CLINICAL CLIN Assessment of PathFinder 1.0 on the CIRRUS 6000 and the CIRRUS 5000

Clinical Protocol CIRRUS-2023-1

Clinical Investigation Plan (CIP)

Version 02 from May 28, 2025

Sponsor
Carl Zeiss Meditec Inc.
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1 Signatures

I have read this version of the protocol (dated) in its entirety and approve all its contents.

I declare that:

- I agree to carry out and conduct this investigation, referenced as CIRRUS-2023-1, in strict compliance with the protocol (and its amendments), according to Good Clinical Practice and to all relevant and applicable regulations and guidance.

- This protocol contains confidential proprietary information with respect to Carl Zeiss Meditec products and clinical studies. By accepting this document, you agree that the information contained herein will not be disclosed to others, without written authorization from Carl Zeiss Meditec Inc. except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

Principal Investigator	**Signature**	**Date**
Principal Investigator		

See hard copy for signatures.

Sponsor's Representative	**Signature**	**Date**
Patty Sha Head of Clinical Research		

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2 Synopsis

Title of the investigation	CLINICAL CLIN Assessment of PathFinder 1.0 on the CIRRUS 6000 and the CIRRUS 5000
Identification number	CIRRUS-2023-1
Investigational devices	CIRRUS HD-OCT Model 5000 Carl Zeiss Meditec, Inc. 5300 Central Parkway Dublin, CA 94568 USA CIRRUS HD-OCT Model 6000 Carl Zeiss Meditec, Inc. 5300 Central Parkway Dublin, CA 94568 USA
Sponsor	Carl Zeiss Meditec, Inc. 5300 Central Parkway Dublin, CA 94568 USA
No. of investigational sites	The study will involve a minimum of six clinical sites in the US. Minimum subject enrollment will be 30 subjects per site. The clinical sites will be chosen to cover the intended subject population and represent diverse geographic locations in the USA (see section 6.4 Study Sites).
Objective	The primary objective of this investigation is to assess the sensitivity and specificity of PathFinder 1.0, a deep learning based, static Artificial Intelligence (AI) decision support tool that aids healthcare professionals in detecting Macular Cube OCT B-scans that have the presence or absence of retinal abnormalities within the macula (see Section 6.3 Group B). For this protocol, “condition” will describe a diagnosis type (epiretinal membrane (ERM), dry age related macular degeneration (dAMD) etc), while a retinal or macular “abnormality” describes a lesion type and/or retinal layers affected

	by the condition (see Section 6.3 Group B). The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline).
Clinical investigation design	This is a prospective, two phase, multi-site study. The clinical investigation is established to assess the sensitivity and specificity of the PathFinder 1.0 algorithm, a decision support tool that detects the presence or absence of macular abnormalities within the macula. Every subject will be scanned on a CIRRUS 5000 and CIRRUS 6000, and both the CIRRUS 5000 and CIRRUS 6000 will be used for Phase 1 and Phase 2. PathFinder 1.0 uses two different algorithms. The first algorithm is an Algorithm Acceptance indicator that differentiates between acceptable and unacceptable B-scans for the second alogorithm. The second algorithm uses only the acceptable B-scans as the input and then differentiates between the presence or absence of a macular abnormality in the B-scans as the binary output. The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists. The Principal Investigator (PI) or designee will identify potential study subjects and invite them to volunteer in the study if they meet the eligibility/inclusion criteria for at least one of their eyes. The clinical investigation targets subjects 18 years or older. Qualified subjects will be consented prior to study enrollment. One visit will be required for the study and will last approximately 30 to 60 minutes depending on if the subject needs to be dilated. One eye per subject will be enrolled in the study. Subjects will undergo imaging with the Macular Cube 512x128 scan and Angiography 6 x 6 mm scan using both the CIRRUS 6000 and CIRRUS 5000 on the same day (see 6.1.1 Study Design). The Angiography 6 mm x 6 mm scans will be acquired for exploration of future algorithm development and will not be included in the PathFinder 1.0 performance analysis. The subjects will be recruited in two phases. For Phase 1, the first dataset will be recruited which is separate from Phase 2. Phase 1 will be a prospective, randomized, multi-site study. Subjects with presence or absence of macular abnormalities within the central 6x6 mm macula region

	will be randomly recruited at sites with different geographic locations (see 6.4 Study Sites). Each site will recruit a minimum of 30 subjects for this phase. A minimum of 234 cummulative subjects will be recruited. Specifically, a minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities will be recruited. A target of 400 subjects will be enrolled to account for study dropout and disqualified scans. There will be a maximum of 20 subjects under 50 years old for subjects with absence of macular abnormalities. Phase 2 will be a prospective, non-randomized, multi-site study (using the same study sites as Phase 1 but different subjects) and will start once the minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities are recruited. For Phase 2, a second dataset will be recruited that is separate from phase 1. Only subjects that meet inclusion criteria for Group B (presence of macular abnormalities) will be recruited. This study population will be enriched to ensure a minimum of 25 subjects per category for Group B (described below) are enrolled, and no maximum will be placed for these categories. A maximum of 1000 subjects will be enrolled in this study. The subject population will be comprised of two groups (all categories below pertain to the central 6x6 mm macula area): Group A 1. Subjects with absence of macular abnormalities Group B 1. Subjects with Disruption of the vitreoretinal interface (VRI) 2. Subjects with Intraretinal hyporeflective space (IRHS) 3. Subjects with Subretinal hyporeflective space (SRHS) 4. Subjects with IS/OS (Ellipsoid Zone) disruption 5. Subjects with Retinal Pigment Epithelium (RPE) elevation 6. Subjects with Retinal Pigment Epithelium (RPE) atrophy 7. Other abnormalities

Study Sites	The clinical sites will be chosen to cover the intended subject population and represent diverse geographic locations in the USA. The clinical trial sites will be independent and separate from the sites whose data was used for PathFinder 1.0 algorithm development (training and tuning/validation). Study sites may include optometry, general ophthalmology, and retina specialist clinics, optometry school clinics, ophthalmology departments of medical schools or may be a combination (e.g. optometry and general ophthalmology, etc.). The same study sites will be used for Phase 1 and Phase 2.
Inclusion/exclusion criteria	**Inclusion and Exclusion criteria** *General Inclusion Criteria:* 1. Able and willing to make the required study visits. 2. Able and willing to give written informed consent and follow study instructions. 3. Able and willing to complete ophthalmic imaging. 4. Adults 18 years of age or older. The subject population will be comprised of two groups (all categories below pertain to the central 6x6 mm macula area): Group A 1. Subjects with absence of macular abnormalities Group B 1. Subjects with Disruption of the vitreoretinal interface (VRI) 2. Subjects with Intraretinal hyporeflective space (IRHS) 3. Subjects with Subretinal hyporeflective space (SRHS) 4. Subjects with IS/OS (Ellipsoid Zone) disruption 5. Subjects with Retinal Pigment Epithelium (RPE) elevation 6. Subjects with Retinal Pigment Epithelium (RPE) atrophy 7. Other abnormalities *General Exclusion Criteria:*

	1. Inability to undergo the required tests. 2. Unable to give consent or follow study instructions. 3. Inability to fixate that precludes obtaining acceptable macula scans in the study eye. 4. Visudyne (verteporfin) injection within the last 48 hours in the study eye. 5. Pilocarpine or Vuity use within the last 24 hours in the study eye. 6. Dense media opacity precluding adequate visualization of the retina in the study eye. 7. Vitreous floaters that preclude obtaining acceptable scans in the study eye.
Performance endpoints	**Primary Performance Endpoints** 1. Sensitivity of PathFinder 1.0 using CIRRUS 5000 2. Specificity of PathFinder 1.0 using CIRRUS 5000 3. Sensitivity of PathFinder 1.0 using CIRRUS 6000 4. Specificity of PathFinder 1.0 using CIRRUS 6000 **Secondary Performance Endpoints** 1. Primary performance endpoints stratified by condition (determined by PI) 2. Primary performance endpoints stratified by macular abnormality type (determined by graders) 3. Positive Predictive Value (PPV) and Negative Predictive Value (NPV) 4. Rate of Acceptable/Unacceptable B-scans by Algorithm Acceptance Indicator 5. Rate of B-scans labeled Ungradable 6. Algorithm Precision (Repeatability) **Exploratory Endpoints** 1. Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-) 2. Agreement between CIRRUS 5000 and CIRRUS 6000 3. Angiography 6 mm x 6 mm scans

Visit Schedule	One visit will be required for the study, and it will last approximately 30 to 60 minutes.

3 Identification and description of the investigational device

Carl Zeiss Meditec, Inc. (CZMI) currently manufactures and distributes the CIRRUS High Definition Optical Coherence Tomography (HD-OCT), a spectral domain OCT (SD-OCT) instrument that uses a scanning beam of light called the superluminescent diode (SLD) to rapidly scan the eye. It is a non-contact, high resolution tomographic and biomicroscopic device that provides a detailed cross-sectional image of various structures of the eye such as the retina.

3.1 Model/type and manufacturer

Model / Type	CIRRUS HD-OCT Model 6000 acquisition with commercial software, and CIRRUS HD-OCT Model 5000 acquisition with commercial software; PathFinder 1.0 analysis will be performed on software version 11.X
Manufacturer	Carl Zeiss Meditec Inc. 5300 Central Parkway Dublin, CA 94568 USA

3.2 Intended purpose, subject population, and indications of the investigational device

The primary objective of this investigation is to assess the sensitivity and specificity of PathFinder 1.0, a deep learning-based, static Artificial Intelligence (AI) decision support tool that aids healthcare professionals in detecting Macular Cube OCT B-scans that have the presence or absence of retinal abnormalities within the macula. For this protocol, a retinal or macular “abnormality” describes a lesion type and/or retinal layers affected by the condition, whereas “condition” will describe a diagnosis type (ex. epiretinal membrane [ERM], dry age related macular degeneration [dAMD], etc). The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline).

PathFinder 1.0 is not used as a sole diagnostic tool, but as a diagnostic aid, and users are advised to still review all 128 B-scans in the macular cube in conjunction with PathFinder 1.0.[1,2]

The study population consist of two groups of subjects: subjects with absence of macular abnormalities and subjects with presence of macular abnormalities which include: disturbance of VRI, intraretinal hyporeflective space (IRHS), subretinal hyporeflective space (SRHS), IS/OS (Ellipsoid Zone) disruption, RPE elevation, RPE atrophy, and/or other abnormalities.

