an initial review of the available information and determine if the event meets the requirements for reporting to the regulatory authorities

8.4 Anticipated Adverse Device Effects

There are no anticipated adverse device effects.

8.5 Subject Discontinuation Criteria

Subjects can withdraw from the study at any time. Subjects who cannot comply with imaging can withdraw but will be asked why they could not complete imaging; this will be recorded for final results.
or the investigator can with draw the subject if they have an adverse event associated with the study procedure. All adverse events must be followed up until resolution, or for at least 30 days after discontinuation of device use, whichever comes first.

9 DATA ANALYSIS AND STATISTICS

9.1 Sample Size

A minimum of 10 glaucoma patients will be enrolled in the study. Patients will have a wide range of glaucoma severity as determined by the investigator and include early, moderate, and severe disease.

9.2 Randomisation

Subjects who agree to participate in the study will be consecutively enrolled within the study population if they meet the inclusion and exclusion criteria until each of the three trial populations are complete (40

eyes from 40 subjects). One eye of qualified subjects will be enrolled into the study. The order of device testing will be randomized. If both eyes are eligible, one eye will be randomly chosen. For diseased eyes, if only one eye is eligible, it can be enrolled as the study eye.

All randomization (device order and eye enrolled) will be determined by a coin toss at the time of enrolment.

9.3 Subject Identification Numbers

Subjects will be assigned a unique subject ID.

9.4 Methods of Analysis

9.4.1 Statistical Plan

In general, descriptive statistics (mean and standard deviation) will be used to summarize the data by grader and device. Results for the clinical utility assessment and the image quality assessment will be presented separately.

The total number of scans taken and the total number of evaluable scans will be summarized by scan type, device and subject population.

A kappa analysis will be performed to determine the level of agreement between the graders and between devices.

These performance results will be reviewed to determine whether the investigational device's images are similar or better than the predicate device.

Analysis of Qualitative Imaging Grading Study Endpoints
Analysis of the image grading results will include descriptive statistics for each scan type and each disease group for both devices. Means and standard deviations will be compared. Agreement between graders and between devices will be determined using a kappa statistic.

Analysis of Safety Endpoints
Adverse events reported will be listed by subject.

9.4.2 Primary Endpoint

The clinical performance testing analysis will include all images that represent the range of equivalent scan pattern for P200TE and the P200TxE as detailed in 6.1. The qualitative image grading will solely focus on the clinical utility and image quality of the B scans (plus the clinical evaluation). Please refer to Table 3.

Assessment Types	Scan Types	Reading Centre
Clinical Utility	OCT scans on P200TE and P200TxE	Qualitative evaluation of all scan types as listed in paragraph 6.1
Image Quality	OCT scans on P200TE and P200TxE	Qualitative evaluation of all scan types as listed in paragraph 6.1

Table 3: Grading Criteria

Three independent, masked, qualified graders will be used. The independent graders will score each scan type using the Grading Assessment Form within the Appendix B. The graders will be asked to evaluate the B scans for each scan type from both devices according to the 4 point grading scale described above. Upon completion by the independent graders, a descriptive summary with be provided.

The number of eyes with unacceptable image quality will be listed and summarised with each trial population.

No identifiable information will leave the data collection site.

9.4.3 Secondary Endpoints

Adverse events reported will be listed by subject.

9.5 Clinical Investigation Plan Violations

Any CIP violations will be investigated and recorded on the case report form and data may be disqualified.

9.6 Clinical Investigation Stopping Criteria

In the event of SADEs, the study will be evaluated for safety to determine whether the trial should continue

10 INVESTIGATOR RESPONSIBILITIES

10.1 Compliance with CFR 21, ICH-GCP, HIPPA and Ethical Considerations

This trial must be conducted in accordance with Institutional review board (IRB), informed consent regulations CFR 21 Parts 11, 50, 56, ICH Guidelines Good Clinical Practice (E6) and the Health Insurance portability & Accountability Act (HIPPA) of 1996. In addition all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of trial subjects.

Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the trial protocol and any amendment(s), written informed consent forms, subject recruitment procedures (e.g. advertisements) and written information to be provided to subjects.

10.2 Informed Consent

The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the trial to each subject, the subject's legally acceptable representative or impartial witness, and obtain written informed consent prior to the subject entering the trial (before initiation of non-routine tests and administration of investigational device.

The final informed consent forms must be approved by the IRB must be compliant with CFR 21 Part 50 requirements and must be written in language that is easily understood by the subject. One original informed consent forms will be signed and dated by the subject (or their legally acceptable representative) and by the person who conducted the informed consent discussion. A copy shall be given to the subject and the investigator will retain the original in the Investigator Site File (ISF).

10.3 Pre-Study Documentation Requirements

The following documentation will be required by the Sponsor before the study can start:

- Signed protocol and amendments
- Copy of the IRB approval letter
- Copy of the approved Consent Form
- Signed confidentiality Agreement
- Signed Clinical Trial Agreement

- Signed Financial Disclosure Statement
- Signed and dated Curriculum Vitae of the Principal Investigator, Co-Investigator(s) and other study personnel

10.4 Confidentiality

The investigator shall maintain subject confidentiality during all audits and inspections of the study site and documentation. Trial subjects will be identified only by their unique subject number on CRFs, in trial correspondence and on the trial database. The investigator will keep a list of identification codes in which each subject is named along with their assigned subject number.

All information provided to the investigator relevant to the investigational device, as well as information obtained during the course of the study, will be regarded as confidential. The investigator and members of his or her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol.

The investigator will take all measures to ensure subject confidentiality is maintained at all times. No identifiable information will be provided to the sponsor or any third parties at any time.

10.5 Source Documentation

The investigator will allow inspections of the study site and documentation by clinical research and audit personnel from the Sponsor, the Sponsor Representative, the IRB, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to medical or clinic records is necessary. The Investigator must inform the Sponsor if they are notified of a forthcoming audit by the IRB or regulatory authorities.

The investigator will ensure that the following information is contained in the medical or clinic records of the subject and that the entries are signed and dated:

- Sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- The day the subject entered the trial describing the trial number, the treatment being evaluated, the unique number assigned to the subject and a statement that informed consent was obtained;
- Each subsequent trial visit including any concerns about adverse events ;
- All concomitant medication taken by the subject, including start and stop dates;
- The date when the subject finished the study, the reason for termination and the subject's general condition at trial completion.
- The primary efficacy endpoint data.
- Those data that are directly entered into the CRF and deemed source data.

10.6 Device Accountability

All Optos P200TxE devices used in this clinical study will be clearly labelled as “Clinical Research Only” . All devices will be stored and maintained in accordance with the corresponding device User Manual in a secure location. A device accountability log will be maintained and will be filed in the Trial Master File (TMF).

10.7 Data Collection

Suitably qualified and trained clinical research personnel of the study centre will ensure compliance with the protocol, adherence to GCP (E6) and CFR 21 obligations, proper maintenance of trial records including device accountability records, correct administration of trial treatments (including storage conditions) and accurate reporting of adverse events and adverse device effects. In addition, suitably qualified and trained clinical research personnel of the sponsor will visit the trial site at regular intervals during the trial for monitoring purposes.

10.8 Case Report Forms, Investigator Site File and Record Retention

The Sponsor will provide the case report forms (CRFs) in paper or electronic format. They will be reviewed against source documentation at each monitoring visit. The Investigator should allocate sufficient time and space for the review and correction process. All corrections on a CRF and on the source documents must be made in a way that does not obscure the original entry. The correct data must be inserted, dated and initialled/authorised by trial site personnel. If reason for the change is not obvious, then a reason should be given. The Principal Investigator must, as a minimum, sign the final CRF page to attest to the accuracy and completeness of all the data.