3.3 Description of the investigational device

The CIRRUS HD-OCT is a class II medical device that is a non-contact, high resolution tomographic and biomicroscopic device that provides a detailed cross-sectional image of various structures of the eye such as the retina. The CIRRUS HD-OCT has recently been updated to include CIRRUS PathFinder 1.0 that automatically detects B-scans with macular abnormalities. Study scans will be acquired on CIRRUS HD-OCT Model 6000 on a commercial software version and CIRRUS HD-OCT Model 5000 on a commercial software version. PathFinder 1.0 analysis on all qualified study scans will be performed on CIRRUS software version 11.X. The study measurements will not be part of the diagnostic assessment nor management plan of any enrolled subjects.

3.4 Specific procedures involved in the use of the investigational device

The following procedures will be done during the visit:

Table 1: Schedule of Procedures

Procedures:

- Obtain Informed Consent
- Issue Subject ID
- Subject Qualification and Demographic Information
- Review of Medical and Ophthalmic History
- Slit lamp exam which includes: anterior segment evaluation, Van Herick grading of the anterior chamber, and evaluation and grading of the crystalline lens
- Fundus photo acquisition (dilate if necessary)
- CIRRUS HD-OCT 6000 scanning (dilate if necessary)
    - Macular Cube 512x128

Procedures:
○ Angiography 6 mm x 6mm • CIRRUS HD-OCT 5000 scanning (dilate if necessary) ○ Macular Cube 512x128 ○ Angiography 6mm x 6mm • Study Exit

3.4.1 **Documentation**

1. Consent Documents
   a. The Principal Investigator's designee will review the following consent document with each subject (as applicable):
      i) Informed Consent Document
      i) HIPAA Consent
      ii) Experimental Subject's Bill of Rights
   b. The subject will sign the consent form if willing to proceed or decline any further participation if unwilling.
2. Subject ID
   a. The subject will be assigned an anonymous, unique alphanumeric identifier that is unrelated to the subject's name and sequentially assigned from a consecutive list of numbers. The subject ID will be used in all study documentation and for entering patient information into the instrument. The subject's name and corresponding identifier will be recorded in a study look-up document separate from the worksheet/ electronic case report form (eCRF) and shall be kept at the study site.
   b. Subject ID numbers of excluded subjects will not be re-assigned to other subjects.
3. Demographic information
   a. Demographic information will be collected from the subject and recorded on the worksheet/eCRF.
4. Ophthalmic History
   a. Ophthalmic history will be obtained from all subjects who sign the consent form to determine further participation in the study and will be recorded on the worksheet/eCRF.
5. Slit lamp exam which includes: anterior segment evaluation, Van Herick grading of the anterior chamber angle, and evaluation and grading of the crystalline lens will be recorded on the worksheet/eCRF
6. Fundus photo results will be recorded on the worksheet/eCRF
7. The PI or designee will record study eye designation, presence or absence of macular abnormalities on the worksheet/eCRF. If there are macular abnormalities present, the

diagnosis/diagnoses of the condition(s) also will be recorded on the eCRF (see Subject Qualification Scans)

8. Operator will record which scans were completed and reasons for OCT rescans, if needed, on the worksheet/eCRF

3.4.2 Subject Qualification Scans

The subject will be evaluated for ocular media opacities and imaged with a commercial fundus camera to verify the absence or presence of a macular abnormality within the central 6x6 mm macula area. For subjects with macular abnormalities, the diagnosis/diagnoses of the condition(s), and the location (OD or OS) will be recorded on the eCRF. For subjects without macular abnormalities, absence of macular abnormalities and the location (OD or OS) will be recorded on the eCRF. The PI or designee will obtain the all of this information from the exam record. Subjects with dense media opacity or vitreous floaters precluding adequate visualization of the retina will be excluded.

3.4.3 Study Eye Assignment (if both eyes qualify)

For Phase 1, if only one eye has presence of a macular abnormality, that eye with the macular abnormality will be used as the study eye. If both eyes qualify and have the same status (both with macular abnormalities or both without macular abnormalities), the eye will be selected at random. For Phase 2, if both eyes qualify, the eye with the macular abnormality/abnormalities which is most underrepresented from Group B categories at that point will be included.

3.4.4 Study Scans

- One acceptable scan of each scan type will be acquired on the CIRRUS 6000 device and the CIRRUS 5000 device for each subject. The scan types will include:
  - Macular Cube 512x128 scan
  - Angiography 6mm x 6mm scan
- The operator will review all 128 B-scans at the time of acquisition for acceptable quality.
- The order of devices on which subjects are imaged will be randomized.
- The subject may be dilated for proper visualization of the fundus photo or OCT scans

In a repeatability subcohort consisting of the 3 site types, (1 optometry, 1 general ophthalmology, and 1 retinal specialist site), 2 additional scans of each scan type (i.e. 3 x Macular Cube 512x128 scans and 3 x Angiography 6mm x 6mm scan) on each CIRRUS 6000 and CIRRUS 5000 will be

acquired until target enrollment for this subcohort is achieved. Target enrollment from this subcohort is a minimum of 30 subjects, maximum of 50 subjects from each of the 3 sites types (optometry, general ophthalmology, and retinal specialist). Combination sites will count toward both site types it consists of; for example, a site with both optometry and general ophthalmology will fulfill the optometry and general ophthalmology site type, and one additional retinal specialist site will be needed to fulfill the 3 site type requirement. Additional sites may be added to accomplish target enrollment. Although some of the above-mentioned imaging might be part of a routine eye exam, any imaging performed for this study is not meant to take the place of the subject's routine eye exam. If testing reveals any macular abnormalities not known previously, the subject will be informed of the findings and be advised to consult an ophthalmologist of their choice.

3.4.5 Scan Acquisition

These instructions are meant to supplement and not replace the instructions found in the instructions for use.[1,2]

Reference Fundus Image Acquisition
Fundus images will be acquired according to the instructions found in the device's user manual.

CIRRUS HD-OCT

1. On the patient information screen, enter the subject's unique identifier as the 'Patient ID' and enter the full date of birth and gender into the patient information screen at the visit. The subject will then be seated and given instructions on the scanning procedure.
2. Select the patient to be scanned, then select Acquire.
3. Select the scan type to be imaged.
4. For all scan types:
   a. Position the subject on the chinrest and ask him or her to fixate on the fixation target.
   b. Align the pupil in the center of the Iris Viewport and adjust the Chinrest distance until the iris is in focus.
   c. Use the Auto Focus, Optimize, Enhance, and Center functions as needed to properly prepare the B-scans for imaging.
   d. Select Capture to acquire the scan. The scan should be acquired with FasTrak tracking feature enabled if possible (Track to Prior may NOT be used).
5. Once the scan is captured, ask the patient to sit back and rest their eyes while scan quality is evaluated.
6. On the Scan Quality Check screen, assess the quality of the scan. See Appendix 1 for acceptance criteria including a signal strength of 7 or more.

7. When scans do not qualify, the reason and number of scans disqualified will be recorded.
8. For acceptable scans, select Save. For unacceptable scans, record the reason it is unacceptable and select Try Again. A maximum of 3 scan retries per scan type on each OCT device may be attempted. If an acceptable scan cannot be acquired, the scan will be excluded from analysis.
9. Artificial tears may be instilled prior to scan acquisition and is encouraged when en face images appear dim or blurry.
10. The patient may be dilated if needed to achieve acceptable image quality.

To reduce subject fatigue and/or corneal drying, subjects are allowed to take rest periods during the visit.

3.4.6 **Subject exit**

Subjects can exit the study with the following status options:

- For Macular Cube Scans:
  - Completed Macular Cube Scans- A subject who has met the Study's inclusion and exclusion criteria, successfully completed all required examinations, and for whom the operator has obtained the necessary number of acceptable Macular cube scans on all instruments.
  - Incomplete Macular Cube Scans - A Subject who has met the Study's inclusion and exclusion criteria but has either not completed all required examinations or was not able to obtain the a full set of acceptable Macular cube scans on all study instruments.

- For Angiography Scans:
  - Completed Angiography Scans- A subject who has met the Study's inclusion and exclusion criteria, successfully completed all required examinations, and for whom the operator has obtained the necessary number of acceptable Angiography scans on all instruments.
  - Incomplete Angiography Scans- A Subject who has met the Study's inclusion and exclusion criteria, but has either not completed all required examinations or the operator has not obtained the necessary number of acceptable Angiography scans on all instruments.

Or one of the following:

- Disqualified - defined as one who does not meet the study eligibility criteria.
- Discontinued - defined as a subject who exits the study by his or her own volition or at the discretion of the Principal Investigator and/or Carl Zeiss Meditec, Inc. Any subject may

decide to voluntarily withdraw from the study at any time without prejudice. The specific reason for discontinuation should be documented on the eCRF

3.5 Training and experience

All study personnel, including operators, will receive training regarding the study protocol. In addition, all operators will receive training similar to real-world clinical practice on the use of the CIRRUS 6000 and CIRRUS 5000 for scan acquisition. This training will take place prior to the enrollment of the first subject. Steps will be taken in the planning and implementation of this study to ensure that the data collected is accurate, consistent, complete, and reliable.

4 Risks and benefits of the investigational device and clinical investigation

4.1 Anticipated clinical benefits

PathFinder 1.0 is a deep learning based, static AI decision support tool that aids healthcare professionals in detecting Macular Cube OCT B-scans that have the presence or absence of retinal abnormalities within the macula. As the detection of abnormalities on OCT images by clinicians has shown to have a wide range of sensitivities (see section 7.4), PathFinder 1.0 will reduce variability among different providers, optometrists, general ophthalmologists, and retina specialists. Additionally, the PathFinder 1.0 algorithm was developed and is validated by the expert assessment of retinal specialists which may aid the non-specialist's analyses.

PathFinder 1.0 results are not meant to be utilized soley for diagnosis, but rather as an aid in the clinical assessment of macular conditions. Therefore, the major anticipated clinical benefit associated with PathFinder 1.0 is to assist optometrists and/or ophthalmologists in identifying B-scans with macular abnormalities, to reduce variability among eyecare providers in detecting abnormalities, and to standardize this assessment against the advanced medical expertise of retinal specialists by utilizing AI as an aid to analyze CIRRUS HD-OCT data.

4.2 Anticipated risks

There are neither anticipated risks nor adverse device effects associated with this clinical investigation.

4.2.1 Residual risks associated with the investigational device

No residual risks for the users are expected as subjects will not experience any invasive procedures.

4.2.2 Risks associated with participation in the clinical investigation

This clinical investigation poses no risk to the safety of the subject as there are no extra assessments required beside the slit lamp exam, CFP photos, and OCT scans. These are often performed as part of routine eye care.

Furthermore, the study poses no risk to confidentiality of the subjects as the data gathered with PathFinder 1.0 is not shared with the site staff or subject. The case management of the subjects therefore will not be influenced.

4.2.3 Possible interactions with concomitant medical treatments

There are no anticipated interactions with concomitant medical treatments.

4.2.4 Steps that will be taken to control or mitigate the risks

There are no risks anticipated with this specific clinical investigation that would require mitigation.

For general study risks, steps to ensure data privacy at each site include assignment of anonymized subject IDs and controlled access to PHI data (see section 9 Compliance and 11.2.1 General Responsibilities of investigators). Data sent to the sponsor will all be anonymized and with controlled access (see section 8.2.1 Study Worksheets and Case Report Forms and 8.2.5 Missing Data Handling).

4.3 Benefit/Risk rationale

Generally, the PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists . After approval, PathFinder 1.0 will be used in the routine practice of optometrists and ophthalmologists.

PathFinder 1.0 has no direct risk to subjects as the study procedures performed on the subjects are the same as what normally takes place in routine eye care. The main benefits of PathFinder 1.0 is its function to assist optometrists and/or ophthalmologists in identifying macular abnormalities, to reduce variability among eyecare providers in detecting abnormalities, and to standardize this assessment against the advanced medical expertise of retinal specialists. In summary, this clinical investigation has an acceptable benefit-risk ratio.

5 Objectives and hypothesis of the clinical investigation

The primary objective of this investigation is to assess the sensitivity and specificity of PathFinder 1.0, a deep learning based, static Artificial Intelligence (AI) decision support tool that aids healthcare professionals in detecting Macular Cube OCT B-scans that have the presence or absence of retinal abnormalities within the macula (see Section 6.3 Group B). The PathFinder 1.0 is fixed (static) and finalized in a market-ready format. The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline).

6 Design of the clinical investigation

6.1 General

6.1.1 Study Design

This is a prospective, two phase, multi-site study. The clinical investigation is established to assess the sensitivity and specificity of the PathFinder 1.0 algorithm, a decision support tool that detects the presence or absence of macular abnormalities within the macula. Every subject will be scanned on a CIRRUS 5000 and CIRRUS 6000 at every site, and both the CIRRUS 5000 and CIRRUS 6000 will be used for phase 1 and phase 2.

PathFinder 1.0 uses two different algorithms. The first algorithm is an Algorithm Acceptance Indicator (e.g. quality control algorithm) that differentiates between:

1. Acceptable B-scans which the second algorithm can assess
2. Unacceptable B-scans which the second algorithm is unable to assess.

The first algorithm is not used as an indication of whether or not a B-scan is clinically acceptable, but is a processing step to determine if the second algorithm can analyze the scan. The second algorithm uses only the acceptable B-scans as the input and then differentiates between the presence or absence of a macular abnormality in the B-scans as the binary output.

The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline).

Study sites may include optometry, general ophthalmology, and retina specialist clinics, optometry school clinics or ophthalmology departments of medical schools.

The Principal Investigator (PI) or designee will identify potential study subjects and invite them to volunteer in the study if they meet the eligibility/inclusion criteria for at least one of their eyes. The clinical investigation targets subjects 18 years or older. Qualified subjects will be consented prior to study enrollment. One visit will be required for the study and will last approximately 30 to 60 minutes depending on if the subject needs to be dilated. One eye per subject will be enrolled in the study. Subjects will undergo imaging with the Macular Cube 512x128 scan and Angiography 6 x 6 mm scan using both the CIRRUS 6000 and CIRRUS 5000 on the same day (see 6.1.1 Study Design). The Angiography 6 mm x 6 mm scans will be acquired for exploration of future algorithm development and will not be included in the PathFinder 1.0 performance analysis.

The subjects will be recruited in two phases. For Phase 1, the first dataset will be recruited that is separate from phase 2. Phase 1 will be a prospective, randomized, multi-site study. Subjects with presence or absence of macular abnormalities within the central 6x6 mm macula region will be randomly recruited at different geographic locations (see 6.4 Study Sites). Each site will recruit a minimum of 30 subjects for this phase. A minimum of 234 cummulative subjects will be recruited. Specifically, a minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities will be recruited. A target of 400 subjects will be enrolled to account for study dropout and disqualified scans. There will be a maximum of 20 subjects under 50 years old for subjects with absence of macular abnormalities.

Phase 2 will be a prospective, non-randomized, multi-site study (using the same study sites as Phase 1 but different subjects) and will start once the minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities are recruited. For Phase 2, a second dataset will be recruited that is separate from phase 1. Only subjects that meet inclusion criteria for Group B (presence of macular abnormalities) will be recruited. This study population will be enriched to ensure a minimum of 10% of the target subject population for each Group B category (described below) are enrolled, and no maximum will be placed for these categories. A maximum of 1000 subjects will be enrolled in this study.

The subject population will be comprised of two groups (all categories below pertain to the central 6 x6 mm macula area):

Group A

1. Subjects with absence of macular abnormalities

Group B

1. Subjects with Disruption of the vitreoretinal interface (VRI)
2. Subjects with Intraretinal hyporeflective space (IRHS)
3. Subjects with Subretinal hyporeflective space (SRHS)

4. Subjects with IS/OS (Ellipsoid Zone) disruption
5. Subjects with Retinal Pigment Epithelium (RPE) elevation
6. Subjects with Retinal Pigment Epithelium (RPE) atrophy
7. Other abnormalities

The PI will record “macular abnormalities absent” or “macular abnormalities present”. If there are macular abnormalities present, the diagnosis/diagnoses of the conditions will also be recorded. These conditions can include: non-proliferative diabetic retinopathy (NPDR) with or without macular edema (ME), proliferative diabetic retinopathy (PDR) with or without ME, dry age related macular degeneration (dAMD), neovascular age related macular degeneration (nAMD), branch or central retinal vein occlusion (BRVO or CRVO) with or without ME, central serous chorioretinopathy (CSCR), macular hole (MH), epiretinal membrane (ERM), and/or other conditions that affect the central 6x6 mm macula area. If “Other” (category B7) is selected, the PI will list the diagnosis (diagnosis should be written out and not in acronym form). If a sole diagnosis cannot be determined (differential diagnosis should not be listed), “N/A” should be recorded in the diagnosis section and 1) lesion type description i.e hyporeflective or hyperreflective lesion(s) 2) description of retinal layer(s) affected by the lesion(s) and/or condition(s) should also be recorded.

Inclusion and Exclusion criteria

General Inclusion Criteria:

1. Able and willing to make the required study visits.
2. Able and willing to give written informed consent and follow study instructions.
3. Able and willing to complete ophthalmic imaging.
4. Adults 18 years of age or older.

The subject population will be comprised of two groups (all categories below pertain to the central 6 x6 mm macula area):

Group A

1. Subjects with absence of macular abnormalities

Group B

1. Subjects with Disruption of the vitreoretinal interface (VRI)
2. Subjects with Intraretinal hyporeflective space (IRHS)
3. Subjects with Subretinal hyporeflective space (SRHS)
4. Subjects with IS/OS (Ellipsoid Zone) disruption
5. Subjects with Retinal Pigment Epithelium (RPE) elevation
6. Subjects with Retinal Pigment Epithelium (RPE) atrophy

7. Other abnormalities

General Exclusion Criteria:

1. Inability to undergo the required tests.
2. Unable to give consent or follow study instructions.
3. Inability to fixate that precludes obtaining acceptable macula scans in the study eye.
4. Visudyne (verteporfin) injection within the last 48 hours in the study eye.
5. Pilocarpine or Vuity use within the last 24 hours in the study eye.
6. Dense media opacity precluding adequate visualization of the retina in the study eye.
7. Vitreous floaters that preclude obtaining acceptable scans in the study eye.

Primary Performance Endpoints

1. Sensitivity of PathFinder 1.0 using CIRRUS 5000
2. Specificity of PathFinder 1.0 using CIRRUS 5000
3. Sensitivity of PathFinder 1.0 using CIRRUS 6000
4. Specificity of PathFinder 1.0 using CIRRUS 6000

Secondary Performance Endpoints

1. Primary performance endpoints stratified by condition (determined by PI)
2. Primary performance endpoints stratified by macular abnormality type (determined by graders)
3. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)
4. Rate of Acceptable/Unacceptable B-scans by Algorithm Acceptance Indicator
5. Rates of B-scans labeled Ungradable
6. Algorithm Precision (Repeatability)

Exploratory Endpoints

1. Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-)
2. Agreement between CIRRUS 5000 and CIRRUS 6000
3. Angiography 6 mm x 6 mm scans

6.2 Investigational device, comparator, and equipment

6.2.1 Investigational device

Details on the investigational device and necessary training requirements are provided in Section 3.5 of this Clinical Investigation Plan (CIP).

6.2.2 Comparator (control) arm

The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline). No other device as comparator is used in this investigation.

6.2.3 Equipment and/or calibration

The only equipment required for this clinical investigation is the CIRRUS 5000, the CIRRUS 6000, any commercial color fundus camera that covers a 12x12 mm area over the fovea, and any slit lamp. CIRRUS 5000 and 6000 will be used for both phases of the study.

The technicians and investigators should be familiar with the instructions for use (IFU) for these instruments before using it on the subject. The maintenance and (if applicable, calibration) of the equipment shall be performed as required by the IFU.

CIRRUS HD-OCT
The CIRRUS HD-OCT is a spectral-domain OCT (SD-OCT) that is a non-contact, high resolution tomographic and biomicroscopic device that provides a detailed cross-sectional image of various structures of the eye such as the retina and the cornea. CIRRUS HD-OCT Model 6000 with commercial software and Model 5000 with commercial software will be used for data acquisition.

Color Fundus Camera
The color fundus camera used should cover the 12x12 mm area over the fovea.

Slit Lamp
The slip lamp used should be a conventional slit lamp biomicroscope that is intended for use in routine eye care. The slit lamp allows for evaluation of the anterior segment, the lens, the vitreous, and the posterior segment, including the retina and optic nerve head.

6.3 Subjects

The subjects will be recruited in two phases. For Phase 1, the first dataset will be recruited that is separate from phase 2. Phase 1 will be a prospective, randomized, multi-site study. Subjects with presence or absence of macular abnormalities within the central 6x6 mm macula region will be randomly recruited at different geographic locations (see 6.4 Study Sites). Each site will recruit a minimum of 30 subjects for this phase. A minimum of 234 cumulative subjects will be recruited. Specifically, a minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities will be recruited. A target of 400 subjects will be

enrolled to account for study dropout and disqualified scans. There will be a maximum of 20 subjects under 50 years old for subjects with absence of macular abnormalities.