The investigator must maintain a site file containing, at a minimum, the current User Manual, the final clinical investigation plan and any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/notification, device accountability, all trial correspondence and signed informed consent forms.

The investigator must keep the Investigator Site File, copies of all CRFs, and subject identification list for a period determined by the Sponsor.

If the investigator retires, relocates, or for other reasons rescinds responsibility for archiving trial records, they must inform the Sponsor in writing and give details of who will be taking over this role.

10.9 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the sponsor, the IEC/IRB and, when appropriate, the national regulatory authority.

10.10 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical investigations and may wish to publish the results of this trial. Publications initiated by the Investigator concerning the scientific data obtained from this trial will not be made without the written permission of the Sponsor and the Sponsor having at least 30 days in which to review and provide comment. The Sponsor reserves the right to include the report of this clinical investigation in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

11 SPONSOR RESPONSIBILITIES

11.1 General Responsibilities

This trial must be conducted in accordance with CFR21 Parts11, 50, 56, ICH GCP Guidelines and the Health Insurance portability & Accountability Act of 1996. In addition all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of trial subjects.

11.2 Insurance

Optos Inc. public insurance will cover compensation for an injury directly arising from the use of the P200TE and or the P200TXE in this study

11.3 Data Monitoring and Collection

Suitably qualified and trained clinical research personnel of the sponsor will visit the study centre at regular intervals during the study for monitoring purposes and to assist the research staff with any queries they may have. Case report forms and source documentation will be available for review during monitoring visits to the centre. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory (CFR 21 §812.46and GCP (E6) 5.18 obligations, proper maintenance of records including device accountability records, correct administration of trial devices including storage conditions and accurate reporting of adverse events and adverse device effects.

The case report forms will be reviewed and checked and the data may be verified against the patient's source data.

11.4 Audit

The sponsor has the right to audit a proportion of studies. A department other than the clinical research department usually undertakes this. Therefore the sponsor, an independent auditor or a regulatory authority or IRB may wish to audit the trial site and documentation and these audits may take place as the trial is running or up to several years later.

11.5 Confidentiality

The sponsor will not keep any material on file bearing any subject's name. Subject confidentiality will be maintained at all times.

11.6 Finance

This shall be the subject of a separate agreement between the investigator and sponsor.

12 References

1. Nagiel A, Lalane RA, Sadda SR, Schwartz SD. ULTRA-WIDEFIELD FUNDUS IMAGING. Retina [Internet]. 2016 Apr [cited 2018 Jul 19];36(4):660–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27014860
2. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology [Internet]. 2013 Dec 1 [cited 2018 Jul 19];120(12):2587–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23778092
3. Silva PS, Dela Cruz AJ, Ledesma MG, van Hemert J, Radwan A, Cavallerano JD, et al. Diabetic Retinopathy Severity and Peripheral Lesions Are Associated with Nonperfusion on Ultrawide Field Angiography. Ophthalmology [Internet]. 2015 Dec 1 [cited 2018 Jul 19];122(12):2465–72. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642015007733
4. Silva PS, Cavallerano JD, Haddad NMN, Kwak H, Dyer KH, Omar AF, et al. Peripheral Lesions Identified on Ultrawide Field Imaging Predict Increased Risk of Diabetic Retinopathy Progression over 4 Years. Ophthalmology [Internet]. 2015 May [cited 2018 Jul 19];122(5):949–56. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642015000469
5. Fujimoto J, Huang D. Foreword: 25 Years of Optical Coherence Tomography. Investigative Ophthalmology & Visual Science. 2016 Jul 1;57(9):OCTi-i.
6. Dong ZM, Wollstein G, Schuman JS Clinical Utility of Optical Coherence Tomography in Glaucoma. Invest Ophthalmol Vis Sci. 2016 Jul 1;57(9):OCT556-67.
7. Schuman JS, Puliafito CA. OCT: a bright future. Ophthalmic Surg Lasers Imaging. 2011 Jul;42 Suppl:S5.
8. Chow S, Shao J, Wang H. 2008. Sample Size Calculations in Clinical Research. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 86.
9. Hollander, M and Wolfe, D. Nonparametric Statistical Methods. John Wiley & Sons, Second Edition (1999).

APPENDIX A - CRITERIA FOR OPTOS P200TE AND OPTOS P200TXE IMAGE ACCEPTANCE

The criteria for image acceptance are based on overall signal strength, local signal strength, centration of essential structures, eye movements, clipping of the retina.

Image quality will be assessed by the device operators following each image capture. The device operators will document each image taken as evaluable or non-evaluable based on the following image acceptance criteria. The device operators may make three attempts to obtain one evaluable image before moving on to obtaining the next required image. All evaluable and non-evaluable images should be saved with the subject's source documents.

During all OCT imaging, the following criteria should be met:

- The Scanning Laser Ophthalmoscope (SLO) image should have uniform illumination and there should not be any shadowing on the edges of the OCT image. The focus should be sharp and clear. The fovea or optic nerve head should be centered in the SLO image.
- The OCT image should be centred on the fovea or optic nerve head. There should be minimal artefacts that may affect the signal of the OCT scan.

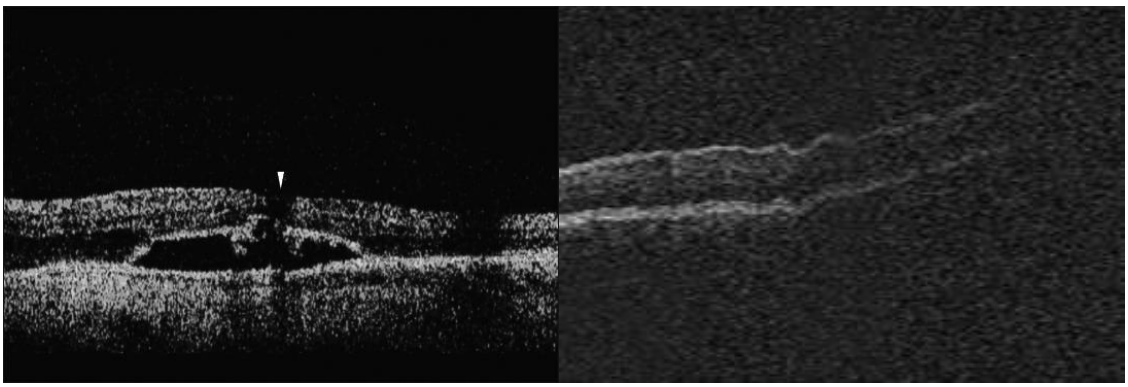
Overall Signal Strength

Overall signal strength is measured by the signal-to-noise ratio (SNR). The SNR is calculated by dividing the overall signal strength by the background noise. SNR has a major impact on OCT image quality and therefore could determine the ability to define inner retinal layers and retinal boundaries. The SNR indicator is displayed during and after the OCT image is captured. Higher SNR results in higher quality images. The SNR has a range of 10/10 (maximum) to 1/10 (minimum). SNR of 9/10 to 10/10 are optimal SNRs, which produce OCT images of the highest quality. Scans with an SNR of 6 or higher are acceptable, scans with SNR of 5 or lower should be excluded and retaken.

OCT SNR is affected by the following patient-dependent (influenced) factors: patient-dependent corneal birefringence, patient eye polarization, pupil size, dry eyes, voluntary and involuntary eye movements, poor focusing of the retina (object), and misalignment of the instrument in relationship to the eye/pupil.

Local Signal Strength

A local weak signal can occur when areas of the image have little to no signal. This can occur even when other areas of the image have a strong signal. Areas with local weak signals appear as black or dark areas from which retinal layers cannot be easily identified. Often, local weak signals are the results of eye movement or blinks. Other causes of local weak signals include media opacities, dry eyes, floaters and improper alignment of the eye during the time the image was taken. If a local weak signal does not cover essential parts of the image (i.e. fovea) the device operator should document the image as evaluable. If a local weak signal covers essential parts of the image, the device operator should document the image as non-evaluable.



OCT scans showing limited local signal strength

1) This is likely due to a local media opacity like a dense floater. Because the retina is not present this scan should be excluded from the study.

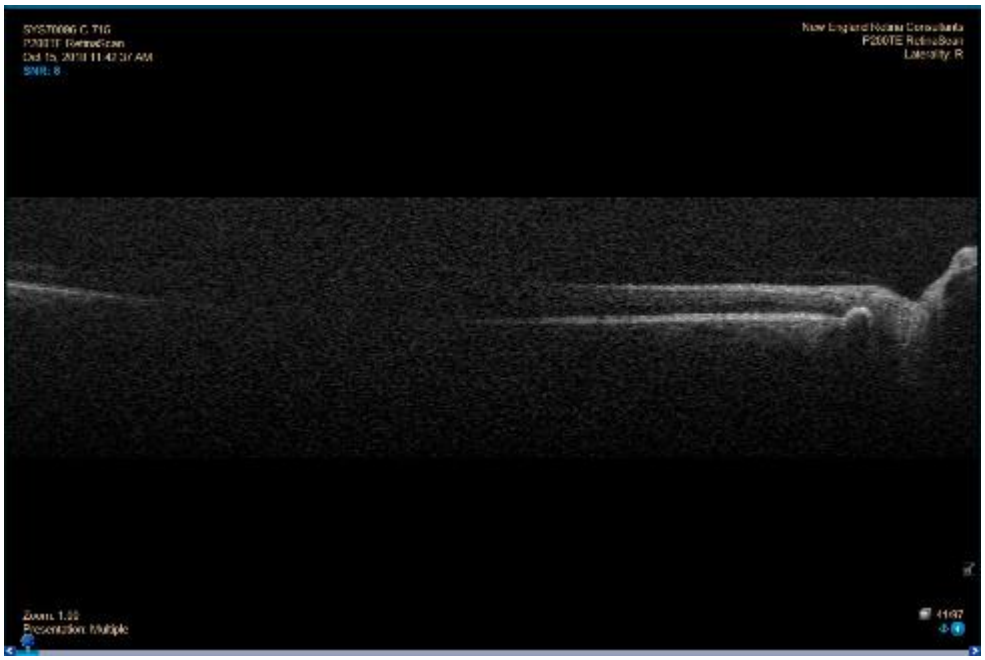


Fig 1. Local Weak signal near the fovea. This image should be excluded.

Figure 2. Another local weak signal with acceptable global SNR. The local weak signal is near the fovea, so the image should be excluded.

Eye movements

Eye Movements – It is possible that the patient may have an eye-movement during the scan acquisition. This can result in a shift or shearing in the resulting image. This can be visualized by a break in the blood vessel patterns or optic disc. It can also make the fovea distorted and lose it regular round appearance. Very small eye movements can be ignored as long as they do not affect important structures such as the fovea or optic disc. If the eye movement is large or if it affects the fovea or optic disc, it should be excluded.

The Optos software will automatically signal the presence of possible eye movements. This is displayed on the image review screen (see Figure 3 below). When eye movements are detected, the operator should review all B scans in the image to confirm the possible presence of eye movements. A review of the B scans will show a strong and sudden shifting of key structures between B scans. If these occur near the fovea or optic disc, the image should be excluded. If the eye movements are not confirmed or do not affect the fovea or optic disc, the image can be accepted into the study.

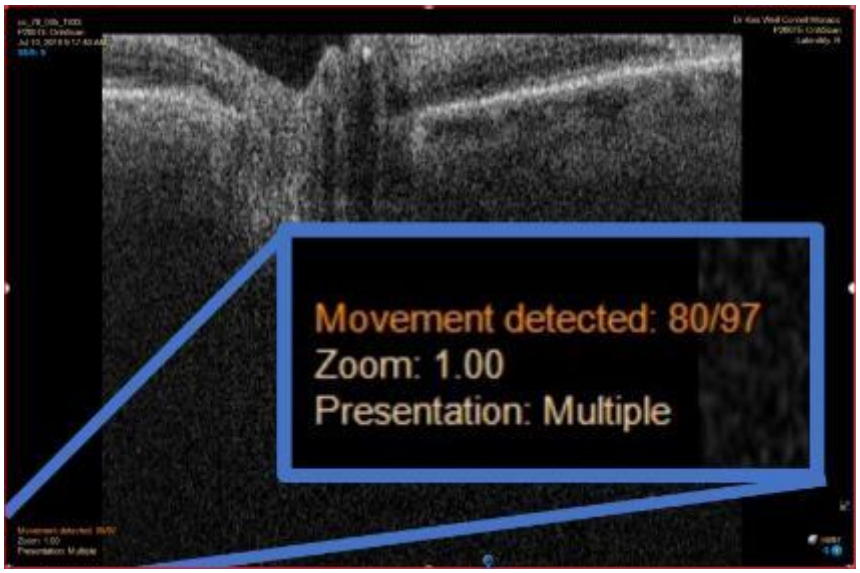


Figure 3. The software detected possible eye movements. The B scans in this image should be reviewed to confirm the presence of eye movements that affect the fovea or optic disc.

Eye Blinks

Eye Blinks – It is possible that the patient may have an eye-blink during the scan acquisition. This can result in a blank B scan (because the eye was closed when the B scan was captured. This can be visualized by the presence of a blank B scan(s) within the scan (see Figure 4). If the blink occurs near the fovea or optic disc, the scan should be excluded.

The Optos software will automatically signal the presence of possible eye blinks. This is displayed on the image review screen (see Figure 4 below). When eye blinks are detected, the operator should review all B scans in the image to confirm the possible presence of eye blinks. A review of the B scans will show a missing B scan(s). If these occur near the fovea or optic disc, the image should be excluded. If the eye blinks are not confirmed or do not affect the fovea or optic disc, the image can be accepted into the study.

Figure 4. The software detected possible eye blinks (see bottom left message). The B scans in this image should be reviewed to confirm the presence of eye blinks that affect the fovea or optic disc. In this case, the B scan is missing and the scan should be excluded.

Clipping

Clipping of the retina – When the operator takes a scan, they must ensure the retina is located within the scan window based on viewing a live OCT B scan image. The height of the retina can be adjusted within this window based on z-motor position and working distance to the eye. If the retina is too high in the window and it touches the top of the scan window, some of it may be clipped and there will be missing retinal data. If the retina is too low in the window and it touches the bottom of the scan window, some of it may be clipped and there will be missing retinal data. If there is clipping of the retina either because it is too high or too low, there will be missing data and the scan should be excluded. If the clipping does not affect the fovea or optic disc measurement area, the scan may be accepted. If it does occur near the fovea or optic disc within the measurement area, it should be excluded.

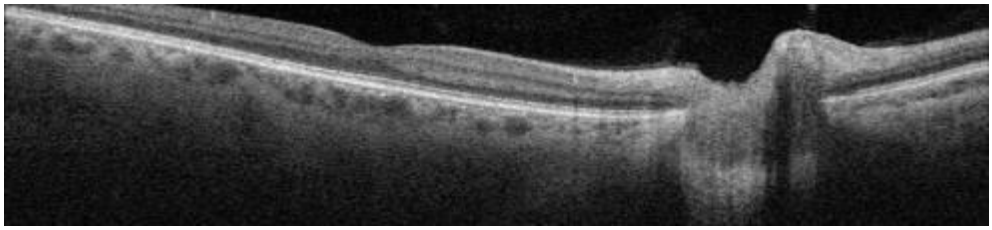


Fig 5. Clipping of the B-Scan. Image should be excluded.