Phase 2 will be a prospective, non-randomized, multi-site study (using the same study sites as Phase 1 but different subjects) and will start once the minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities are recruited. For Phase 2, a second dataset will be recruited that is separate from phase 1. Only subjects that meet inclusion criteria for Group B (presence of macular abnormalities) will be recruited. This study population will be enriched to ensure a minimum of 10% of the target subject population (400 subjects) for each Group B category (described below) are enrolled, and no maximum will be placed for these categories. A maximum of 1000 subjects will be enrolled in this study.

The subject population will be comprised of two groups (all categories below pertain to the central 6x6 mm macula area):

Group A

1. Subjects with absence of macular abnormalities

Group B

1. Subjects with Disruption of the vitreoretinal interface (VRI)
2. Subjects with Intraretinal hyporeflective space (IRHS)
3. Subjects with Subretinal hyporeflective space (SRHS)
4. Subjects with IS/OS (Ellipsoid Zone) disruption
5. Subjects with Retinal Pigment Epithelium (RPE) elevation
6. Subjects with Retinal Pigment Epithelium (RPE) atrophy
7. Other abnormalities

6.3.1 Subject entry

Subject Recruitment and Screening

Subjects will be recruited from the participating investigational sites. Participation in the study is strictly voluntary.

Subject Enrollment

If the volunteer is willing to participate in the study, the PI or their designee will discuss the study and procedures using the informed consent documentation as a basis for discussion. Any questions the volunteer may have will be answered. The nature of the study will be explained to each subject.

The purpose of the study, the procedures involved, the expected duration, the potential risks/benefits, and any discomfort it might entail will be explained to the subject. Each subject will be informed that participation in the study is voluntary and that he/she can withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject can take the document home to review and discuss with family, if desired. The subject will be enrolled in the study once he/she has signed the consent documents.

Phase 1

Participating optometry and ophthalmology sites will randomly select potentially interested subjects who present for routine eye examination, triage exam, or a follow up for a condition. A minimum of 234 cummulative subjects will be recruited. Specifically, a minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities will be recruited. A target of 400 subjects will be enrolled to account for study dropout and disqualified scans. There will be a maximum of 20 subjects under 50 years old for subjects with absence of macular abnormalities.

Phase 2

At the conclusion of Phase 1 of the investigation, a distribution overview of Group B's abnormality types confirmed by the independent graders will be generated. The distribution overview will be used to determine the number of additional subjects needed for phase 2 of the study. Phase 2 will be conducted at the same sites as phase 1.

Participating optometry and ophthalmology sites will select potentially interested. Phase 2 will only enroll subjects with presence of macular abnormalities. This study population will be enriched to ensure a minimum of 10% of the target subject population for each of the Group B categories are enrolled, and no maximum will be placed for these categories. Subjects with multiple categories of macular abnormalities will count for each of the target macular abnormality categories that are present in the suject's scan. A maximum of 1000 subjects will be enrolled in this study.

Subject ID and Demographic Information

After the subject signs the informed consent form (ICF), the subject is assigned a unique subject ID. A routine OCT procedure is performed using the CIRRUS 5000 and CIRRUS 6000. During the OCT procedure, the investigator ensures that no personal data (name and address,) are recorded in the associated OCT file (DICOM file) and that the subject study ID is used instead for subject pseudonymization.

In the eCRF, data will be captured regarding demographic information (age, sex, ethnicity, birthdate) of the subject, date, and eye of the OCT image.

The PI will record the diagnosis of no retinal disease or the retinal disease diagnosis and the location (OD or OS) on the CRF.

Selection of the primary analysis eye

Only one eye per subject will be selected for the primary analysis, according to the following processes:

For Phase 1, if only one eye has presence of a macular abnormality, that eye with the macular abnormality will be used as the study eye. If both eyes qualify and have the same status (both with macular abnormalities or both without macular abnormalities), the eye will be selected at random.

Phase 1

1. If only one eye fulfills the eligibility criteria, then that eye will be automatically designated as the primary analysis eye.
2. If both eyes fulfill the eligibility criteria and only one eye has presence of a macular abnormality, that eye with the macular abnormality will be used as the study eye.
3. If both eyes qualify and have the same status (both with macular abnormalities or both without macular abnormalities), the primary analysis eye is randomly selected based upon subject ID.
   - OD (right eye) will be the primary analysis eye if the Subject ID is an odd number
   - OS (left eye) will be the primary analysis eye if the Subject ID is an even number

Phase 2

1. If only one eye fulfills the eligibility criteria, then that eye will be automatically designated as the primary analysis eye.
2. If both eyes fulfill the eligibility criteria, the primary analysis eye is selected based on the eye with the macular condition that is least represented in the study subject population at that point in time. If macular conditions of both eyes are equally represented, the primary analysis eye is randomly selected based upon subject ID.
   - OD (right eye) will be the primary analysis eye if the Subject ID is an odd number
   - OS (left eye) will be the primary analysis eye if the Subject ID is in an even number

An overview of the current distribution of images across the seven abnormality types will be generated regularly to determine the recruitment requirements needed for the abnormality types.

If the subject is in the repeatability subcohort, the first qualified scan acquired will be used for the primary analysis.

Concomitant Medications and use of Contact Lenses

Subjects using pilocarpine or Vuity may yield poor image quality results. If the subject is taking pilocarpine for a medically necessary condition, the subject should continue taking the medication.

If the subject is taking Vuity, the medication should be discontinued for at least 24 hours prior to the study visit. The subject may be disqualified from the study if the images are poor due to the size of the pupil in this case. Subjects enrolled in the study should continue use of any other medications that they are taking.

The subjects may be a contact lens wearer, but contact lenses must be removed at least immediately prior to data collection during the study visit.

6.3.2 Clinical Investigation duration and visit windows

Each subject will undergo one study visit. The expected duration of each subject's visit is 30-60 minutes. The study will continue until Phase 1 and Phase 2 have been completed. The total expected duration of the clinical investigation is 12 months.

6.3.3 Subject exit

See Section 3.4.6.

6.3.4 Subject Compensation

The subjects will be compensated for enrollment and participation in the study based on the amount of compensation listed in the Informed Consent Form.

6.4 Study Sites

At least six sites will participate in patient recruitment, informed consent, and data collection. Minimum subject enrollment will be 30 subjects per site. The clinical sites will be chosen to cover the intended subject population and represent diverse geographic locations in the USA. The clinical trial sites will be independent and separate from the sites whose data was used for PathFinder 1.0 algorithm development (training and tuning/validation).

Study sites that were used for PathFinder 1.0 algorithm hold-out test set (which was used for internal testing only, not algorithm development) data collection will ensure that there will be no subject overlap between the subjects used in the hold-out test set and this pivotal trial study (Assessment of PathFinder 1.0 on the CIRRUS 6000 and the CIRRUS 5000). At these sites, the date of birth of potential subjects for this study will be compared to those of subjects included in the hold-out test set, potential subjects with the same exact date of birth to subjects from the hold-out test set will not be enrolled in this study.

Study sites may include optometry, general ophthalmology, and retina specialist clinics, optometry schools, ophthalmology medical schools or may be a combination (e.g. optometry and general ophthlamology, etc.). The same study sites will be used for Phase 1 and Phase 2. The range in practice types/specialties and geographic locations will achieve recruitment of subjects with a spectrum of lesions (Group B categories) that are generalizable to the intended use population.

6.5 Clinical investigation-related procedures

The duration of the investigation for each subject is expected to be 1 day and will last approximately 30 to 60 minutes (from signed ICF until subject exit).

6.5.1 Assessor masking

Independent Grader Review

The PathFinder 1.0 algorithm will be compared to a ground truth reference assessment that will be performed by three retinal specialists (see Annotation Guideline).

6.6 Monitoring

Carl Zeiss Meditec Clinical personnel will monitor all clinical investigations in a manner consistent with any applicable health authority regulations and the clinical research standards adopted by Carl Zeiss Meditec's Clinical Department.

6.7 End of clinical investigation

The study is completed when a minimum of 400 completed and qualified Macular 512x128 OCT scans are acquired. This data set will be comprised of a minimum of 55 subjects with absence of macular abnormalities and a minimum of 179 subjects with presence of macular abnormalities . A minimum enrollment of 10% of the target subject population for each of the Group B categories is also required (see Section 6.1.1) .

7 Statistical considerations

7.1 General Considerations

All quantitative study assessments will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All qualitative study assessments will be summarized by using frequency counts and percentages.

7.2 Unit of analysis

The unit of analysis in this study will be B-scans measured on the primary analysis eye.

7.3 Performance variables

The Primary performance variable will be the presence or absence (binary) of macular abnormalities within each B-scan ("presence"/"absence"). Presence of macular abnormalities will be considered the "positive" outcome for this study; absence of macular abnormalities will be considered the "negative" outcome.

7.4 Statistical hypotheses

1. Sensitivity of PathFinder 1.0 using CIRRUS 5000
- H_0: $p_{sens} = 0.80$ vs. H_1: $p_{sens} > 0.80$
2. Specificity of PathFinder 1.0 using CIRRUS 5000
- H_0: $p_{spec} = 0.80$ vs. H_1: $p_{spec} > 0.80$
3. Sensitivity of PathFinder 1.0 using CIRRUS 6000
- H_0: $p_{sens} = 0.80$ vs. H_1: $p_{sens} > 0.80$
4. Specificity of PathFinder 1.0 using CIRRUS 6000
- H_0: $p_{spec} = 0.80$ vs. H_1: $p_{spec} > 0.80$

Where p_{sens} and p_{spec} denote the sensitivity (to detect presence) and specificity (to detect absence) of the respective device. CIRRUS 5000 and CIRRUS 6000 data will be summarized and analyzed separately.

In literature, the agreement of human graders to detect key OCT morphological features (including intraretinal fluid, subretinal fluid, pigment epithelial detachments [PEDs], vitreomacular interface conditions) varied from fair to reproducible, with kappa coefficients of 0.37 to 0.85 for ERM and subretinal fluid, respectively. In another study, the intergrader variability for independent retinal

specialists to identify OCT features such as ellipsoid zone loss, intraretinal fluid, drusen, PEDs, RPE loss, subretinal fluid, resulted in a wide range of kappa coefficients of 0.160 to 0.823 for RPE loss and subretinal fluid, respectively.[4,5]

In performance studies, the evaluation of retinal specialists in detecting the presence of retinal fluid (both intraretinal and subretinal fluid) from OCT scans relative to ground truth, resulted in sensitivity of 0.468 and specificity of 0.970.[6] Additionally, the performance of clinicians in determining various PED retinal abnormalities on OCT was reported to be a wide range of sensitivity: 0.11-1.00 and specificity: 0.32 - 0.89.[7]

The target performance of PathFinder was selected as 80% sensitivity and 80% specificity to reduce intergrader variability and as a clinically reasonable performance value within the range of the advanced medical expertise of retinal specialists to standardize against. Furthermore, the sensitivity and specificity values for the null hypotheses were constructed by taking into account that the PathFinder 1.0 tool is not intended to be used as a sole diagnostic tool, but it is intended to be used by the clinician in conjunction with a review of all 128 macular B-scans and other data from the clinical examination in determining the diagnosis.

There are no statistical hypotheses for secondary or exploratory endpoints.

7.5 Multiplicity Considerations

All primary endpoints will be evaluated using a one-sided alpha of 0.025. Multiplicity adjustments are not needed as all four primary endpoints must be met for the study to be successful.

7.6 Sample size calculation

A total sample size of at least 234 subjects (which includes 179 subjects with presence of macular abnormalities and 55 subjects with absence of macular abnormalities) in the Prospective Analysis Set (PAS) is required to achieve 80% power to reject the sensitivity null hypothesis using a one-sided binomial test with an alpha of 0.025, assuming a true sensitivity of 0.878, and 80% power to reject the specificity null hypothesis using a one-sided binomial test with an alpha of 0.025, assuming a true specificity of 0.929 per the CIRRUS ATR Unit Algorithm Test Report B-scan of interest (P/N 0000043426-01).

While the accuracy of the PathFinder 1.0 tool is evaluated using individual B-scans, the sample size above is calculated using a hypothetical subject-level assessment. This is to account for intra-subject

correlation between B-scans, and to achieve a sample size for the PAS that may be considered representative of the subject population.

7.7 Analysis population

- The Full Analysis Set (FAS) will include all subjects scanned from Phase 1 and Phase 2.
- The Prospective Analysis Set (PAS) includes all subjects scanned during Phase 1. Eyes with presence or absence of macular abnormalities will be scanned.
- The Enriched Analysis Set (EAS) includes all subjects scanned during Phase 2. Only eyes with presence of macular abnormalities will be scanned.

The subjects do not have to complete all scans for CIRRUS 6000 and CIRRUS 5000 to be included in any of these populations. For the FAS, PAS, and the EAS, all of the following criteria must be met:

1. At least one qualified Macular cube scan must be acquired
2. Signal strength (SS) must be 7 or higher.

7.8 Subject disposition

Study conduct summaries including subject disposition and scan (cube) accountability will be summarized for the FAS, PAS and EAS. Additionally, a subject listing will be provided for protocol deviations which will include the date of the deviation and the deviation description.

7.9 Subject demographics and baseline characteristics

Demographics such as sex, age, race, and ethnicity will be summarized descriptively. Baseline variables such as condition (determined by PI) will also be summarized.

7.10 Safety analysis

Any adverse events, adverse device effects and device deficiencies that may occur in this investigation will be summarized (see section 12).

7.11 Performance analyses

Each subject with qualified scans will have only one of each scan type per device included in the Primary analysis.

Each subject that is part of the repeatability subcohort will have three scans of each scan type per device acquired. The first scan saved of each scan type per device will be included in the Primary analysis.

7.11.1 Primary performance analysis

The Primary Performance Endpoints are as follows:

1. Sensitivity of PathFinder 1.0 using CIRRUS 5000
2. Specificity of PathFinder 1.0 using CIRRUS 5000
3. Sensitivity of PathFinder 1.0 using CIRRUS 6000
4. Specificity of PathFinder 1.0 using CIRRUS 6000

As sensitivity and specificity are not dependent on condition prevalence, the primary analysis will be conducted on the FAS using gradable B-scans, i.e. B-scans for which ground truth is available, and acceptable B-scans per the Algorithm Acceptance Indicator.

Sensitivity and specificity will be calculated using B-scan as the unit of analysis using the following formulas:

$$\text{Sensitivity} = \frac{\#\text{ of positive scans graded as having any abnormality}}{\#\text{ of scans graded as having any abnormality}}$$

$$\text{Specificity} = \frac{\#\text{ of negative scans graded as having absence of abnormality}}{\#\text{ of scans graded as having absence of abnormality}}$$

For sensitivity, the numerator corresponds to PathFinder 1.0's true positive (i.e. presence) results and the denominator corresponds to the retinal specialists' ground truth positive results. For specificity, the numerator corresponds to PathFinder 1.0's true negative (i.e. absence) results and the denominator corresponds to the retinal specialists' true negative results. Note that these point estimates of sensitivity and specificity do not depend on intra-subject correlation between B-scans.[9]

As within-eye B-scan results are expected to be spatially correlated, the primary analysis of the primary endpoints will be conducted using clustered bootstrapping, randomly sampling entire subjects with replacement. B=10000 bootstrapped samples of the same size as the actual sample size will be taken using the FAS.[7] The randomized sample selection will be conducted using a starting seed of 797683.

For each bootstrapped sample, the overall sensitivity and specificity point estimates will be calculated using the formulae above. 95% confidence intervals will be estimated using the 2.5th percentile and 97.5th percentile of the corresponding 10000 results. Should the lower bound of the 95% confidence interval exceed the null hypothesis value for a particular primary endpoint, then the result for that endpoint will be concluded to be statistically significant and that endpoint will be successful.

7.11.1.1 Sensitivity analysis

In the event of the presence of B-scans that are either ungradable or indicated as unacceptable to the algorithm and therefore, not analyzable by Pathfinder, the B-scans will be imputed using each of the following methods:

1. (Worst Case)
   - For B-scans that are gradable but not analyzable by Pathfinder, the missing Pathfinder values will be assigned the opposite designation from the graders. That is, if a B-scan is graded as positive, then the missing value from Pathfinder will be assigned to negative; if a B-scan is graded as negative, then the missing value will be assigned to positve.

   - For B-scans that are analyzable by Pathfinder but not gradable, the missing grader values will be assigned the opposite designation from Pathfinder.

   - In the event of scans that are both ungradable and not analyzable by Pathfinder, the Sensitivity endpoints will be imputed as grade=positive and Pathfinder=negative. Similarly, the Specificity endpoints will be imputed as grade=negative and Pathfinder=positive.

2. (Best Case)
   - For B-scans that are gradable but not analyzable by Pathfinder, the missing Pathfinder values will be assigned the same designation from the graders. That is, if a B-scan is graded as positive

then the missing value from Pathfinder will be assigned positive; if a B-scan is graded as negative then the missing value will be assigned to negative

- For B-scans that are analyzable by Pathfinder but not gradable, the missing grader values will be assigned the same designation from Pathfinder.

- In the event of scans that are both ungradable and not analyzable by Pathfinder, the Sensitivity endpoints will be imputed as grade=positive and Pathfinder=positive. Similarly, the Specificity endpoints will be imputed as grade=negative and Pathfinder=negative.

The primary performance endpoints will then be re-evaluated each of these imputation methods. The results between the available data (Primary analysis) and the available data with imputation (Sensitivity analysis) will be compared.

7.11.2 Secondary performance analyses

Unless otherwise specified, analyses of the secondary endpoints will be stratified by device.

Secondary Performance Endpoints

1. Primary performance endpoints stratified by condition (determined by PI)
2. Primary performance endpoints stratified by macular abnormality type (determined by graders)
3. Positive Predictive Value (PPV) and Negative Predictive Value (NPV)
4. Rate of Acceptable/Unacceptable B-scans by Algorithm Acceptance Indicator
5. Rate of B-scans labeled Ungradable
6. Algorithm Precision (Repeatability)

7.11.2.1 Primary performance endpoints stratified by condition

Using the FAS, the sensitivity and specificity of the PathFinder 1.0 tool for each device will be summarized descriptively for subjects with the following conditions based on the PI diagnosis/diagnoses, e.g. NPDR with ME, NPDR without ME, PDR with ME, PDR without ME, dAMD, nAMD, BRVO or CRVO with ME, BRVO or CRVO without ME, CSCR, MH, ERM, and Other macular abnormalities. While there are no statistical hypotheses for this endpoint, 95% bootstrapped confidence intervals for sensitivity will be calculated using the methods described in the primary endpoint analysis.

7.11.2.2 Primary performance endpoints stratified by macular abnormality

Using the FAS, the sensitivity of the PathFinder 1.0 tool for each device will be summarized descriptively for B-scans with the following: disturbance of VRI, intraretinal hyporeflective space, subretinal hyporeflective space, IS/OS (Ellipsoid Zone) disruption, RPE elevation, RPE atrophy, and ther abnormalities. This will be based on the grader labeling. While there are no statistical hypotheses for this endpoint, 95% bootstrapped confidence intervals for sensitivity will be calculated using the methods described in the primary endpoint analysis.

7.11.2.3 Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

The following formulas will be used to calculate point estimates of PPV and NPV:

$$\text{PPV} = \frac{\#\text{ of positive scans graded as having any abnormality}}{\#\text{ of positive scans}}$$

$$\text{NPV} = \frac{\#\text{ of negative scans graded as having absence of abnormality}}{\#\text{ of negative scans}}$$

For PPV, the numerator corresponds to PathFinder 1.0 true positive results and the denominator corresponds to the PathFinder 1.0 sum of true positive and false positive results. For NPV, the numerator corresponds to PathFinder 1.0 true negative results and the denominator corresponds to the PathFinder 1.0 sum of true negatives and false negative results.

As PPV and NPV are dependent on condition prevalence, the PAS will be used for this endpoint. PPV and NPV will be summarized descriptively, including 95% bootstrapped confidence intervals using the same bootstrapped samples from the primary analysis.

The analysis of PPV and NPV above will be repeated on the FAS.

7.11.2.4 Rate of Acceptable/Unacceptable B-scans by Algorithm Acceptance Indicator

B-scan algorithm acceptance (“acceptable” or “unacceptable”) is analyzed as part of the PathFinder 1.0 tool. Overall B-scan rate of algorithm acceptance will be summarized using the FAS. Subjects with a

Macular Cube scan with 13 or more (>10%) unacceptable B-scans will be listed in a table with the number of unacceptable B-scans for each Macular Cube.

The percentage of unacceptable B-scans within cube will be summarized in a histogram for all cubes (all eyes pooled) for each device.

7.11.2.5 Rate of B-scans Labeled Ungradable

B-scans that are found to be ungradable by two or more graders will be summarized using the FAS. Subjects with a Macular Cube scan with 13 or more (>10%) ungradable B-scan images will be listed in a table with the number of ungradable B-scans for each Macular Cube.

The percentage of ungradable B-scans within cube will be summarized in a histogram for all cubes (all eyes pooled) for each device.