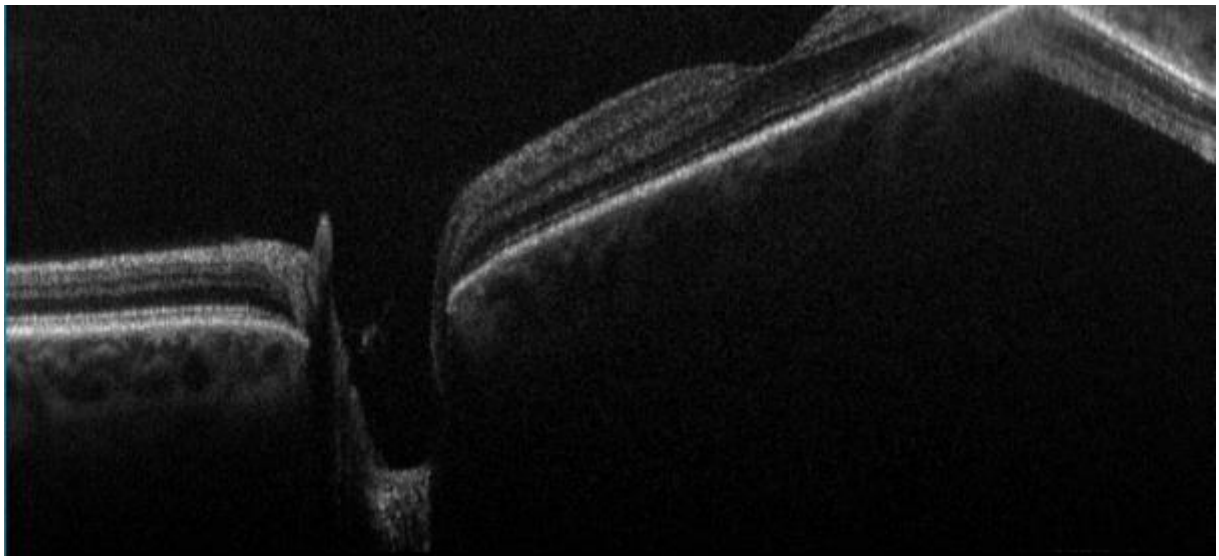


Figure 6. Clipping near the fovea. Image should be excluded.

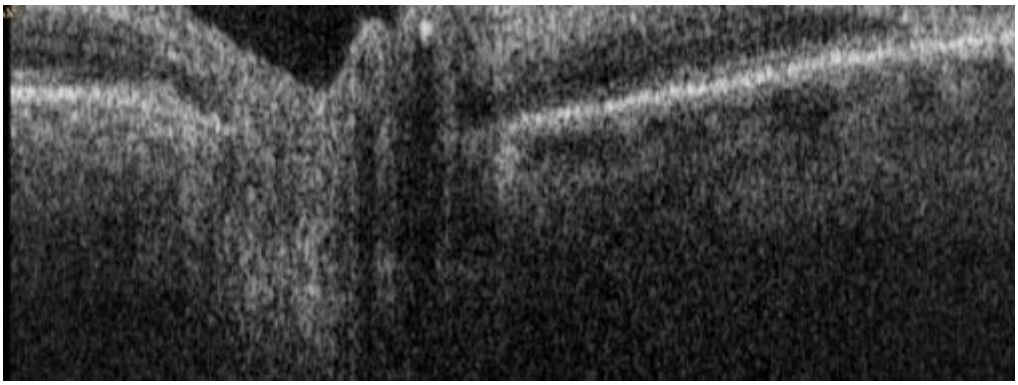


Figure 7. Clipping at the optic disc. Image should be excluded.

Centration of Essential Structures

The fovea should be in the center of the image for all macula scans, and the optic disc should be centered for all optic disc scans. The device operator should document any images in which the alignment grid reaches the edge of the image as non-evaluable.

APPENDIX B – INDEPENDENT GRADERS ASSESSMENT CRITERIA FOR OPTOS P200TE AND OPTOS P200TXE IMAGES

For each of the scan types per subject please answer the following statements by scoring according to your qualitative assessment of the images. Definitions for Clinical Utility and Image Quality are detailed in the Definitions section of this protocol

Grader ID:	**Date:**
Image Reference Number:	
Scan Time Stamp:	___ ___ / ___ ___ /___ ___ **HH MM SS**

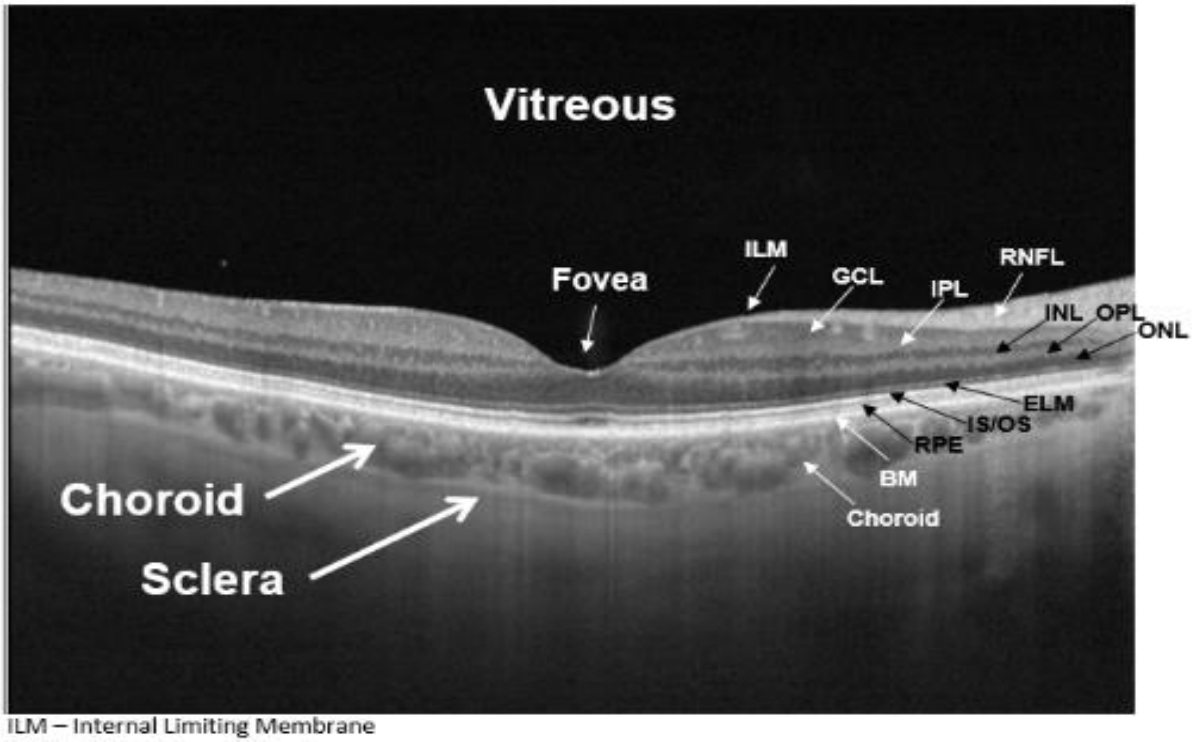
Section 1
Please indicate the clarity or quality of the following features on a scale of 0-3 for each B scan

#	Question	Fail	Poor	Average	Good
1.	Clinical Utility of the RNFL	0	1	2	3
2.	Clinical Utility of the inner and outer retinal layers	0	1	2	3
3.	Clinical Utility of the RPE complex (IS/OS boundary to Bruch's Membrane	0	1	2	3
4.	Clinical Utility of the choroid	0	1	2	3
5.	Overall Image Quality	0	1	2	3

APPENDIX C – B SCAN IMAGE GRADING GUIDE AND INSTRUCTIONS

This guide provides the descritpion and instructions for grading of B scans for Image content and Quality. It is useful as a training guide to explain the scoring system with examples.