7.11.2.6 Algorithm precision (Repeatability)

To evaluate the repeatability of the Pathfinder algorithm, the proportion of abnormal B-scans (# Abnormal / # B-Scans) with each macular cube by subject will be analyzed. Only scans rated as acceptable by the algorithm acceptance indicator will be used for this analysis. Only eyes with at least two macular cube scans on the same device will be included.

Repeatability will be summarized by device using a generalized linear mixed model with a logit link function and subject as a random effect, defined as follows:

$$Y_{ij} \sim overdispersed\ binomial(m_{ij}, p_{ij}, \omega),$$
$$p_{ij} = logit^{-1}(\beta_0 + \alpha_i)$$
$$\alpha_i \sim N(0, \sigma_\alpha^2)$$

Where Y_{ij} is the number of abnormal B-scans in macular cube *j* from subject *i*, m_{ij} is the total number acceptable scans in said macular cube, p_{ij} is the latent probability of abnormality for a B-scan from macular cube *j* from subject *i*, β_0 is the intercept on the latent scale, α_i is the (random) subject effect with a variance of σ_α^2 and an overdispersion parameter of ω.

Repeatability will be derived from this model using methods presented in Nakagawa & Schielzeth[18], where latent-scale repeatability is defined as

$$R_{logit} = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \omega \cdot (\pi^2/3)}$$

which may be interpreted as an intraclass correlation coefficient (ICC). The repeatability statistic and 95% confidence interval (calculated using parametric bootstrapping) will be presented.

As measures of repeatability are generally dependent on inter-subject variation, it is expected that repeatability measures for eyes without abnormalities would be low. Consequently, subjects will be stratified by condition (abnormalities present; abnormalities absent) for this analysis.

7.11.3 **Exploratory analyses**

Exploratory Endpoints

1. Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-)
2. Agreement between CIRRUS 5000 and CIRRUS 6000
3. Angiography 6 mm x 6 mm scans

7.11.3.1 **Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-)**

The following formulas will be used to calculate point estimates of LR+ and LR-.

$$\text{LR}+ = \frac{\text{Sensitivity}}{1 - \text{Specificity}}$$

$$\text{LR}- = \frac{\text{Specificity}}{1 - \text{Sensitivity}}$$

These values will be summarized descriptively for the PAS by device, including 95% bootstrapped confidence intervals using the same bootstrapped samples from the primary analysis. ROC curves for each device will also be presented.

7.11.3.2 **Agreement between CIRRUS 5000 and CIRRUS 6000**

The same subjects will be scanned with both a CIRRUS 5000 and CIRRUS 6000 device. Since individual B-scan numbers do not align between devices, agreement between the devices will be defined at the eye

level. CIRRUS 5000 and CIRRUS 6000 within-eye sensitivity with be visualized on a scatter plot, including Spearman correlation, to assess the agreement between devices. The same analysis will be conducted for specificity. The analysis will be performed using the FAS.

7.11.3.3 Angiography 6 mm x 6 mm scans

The Angiography 6 mm x 6 mm scans will be acquired for exploration of future algorithm development and will not be included in the PathFinder 1.0 performance analysis.

7.12 Poolability and subgroup analyses

Consistency of the primary performance endpoints across sites will be evaluated through summaries of each of the primary performance endpoints by site.

Consistency of the primary performance endpoints across demographic variables will be evaluated through summaries of each of the primary performance endpoints by sex, age group, race and ethnicity.

7.13 Grader Agreement

In order to evaluate the inter-grader difference with grading the B-scans, the number and percent of B-scans with the same grade for all three graders along with the corresponding 95% binomial distribution confidence interval will be calculated. Additionally, the number and percent of B-scans with the same grade for at least two graders will be calculated. 2x2 tables comparing the agreement between each pair of graders (of the three) will be presented. The analysis will be performed using the FAS. (see Annotation guideline)

8 Data management

8.1 Ownership of the data

All the data or results from this study are the property of Carl Zeiss Meditec, Inc.

8.2 Data reporting

The OCT cube scan can be disqualified due to the image quality during data qualification. The criteria for evaluating the OCT cube image quality (see Appendix 1) and selection of the proper scan images for data analyses will be established prior to database lock. Scans that meet the criteria will be included in analysis and the scans that do not meet the quality criteria will be excluded. The entire study population will include those subjects whose CIRRUS HD-OCT scans meet the criteria for acceptable image quality. The reasons for excluding screened subjects or images will be documented and summarized.

8.2.1 Study Worksheets and Case Report Forms

All study data will be completed on source documents, e.g., worksheets and/or Electronic case report form (eCRF). Information required by the protocol will be collected and entered on case report forms (eCRF) for all subjects. All study worksheets will be completed in an electronic data capture system compliant with 21 CFR Part 11, ISO 9001, GDPR, and HIPAA regulations.

During the study, the quality of the data will be monitored by the study monitor who will check the eCRFs against the site's source documents, for completeness and to ensure that data is collected in adherence to the protocol. Errors will be brought to the attention of site personnel for correction.

8.2.2 Device Image Data

Electronic data will be generated by the CIRRUS 6000, CIRRUS 5000, and fundus imager. Image data files from these devices will be copied onto transferable media and evaluated using appropriate OCT acceptance criteria. See Appendix 1 for acceptance criteria for OCT data.

8.2.3 Manually Corrected Errors

Manual corrections will not be made to the OCT data.

8.2.4 Data Management and Quality Control

A clinical study database will be generated by the sponsor and/or by their representative to record all clinical data. Deviations, discrepancies, and missing data will be investigated and resolved with the study site. After all protocol deviations and/or discrepancies are resolved and all corrections and clarifications are made to the database, the database will be declared complete and accurate.

Selection of the acceptable subjects/scans for data analyses will be established prior to the database lock. Data may be disqualified if it does not meet pre-determined quality criteria (Appendix 1). A discussion of any outliers, modifications, and reasons for excluding subjects or data will be documented and summarized in the clinical investigation report (CIR).

Carl Zeiss Meditec, Inc. anticipates future development of new features. The data collected in this study may be used in future studies/analyses.

8.2.5 Missing data handling

Any missing, unused, or spurious data will be noted in the study records. Data may be excluded if it does not meet pre-determined quality criteria. Any data excluded after the study visit by the sponsor will be noted.

8.2.6 Subject Disposition

The number of subjects, eyes enrolled, and screen failed and the reasons for screen failure will be summarized. The number of discontinued subjects will also be provided.

8.3 Clinical investigational report

The sponsor, with contribution from the coordinating investigators, is responsible for preparing the report.

9 Compliance

The study must be carried out in compliance with the protocol. The clinical sites must comply with:
1. Code of Federal Regulations, Title 21, Parts 50, 56, and 812.
2. Good Clinical Practices Guidelines
3. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (adopted in Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, and Edinburgh 2000).

The Investigator agrees, when signing the CIP, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP/ISO14155 to which it conforms.

9.1 Abbreviated Investigational Device Exemptions (IDE)

Both the Investigator and the Sponsor agree to conduct the research in compliance with the Sponsor and Investigator regulations in 21 CFR 812.2 as applicable and 50 & 56.

21 CFR 812.2(b) states:

"*Abbreviated requirements*. The following categories of investigations are considered to have approved applications for IDE's, unless FDA has notified a sponsor under section 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

i. Labels the device in accordance with section 812.5;
ii. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
iii. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under section 56.109(c).
iv. Complies with the requirements of section 812.46 with respect to monitoring investigations;
v. Maintains the records required under section 812.140(b) (4) and (5) and makes the reports required under section 812.150(b) (1) through (3) and (5) through (10);
vi. Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under section 812.150(a) (1), (2), (5), and (7); and
vii. Complies with the prohibitions in section 812.7 against promotion and other practices."

9.2 Amendments to the clinical investigation plan

No changes to the protocol are permitted without the prior written approval of the Sponsor. Proposed amendments to the CIP will be agreed upon between the sponsor and principal investigators. The amendments to the CIP and the subject's informed consent form will be approved by the regulatory authorities. Only after approval or notification by the regulating authorities, the new version shall be distributed to each investigational site and implemented in the study.

9.3 Deviations from the clinical investigation plan

The Institutional Review Board (IRB) will be informed of all protocol changes by the sponsor or the investigator in accordance with applicable regulations and the IRB's established procedures. The Investigators will not deviate from the protocol without written approval from the IRB and the sponsor.

In medical emergencies, the Investigator will use their judgement and remove the subject from immediate hazard. Any significant changes or deviations in the protocol will be the subject of a protocol amendment and must be pre-approved by IRB.

If an unexpected deviation from the protocol occurs, the Investigator must notify the sponsor and the deviation from the protocol will be documented and resolved on a Protocol Deviation Form. If necessary, site staff will be re-trained on the specific topics.
The investigational medical device must NOT be used for any purpose other than that outlined in this CIP, including other human studies, animal investigations, or in-vitro testing.

The investigational device will be returned to the sponsor after the last subject completes the study.

9.4 Informed consent process

It is the responsibility of the Principal Investigator or authorized designee to give each subject prior to inclusion in the study full and adequate verbal and written information regarding the objective and procedures of the clinical investigation and the possible risks involved. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subjects will be informed about their right to refuse to participate in the study and given ample time to decide.

The subject's willingness will be determined and when subject eligibility is established, written informed consent will be obtained. The EC/IRB-approved study informed consent form must be used for administration of informed consent. It is the responsibility of the Investigator or designee at each study site to obtain a signed copy of the Informed Consent documents from all subjects (as applicable) prior to enrollment into the study:

- Informed Consent Document
- HIPAA Authorization Form
- Experimental Subject's Bill of Rights

The investigator conducting the consent process will also sign and date the consent form. The signed original of the informed consent form will be retained with the subject's records and a copy of the signed form will be provided to the subject unless they decline the copy.

A subject is considered enrolled when he or she signs and dates the Informed Consent. No clinical-investigation-specific examinations may be performed prior to the Informed Consent process.

The consent documents and subject recruitment material must be approved by the EC/IRB. The study Sponsor has supplied proposed Informed Consent documentation and proposed study recruitment material, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent documents or subject recruitment material (a study flyer or letter, for example) that are suggested by the Investigator or local IRB must be agreed upon by the study Sponsor before initiation of study enrollment at a local site. A copy of the approved version(s) must be provided to the study Sponsor after EC/IRB approval.

10 Device accountability

Each clinical site will be provided with one CIRRUS 6000 device, one CIRRUS 5000 device, and a commercial fundus imager, if needed.

Installation and de-installation will be recorded in installation / de-installation reports. Copies of these reports will be filed in the Investigator's Site File and the Sponsor´s Trial Master File.

11 Filing and Archiving

11.1 Sponsor Obligations

11.1.1 General Responsibilities of Sponsors

Sponsors are responsible for selecting qualified Investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, and ensuring that Ethics Committee review and approval are obtained.