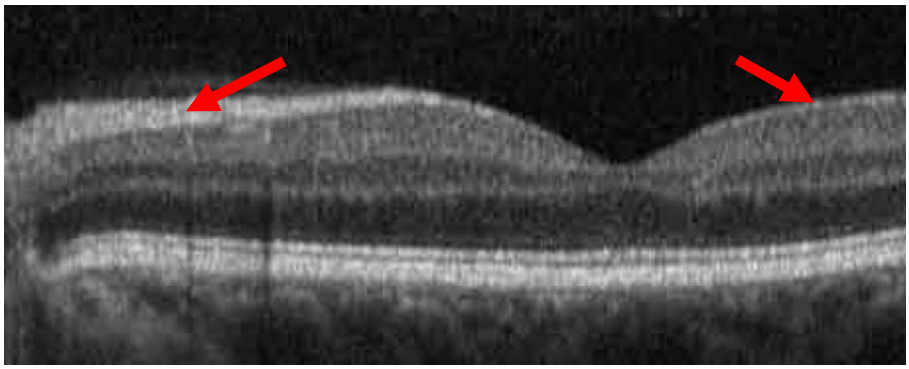
Below is a high quality B scan through the fovea that clearly shows and labels the major retina features that can be visible in a B scan (Figure 1). Not all of these features in the retina will be graded, only major retina features including: 1) the RNFL, 2) the inner and outer retina layers, 3) The RPE complex, 4) the choroid, and 5) overall quality.



ILM – Internal Limiting Membrane
RNFL – Retinal Nerve Fiber Layer
GCL – Ganglion Cell Layer
IPL – Inner Plexiform Layer
INL – Inner Nuclear Layer
OPL – Outer Plexiform Layer
ONL – Outer Nuclear Layer
ELM – External Limiting Membrane
IS/OS – Photoreceptor Inner Segment / Outer Segment
RPE – Retinal Pigment Epithelium
BM – Bruch's Membrane
Choroid
Sclera

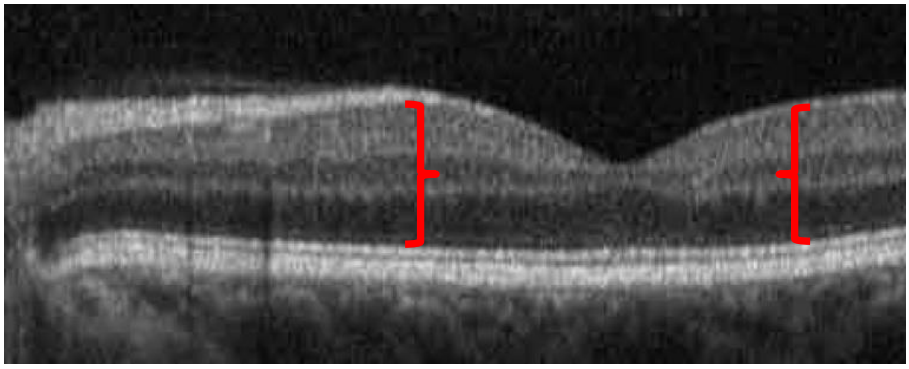
The following retina features will be assessed in the B scan grading Study.

1) **The RNFL** is the bright band at the top of the retina. It is thickest on the nasal side especially near the optic disc. On the temporal side of the fovea, the RNFL becomes very thin and may not always be visible.



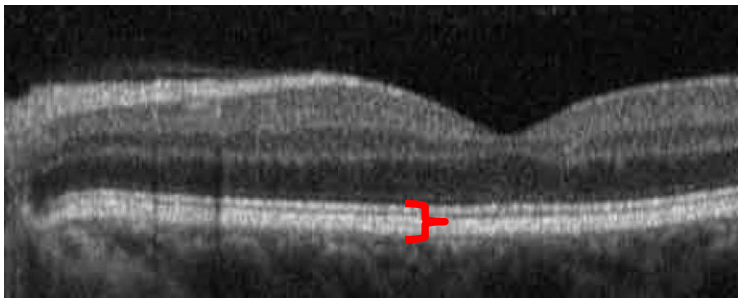
Red Arrows point to the RNFL layer in this B scan image

2) **The inner and outer retina layers** include: The ganglion cell layer (GCL is the dark band just below the RNFL), the inner plexiform layer (IPL is bright band below the GCL), the inner nuclear layer (INL is dark band below the IPL), the outer plexiform layer (OPL is bright band below the INL), and the outer nuclear layer (ONL is dark band below the OPL and above the RPE complex).



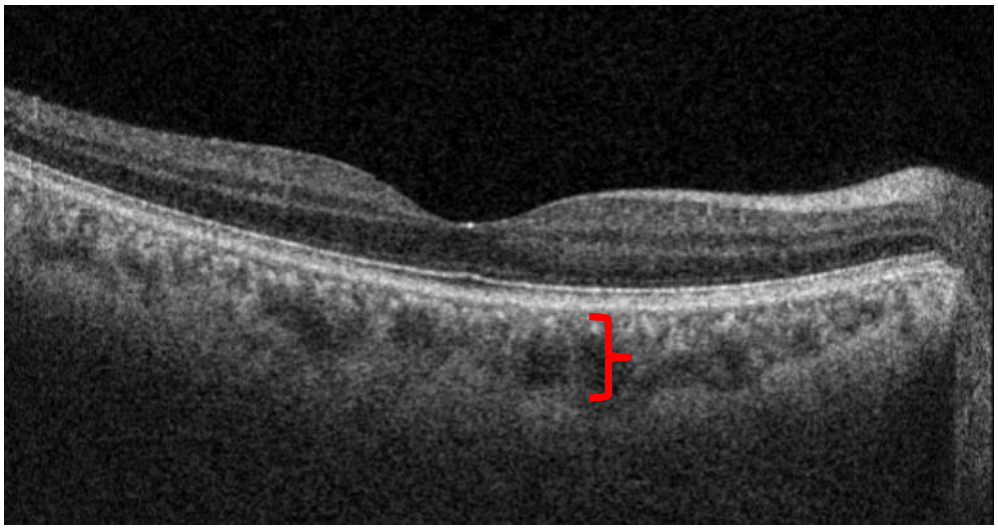
Red brackets shows the inner and outer retinal layers in this B scan image

3) **The RPE Complex** is the thick bright band at the bottom of the retina. It is actually made up of several features including the IS/OS boundary (the boundary between the inner and outer segments of the photoreceptors), the RPE proper (true retinal pigment epithelial layer), and Bruch's Membrane (BM is thin layer just below the RPE). Sometimes these three features can be distinguished as three bands, but at times they appear to merge into a single bright band.



Red bracket shows the RPE complex in this B scan image

4) **The Choroid** is the area just below Bruch's membrane and extends down to the sclera. It consists of smaller and larger blood vessels.



5) **Overall Image Quality** is a general impression of the overall quality of the entire B scan. It is not an evaluation of any specific feature, but an overall sense of the clarity of the image as a whole. A gestalt view for quality.

Scoring System

Scoring will be based on the quality and clarity of the images. Scores will be based on a 4 point grading scale (0 to 3), with 0 corresponding to failure, 1 is poor, 2 is fair, and 3 is good. The details of the scoring are as follows:

The four point scale is defined as follows:

A score of 0 indicates the scan is a failure, and contains no clinically useful information. No relevant structures are visible in the scan.

A score of 1 indicates the condition of the structure or feature being assessed is **poor**, and it contains very limited clinical utility. Only limited structural information is available in the scan and the feature being evaluated is difficult to assess. This type of scan provides only very limited clinical information and is not very helpful for making clinical decisions. The clinical utility is low or poor.

A score of 2 indicates the condition of the structure or feature being assessed is **fair** or average. It contains some useful clinical information and therefore provides adequate clinical utility. Relevant structures are generally visible in the scan and the scan contains useful information to help guide clinical decisions. The clinical utility of this scan is acceptable or average for a typical B scan.

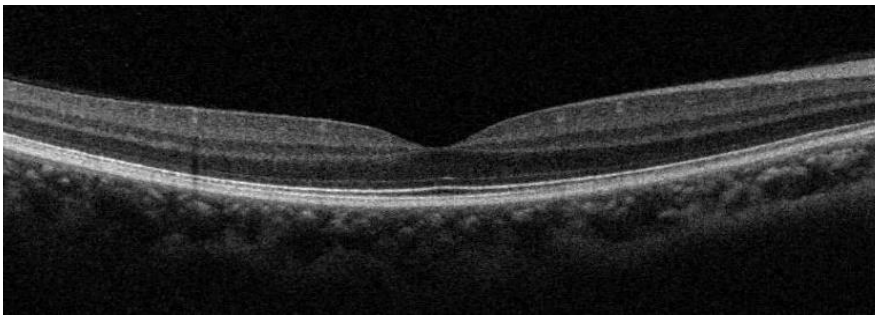
A score of 3 indicates the condition of the structure or feature being assessed is **good**. It contains useful clinical information. Relevant structures are clearly visible and it is helpful to guide clinical decisions. The clinical utility is high or good.

For 3D cube or volumetric scans, all B scans will be reviewed and grading will be performed on the entire image set as a whole (all B scans graded together as a whole).

Example Images and Scores

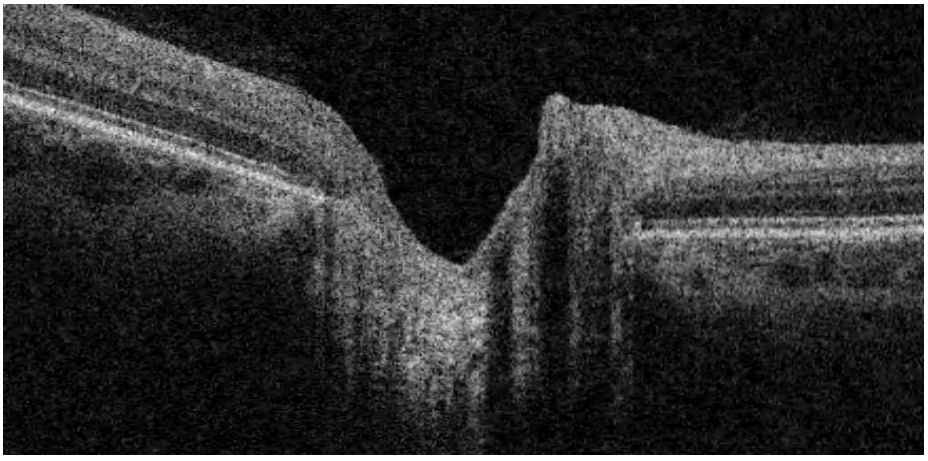
The following images and their scores are examples for each type of score. They are to serve as simple examples to illustrate the scoring procedure and how it relates to the image content and quality. These examples are guides and are not meant to be an exact or correct score.

Example 1.



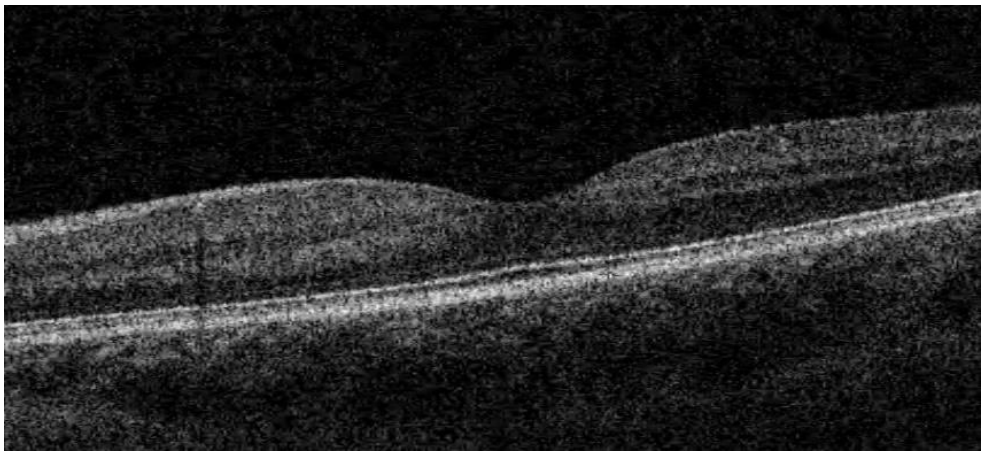
1. RNFL: Score 3 (Good) -> RNFL is very clear and well delineated from the rest of the retina
2. Inner/Outer Layers: Score 3 (Good) -> all inner and outer retinal layers are clearly visible
3. RPE Complex: Score 3 (Good) -> The RPE complex features are clearly visible and distinct layers can be seen
4. Choroid: Score 3 (Good) -> The vessels in the choroid can be seen and the choroid/scleral boundary can be seen as well.
5. Overall Image Quality: Score 3 (Good) -> The general quality is very good for this image. There is little background noise and all relevant features can be seen.

Example 2.



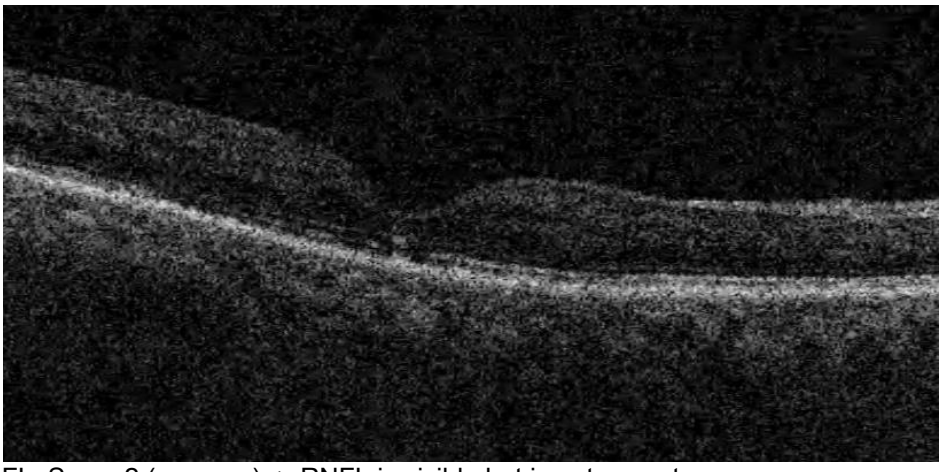
1. RNFL: Score 3 (Good) -> RNFL is very clear and well delineated from the rest of the retina
2. Inner/Outer Layers: Score 3 (Good) -> all inner and outer retinal layers are clearly visible
3. RPE Complex: Score 3 (Good) -> The RPE complex features are clearly visible and distinct layers can be seen
4. Choroid: Score 2 (Average) -> The choroid vessls can be seen but are not clearly defined.
5. Overall Image Quality: Score 3 (Good) -> The general quality is very good for this image. There is little background noise and all relevant features can be seen.

Example 3.