11.1.2 Specific Responsibilities of Sponsors

1. *Selecting Investigators*. A Sponsor shall select Investigators qualified by training and experience to investigate the device.
2. *Obtaining agreements*. A Sponsor shall obtain from each participating Investigator a signed agreement that includes:
   a) The Investigator's curriculum vitae.
   b) Where applicable, a statement of the Investigator's relevant experience, including the dates, location, extent, and type of experience.
   c) A statement of the Investigator's commitment to:
      i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable regulations, and conditions of approval imposed by the reviewing Ethics Committee or competent authority
      ii) Supervise all testing of the device involving human subjects; and
      iii) Ensure that the requirements for obtaining informed consent are met (21CFR Part 50).

11.1.3 Sponsor Records

A Sponsor shall maintain the following accurate, complete, and current records relating to an investigation for a period of 3 years after completion of the study:
1. All correspondence with a monitor, an Investigator, an Ethics Committee, or Competent Authority, including required reports
2. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and serial number
3. Signed Investigator agreements
4. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints
5. Any other records that the Ethics Committee or Competent Authority requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation

11.1.4 Sponsor Reports

A Sponsor shall prepare and submit the following complete, accurate, and timely reports:

1. *Unanticipated adverse device effects.* A Sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to the Competent Authority and to all reviewing Ethics Committees and participating Investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the

Sponsor shall submit such additional reports concerning the effect as the Ethics Committees and/or Competent Authority requests.

2. *Withdrawal of Ethics Committee approval.* A Sponsor shall notify the Competent Authority and all reviewing Ethics Committees and participating Investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing Ethics Committee within 5 working days after receipt of the withdrawal of approval.
3. *Withdrawal of FDA approval.* A Sponsor shall notify all reviewing Ethics Committees and participating Investigators of any withdrawal of FDA approval of the investigation and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
4. *Progress reports*. At regular intervals, and at least yearly, a Sponsor shall submit progress reports to all reviewing Ethics Committees.

11.2 Investigator Obligations

11.2.1 General Responsibilities of Investigators

An Investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan, and applicable regulations, for protecting the rights, safety, and welfare of subjects under the Investigator's care, and for the control of devices under investigation. An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR 812.

11.2.2 Specific Responsibilities of Investigators

1. Awaiting approval. An Investigator may determine whether potential subjects would be interested in participating in an investigation but shall not request the written informed consent of any subject to participate and shall not allow any subject to participate before obtaining Ethics Committee approval.
2. Subject qualification. The Investigator is responsible for ensuring that all subjects entering the study conform to the subject selection criteria.
3. Compliance. An Investigator shall conduct an investigation in accordance with the signed agreement with the Sponsor, the investigational plan, all applicable Competent Authority regulations, and any conditions of approval imposed by an Ethics Committee or Competent Authority.

11.2.3 Investigator Records

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for a period of 3 years after completion of the study:

1. All correspondence with another Investigator, an Ethics Committee, the Sponsor, a monitor, or Competent Authority, including required reports.
2. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including:
   a) Documents evidencing informed consent
   b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon enrollment and during the course of the investigation, and information about relevant previous medical history and the results of all diagnostic tests
3. The protocol, with documents showing the dates of and reasons for each deviation from the protocol
4. Any other records that the Competent Authority requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation

11.2.4 Investigator Reports

An Investigator shall prepare and submit the following complete, accurate, and timely reports:

1. *Unanticipated adverse device effects (*UADE)*:* An Investigator shall submit to the Sponsor and to the reviewing Ethics Committee a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but no later than 10 working days after the Investigator first learns of the effect.
2. *Withdrawal of Ethics Committee approval:* An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing Ethics Committee of the Investigator's part of an investigation.
3. *Progress:* An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing Ethics Committee at regular intervals, but no less often than once a year.
4. *Deviations from the investigational plan*: An Investigator shall document and report to the Sponsor any deviation from the investigational plan
5. *Informed consent:* If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing Ethics Committee within 5 working days after the use occurs.

6. *Final report:* An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing Ethics Committee, if required.
7. *Other:* An Investigator shall, upon request by a reviewing Ethics Committee or the Competent Authority, provide accurate, complete, and current information about any aspect of the investigation.

12 Adverse events, adverse device effects and device deficiencies

12.1 Definitions (ISO 14155:2020)

The Principal Investigator and Coordinator at CZMI will evaluate, characterize, and record in the eCRF all adverse events (AEs) occurring in all subjects from the time of enrollment to study exit (or premature withdrawal). AEs may be reported spontaneously by the subject or detected by the Investigator or Coordinator. Subjects for whom an AE was recorded will be evaluated for diagnoses and not just symptoms (i.e., "angina", not "chest pain").

12.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended abnormal or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.
NOTE 1. This definition includes events related to the investigational medical device or the comparator.
NOTE 2. This definition includes events related to the procedures involved.
NOTE 3. For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.

12.1.2 Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device or the comparator or to the procedure.
NOTE 1. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device or the comparator.
NOTE 2. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device or the comparator.

12.1.3 **Device deficiency (DD)**

An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety usability, safety, or performance.
NOTE 1. Device deficiencies includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.
NOTE 2. This definition includes device deficiencies related to the investigational medical device or the comparator.

12.1.4 **Serious adverse event (SAE)**

Adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury
  - a permanent impairment of a body structure or a body function including chronic diseases
  - in-patient or prolonged hospitalization
  - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to body structure or a body function
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

NOTE 1 This includes device deficiencies that might have led to an SAE if

a) suitable action had not been taken, or
b) intervention had not been made, or
c) if circumstances had been less fortunate

These DDs are handled using the SAE reporting system.
NOTE 2 Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Any adverse events that do not satisfy these descriptions are defined as being non-serious.

12.1.5 Serious adverse device effects (SADE)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

12.1.6 Unanticipated serious adverse device effects (USADE)

A Serious Adverse Device Effect (SADE) which by its nature, incidence, severity, or outcome has not been identified in the study protocol.
NOTE. Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the study protocol.

12.1.7 Adverse Severity and Relatedness

Each AE occurring in the study will be characterized by the study Investigator based on severity (Table 1) and relatedness (Table 2).

Table 1. AE Severity Grading System

Severity Grade	AE Description
Mild	AE is transient and easily tolerated by the subject, even if it causes discomfort
Moderate	AE causes the discomfort and interrupts usual activities
Severe	AE causes considerable interference with usual activities and may be incapacitating or life-threatening

Table 2. AE Relatedness Grading System*

Grade	Relationship of AE to study device	Description
5	Definite	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is confirmed by improvement on stopping.

4	Probable	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.
3	Possible	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; but may have been caused by concurrent/underlying illness, drugs, procedure, or other causes.
2	Unlikely	An event that does not follow a reasonable temporal sequence from administration of the study device; that does not follow a known or expected response pattern to the study device, or most likely was caused by concurrent/underlying illness, drugs, procedure, or other causes, because of their known effects.
1	Not related	An event almost certainly caused by concurrent/underlying illness, drugs, procedure, or other causes.

*Note that an AE occurring before scanning with the study device will be categorized as unrelated to the study device.

It should be noted that an adverse event that is labeled as severe is not necessarily serious. Regardless of the severity, serious adverse events must be reported as described in section 12.1.4 Serious Adverse Event.

12.1.8 **Categories of outcomes**

The outcome of each AE will be categorized into one of the following groups for reporting purposes:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae (specify type of sequelae)
- Fatal
- Unknown

If there is more than one AE, only the AE leading to death will be attributed with a “fatal” outcome.

12.1.9 Observation period and follow-up after an adverse event

The observation period for adverse events starts when the ICD is signed to study exit. If a subject presents with an active adverse event possibly related to the investigational device at the last visit, the subject will be exited from the clinical investigation, but followed by the clinical site until the condition is stable with no expected further improvement or worsening.

All unresolved or ongoing non-device related adverse events at study exit will be documented as such in the eCRF and the subject exit will be classified as per section 7.3.4. All subjects will be followed-up per the investigator's routine standard of care.

Serious adverse events occurring after the end of the clinical investigation must be documented in the subject file and reported to the sponsor if the investigator considers the event to be related or possibly related to the investigational device.

12.2 Report and documentation of safety data

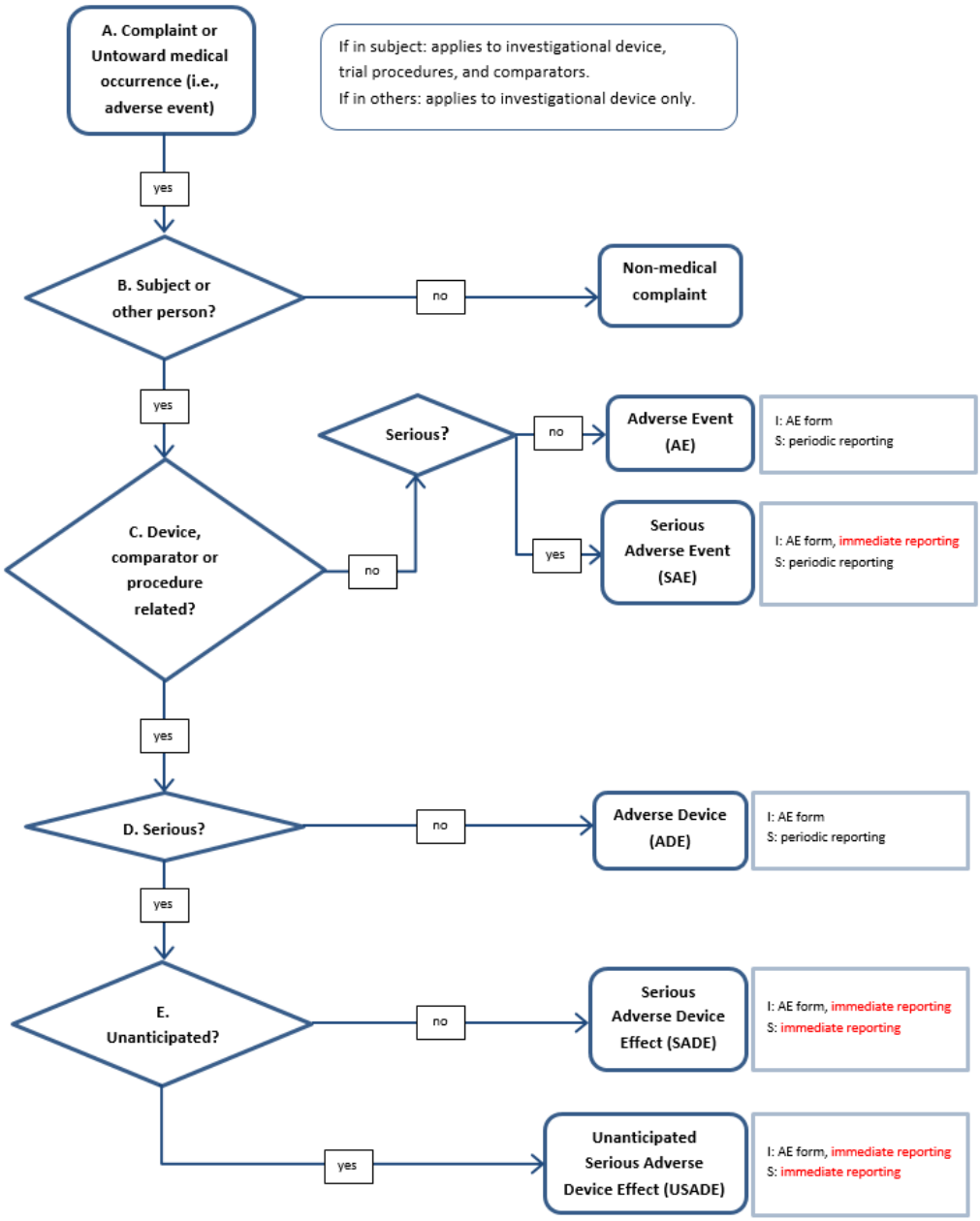
Data pertaining to AEs and DDs will be collected during each study visit based on the subject's description, through investigator inquiry, or discovered in the course of examinations done during the visit. The investigator will assess and record any AE in detail in the subject file and on the respective eCRF report form.