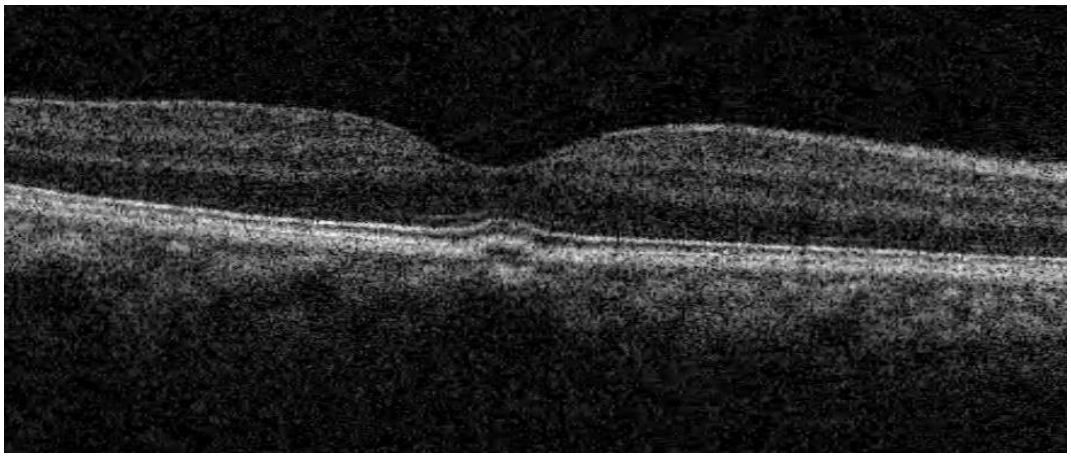
1. RNFL: Score 3 (good) -> RNFL is clear and well delineated from the rest of the retina
2. Inner/Outer Layers: Score 2 (average) -> most inner and outer retinal layers are visible
3. RPE Complex: Score 3 (Good) -> The RPE complex features are visible and distinct layers can be seen
4. Choroid: Score 1 (Poor) -> The choroid does nto reveal distinct vessels or other structures very well.
5. Overall Image Quality: Score 3 (Good) -> The general quality is very good for this image. There is little background noise and most relevant features can be seen.

Example 4.



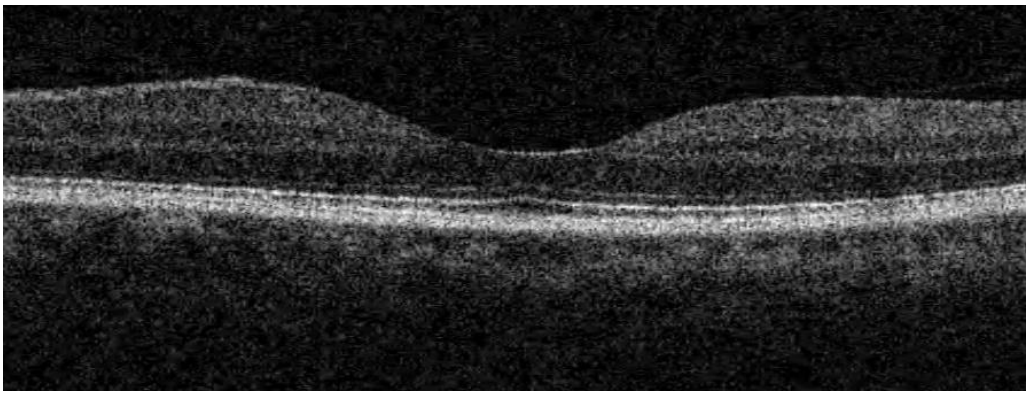
1. RNFL: Score 2 (average) -> RNFL is visible but is not very strong.
2. Inner/Outer Layers: Score 1 (poor) -> most inner and outer retinal layers are not clearly visible, it is difficult to make out the retinal layers
3. RPE Complex: Score 2 (Average) -> The RPE complex is visible, but the features are not clear. The distinct layers cannot be clearly seen
4. Choroid: Score 1 (Poor) -> Choroid vessels are not clearly visible.
5. Overall Image Quality: Score 2 (Average) -> The general quality is OK. Major features are visible but most are not very clear.

Example 5.



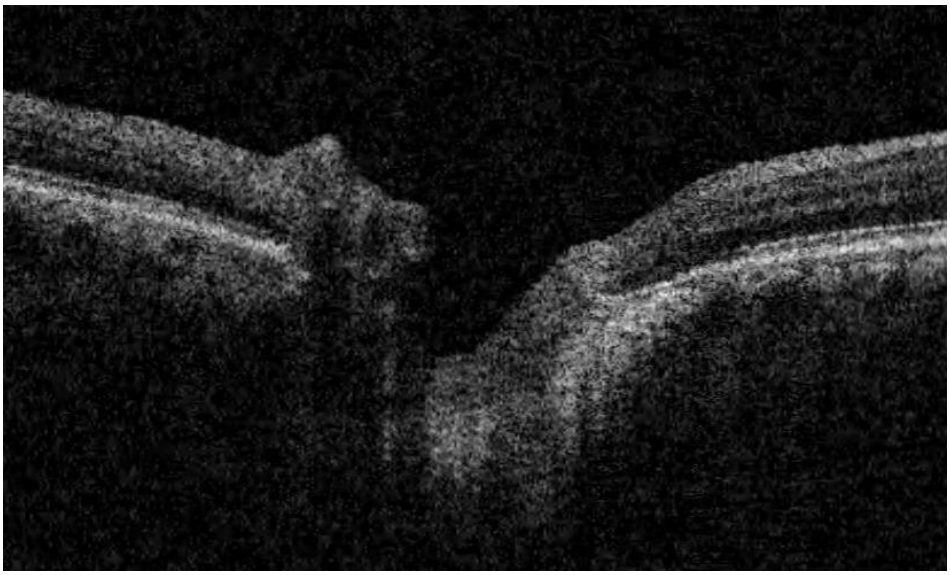
1. RNFL: Score 3 (Good) -> RNFL is clearly visible
2. Inner/Outer Layers: Score 3 (Good) -> The inner and outer retinal layers are visible.
3. RPE Complex: Score 3 (Good) -> The RPE complex is visible and distinct layers can be seen.
4. Choroid: Score 2 (Average) -> Some choroid vessels can be seen.
5. Overall Image Quality: Score 3 (Good) -> The general quality is good. Major features are clearly visible.

Example 6.



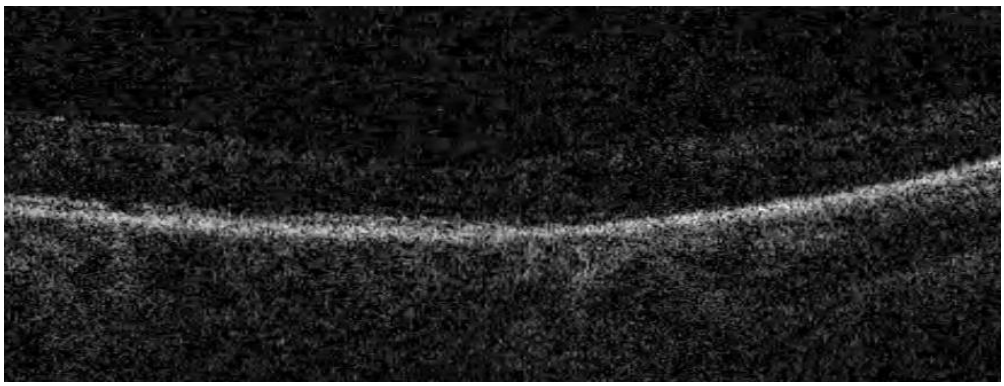
1. RNFL: Score 2 (Average) -> RNFL is visible but is not very strong
2. Inner/Outer Layers: Score 2 (Average) -> Some inner and outer retinal layers are visible but some are not in some areas.
3. RPE Complex: Score 2 (Average) -> The RPE complex is visible and distinct layers can be seen in some areas but not all.
4. Choroid: Score 1 (Poor) -> The choroid vessels are difficult to visualize
5. Overall Image Quality: Score 2 (Average) -> The general quality is average. Most features are visible.

Example 7.



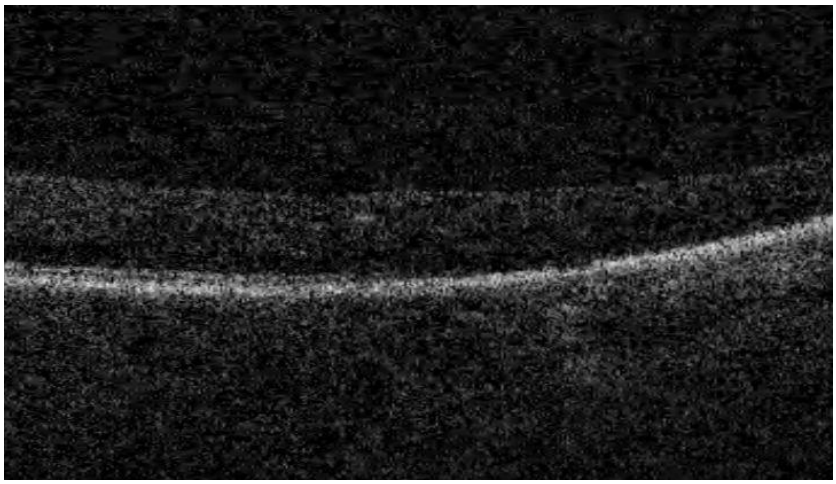
1. RNFL: Score 2 (Average) -> RNFL is visible but is not very strong
2. Inner/Outer Layers: Score 2 (Average) -> Some inner and outer retinal layers are visible but some are not in other areas.
3. RPE Complex: Score 2 (Average) -> The RPE complex is visible and distinct layers can be seen in some areas but not all.
4. Choroid: Score 1 (Poor) -> The choroid vessels are difficult to viusalize.
5. Overall Image Quality: Score 2 (Average) -> The general quality is average. Most features are visible.

Example 8.



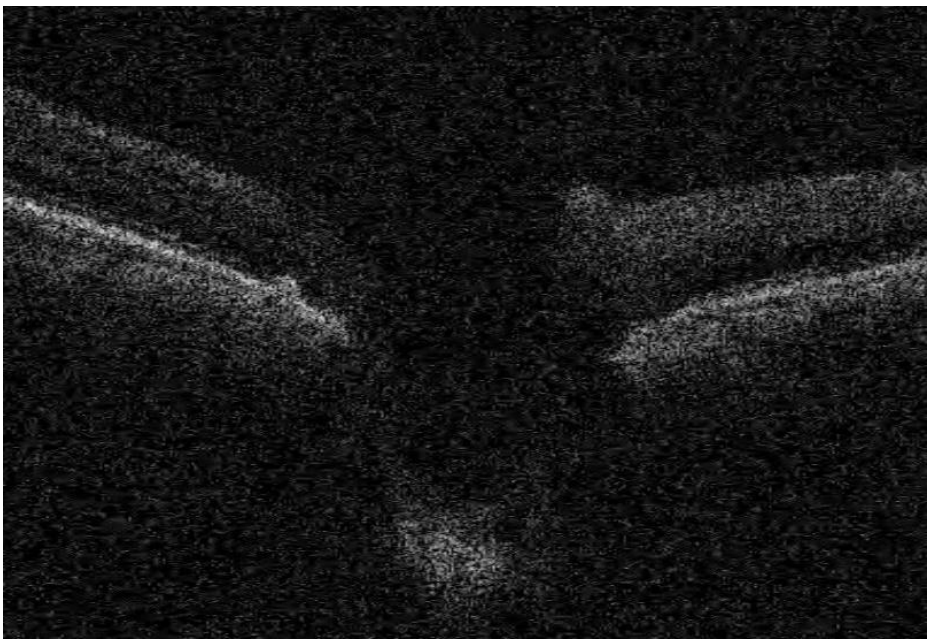
1. RNFL: Score 1 (Poor) -> RNFL is not very visible
2. Inner/Outer Layers: Score 1 (Poor) -> The inner and outer retinal layers are not visible.
3. RPE Complex: Score 1 (Poor) -> The RPE complex is visible, but not distinct and individual layers cannot be seen.
4. Choroid: Score 1 (Poor) -> It is difficult to see the choroidal vessels.
5. Overall Image Quality: Score 1 (Poor) -> The general quality is very poor. Most features are not clearly visible.

Example 9.



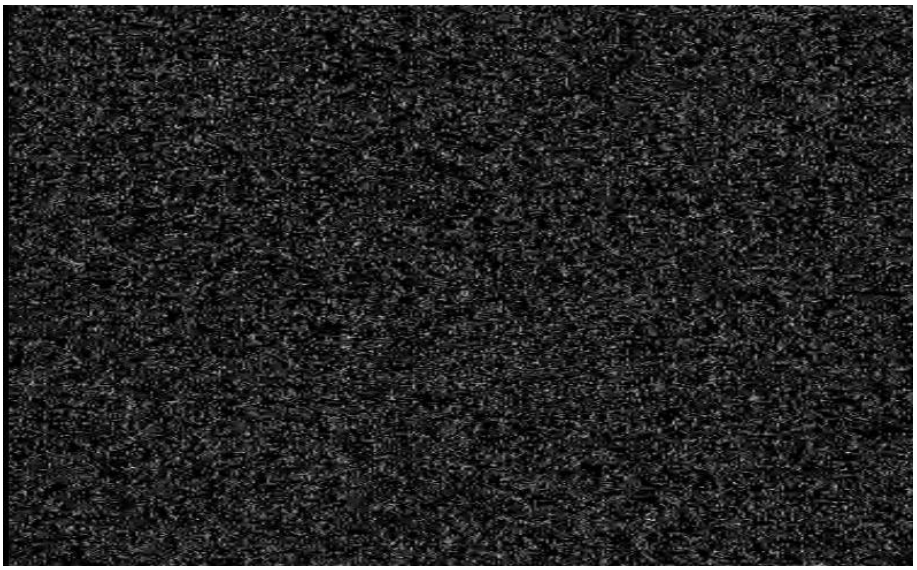
1. RNFL: Score 1 (Poor) -> RNFL is not very visible
2. Inner/Outer Layers: Score 1 (Poor) -> The inner and outer retinal layers are not visible.
3. RPE Complex: Score 1 (Poor) -> The RPE complex is visible, but not distinct and individual layers cannot be seen.
4. Choroid: Score 0 (Fail) -> It is difficult to see any choroid structure.
5. Overall Image Quality: Score 1 (Poor) -> The general quality is very poor. Most features are not clearly visible.

Example 10.



1. RNFL: Score 1 (Poor) -> RNFL is not very visible
2. Inner/Outer Layers: Score 1 (Poor) -> The inner and outer retinal layers are not visible.
3. RPE Complex: Score 1 (Poor) -> The RPE complex is visible, but not distinct and individual layers cannot be seen.
4. Choroid: Score 0 (Fail) -> It is difficult to see any choroid structure
5. Overall Image Quality: Score 1 (Poor) -> The general quality is very poor. Most features are not clearly visible.

Example 11.



1. RNFL: Score 0 (Fail) -> RNFL is not visible at all
2. Inner/Outer Layers: Score 0 (Fail) -> The inner and outer retinal layers are not visible.
3. RPE Complex: Score 0 (Fail) -> The RPE complex is not visible.
4. Choroid: Score 0 (Fail) -> The choroid is not visible
5. Overall Image Quality: Score 0 (Fail) -> The general quality is very poor. Most features are not clearly visible.