Pre-existing conditions that do not worsen during the course of the study are not reportable as AEs. They should be recorded in the Medical History section of the eCRF. To determine whether a condition has worsened, it is compared to the condition of the subject at screening. Pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened is not considered a SAE.

Any complaints related to non-study marketed devices (e.g., OVD, delivery systems etc.) should be communicated directly to the device's manufacturer as per manufacturer's instruction and per local requirement.

The sponsor will assess the reported AEs and may upgrade the investigator's assessment of seriousness and/or causality. The sponsor will notify the investigator of any AEs that are upgraded from non-serious to serious or from unrelated to related.

The following figure shows a decision tree on the reporting duties. Detail on reporting and documentation are given in the sections below:



I: Investigator; S: Sponsor

12.2.1 Immediate notification

Under consideration of the adverse event definitions in Section 13.1 as well as the classification and causality assessment criteria defined in Sections 13.1.7, **immediate notification to the sponsor** is required in case of:
Expected or unexpected adverse event during a clinical study, which directly or indirectly caused, may have caused in the past, or may cause in the future, death, or a serious aggravation of the state of health of a subject, a user, or another person (does not necessarily imply a causal relationship with either the study product or the procedure for the medical device implementation).

Investigator responsibilities

SADE and USADE

Under consideration of the adverse event definitions as well as the classification and causality assessment criteria defined in Section 13.1, **immediate notification to the sponsor** is required in case of Serious Adverse Device Effect (SADE) and an Unanticipated Serious Adverse Device Effect (USADE).

ADE, DD, Incident and SAE (other than SADE/USADE)

The Investigator is obligated to report any Adverse Device Effect (ADE), Device Deficiency (DD), Incident and other than above listed Serious Adverse Event (SAE), to the Sponsor within **2 business days** of becoming aware of the event to ensure the safety of all participants in the study and to meet regulatory reporting requirements. Although all information required for completion of an SAE report form may not be available within the specified time period, an initial report should be submitted with the available information. Any new information obtained about the serious adverse event must be added to the existing eCRF form.

AE

Adverse events will be reported within **10 business days** after becoming aware of the event.
The investigators report all occurring events by completing the designated page in the eCRF system. The signed form will then be sent to:

Patricia Sha, OD
5300 Central Parkway
Dublin, CA 94568
Phone 925-307-1588
Email patricia.sha@zeiss.com

The investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/EC.

Sponsor responsibilities

The sponsor evaluates in close collaboration with the investigator and the advisory board, whether the serious adverse event requires expedited, periodic and/or vigilance reporting or documentation only according to the applicable regulations. Expedited reporting is necessary when the SAE can be related or potentially related to the medical device, its comparator, or the medical procedure.

The sponsor or its representative will take responsibility for notifying serious adverse events immediately to the Competent Authority and the Ethics Committee of the country in which the adverse event occurred.

Minimum information required to declare are the following:

- identification of the suspected medical device
- identification of the concerned subject (subject ID and site number)
- unexpected serious adverse event for which the causal relationship can be reasonably considered by the investigator or the sponsor
- identification of the declarer
- the registration number of the study given by the Health Authorities if available

Relevant additional information must be reported by the sponsor within 8 days after the first notification to the Health Authorities of every country in which the study is carried out. All other information can be handed in later.

In compliance with §14, MPSV, anticipated Adverse Device Effects and Unanticipated Adverse Device Effects will be handled according to the internal processes of the medical device post-market surveillance (PMS) system established by Carl Zeiss Meditec, Inc. The PMS system maintains systematic procedures to review experience gained from devices in the postproduction phase and to apply any necessary corrective action.

12.3 Anticipated adverse device effects

There are no anticipated major side effects associated with the CIRRUS 6000 or CIRRUS 5000. The use of anesthetic or mydriatic eye drops may cause a brief stinging or burning sensation and a bitter taste in the mouth. Mydriatic eye drops will cause the eyes to remain dilated after the procedure for 3-6 hours. The eyes may be light sensitive during this time. VanHerick angles and

gonioscopy will may be performed if any subjects show signs of narrow angles prior to dilation. If gonioscopy shows narrow angles, then dilation will not be performed.

The overall level of risk is similar to that of a full eye examination in a doctor's office. However, because of the number of tests that will be performed, the subject may experience some fatigue and/or other side effects like transient after-images that may be associated with ophthalmoscopy and imaging devices, which are typical of a standard ophthalmic examination.

Throughout the course of the proposed study, all efforts will be made to remain alert to possible adverse events. If an adverse event occurs, the first concern will be the safety of the subject. Appropriate medical intervention will be made. Any adverse events observed by the Investigator or reported by the subjects and regardless of severity and whether or not ascribed to the research procedures, will be recorded in the appropriate section of the subject's eCRF. Any serious adverse events, whether ascribed to the research procedure or not, will be communicated promptly by telephone to the Sponsor. These reports must be confirmed in writing within one week of the occurrence. Any subjects who are terminated from the study due to adverse events will be followed until their medical outcome is determined, and the PI will provide written reports to the Sponsor. The Sponsor will notify the Ethics Committee and all participating PIs of any adverse event associated with use of any device that is both serious and unexpected (i.e. UADE). This notification will be made as soon as possible and no later than ten working days after the Sponsor's initial receipt of the information.

13 Vulnerable population

Pregnant and breastfeeding women may be enrolled in this clinical investigation. Slit lamp exam, fundus photography, and OCT scans are typical procedures done in a routine eye examination, therefore there is no meaningful reason to exclude this vulnerable population from participation in this clinical investigation. Dilation will not be performed in this population.

14 Suspension or premature termination of the clinical investigation

The Sponsor has the right to terminate or interrupt this investigation at any time. Reasons may include the following:

- The incidence of device deficiencies indicates a technical problem with the medical device which needs to be addressed.

- The incidence or severity of adverse events in this or other investigations indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory

The Sponsor will be responsible for contacting all recruited investigators, all Ethics Committees and, as per local regulations if applicable, Competent Authorities to terminate the investigation. Competent Authorities shall be informed by the sponsor within 15 days, providing a justification. In the event that the investigation is suspended or prematurely terminated on safety grounds, the sponsor shall inform all Competent Authorities within 24 hours.

Additionally, the Sponsor or its representatives may discontinue participation at an individual investigational site at any time by providing written notice of reasonable cause to the other party. This written notice should be given within ten days of anticipated termination date. The Institutional Review Board (IRB) must be notified within five working days. Reasons for discontinuing participation may include the following:

- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Substantial protocol violations
- Lack of compliance by the investigator or EC with current ICH Good Clinical Practice requirements or other applicable regulatory requirements

In case of the termination of the clinical investigation

- enrollment will be stopped
- all subjects which are not scanned with the investigational device will be exited from the clinical investigation as described in section 3.4.6 Subject Exit.

Carl Zeiss Meditec, Inc. reserves the right to use data from the site if they do not complete their entire enrollment commitment.

Abbreviation	Definition
510(k)	The section of the Medical Device Amendment to the FDC Act which defines the manner in which medical products that have established performance standards, or that are substantially equivalent to products already on the market, can gain clearance from the FDA to be sold in interstate commerce in the USA.
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
AE	Adverse Event
AI	Artificial Intelligence
AMD	Age-Related Macular Degeneration
BRVO	Branch Retinal Vein Occlusion
CRVO	Central Retinal Vein Occlusion
CSCR	Central Serous Chorioretinopathy
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CV	Coefficient of Variation
CZMI	Carl Zeiss Meditec, Inc.
DD	Device Deficiency
DR	Diabetic Retinopathy
dAMD	Dry Age Related Macular Degeneration
EC	Ethics Committee
eCRF	Electronic Case Report Form
ERM	Epiretinal Membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCA	Ganglion Cell Analysis
GCL	Ganglion Cell Layer
HD-OCT	High-Definition Optical Coherence Tomography
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions For Use
ILM	Internal Limiting Membrane
IRB	Institutional Review Board
IRF	Intraretinal fluid
IPL	Inner Plexiform Layer
IRB	Institutional Review Board

LR	Likelihood Ratio
MH	Macular Hole
MTA	Macula Thickness Analysis
ME	Macular Edema
NA	Not Applicable
nAMD	Neovascular Age Related Macular Degeneration
NPV	Negative Predictive Value
NPDR	Non-Proliferative Diabetic Retinopathy
OD	Right Eye
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
OS	Left Eye
PAS	Prospective Analysis Set
PPV	Positive Predictive Value
PI	Principal Investigator
PMS	Post-Market Surveillance
PDR	Proliferative Diabetic Retinopathy
RPE	Retinal Pigment Epithelium
SADE	Serious Sdverse Device Effects
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SLD	Superluminescent Diode
SRF	Subretinal Fluid
SS	Signal Strength
HD-OCT	Swept Source Optical Coherence Tomography
SW	Software
UADE	Unanticipated Adverse Device Effect
VRI	Vitreoretinal Interface
WHO	World Health Organization
ZICC	ZEISS Innovation Center California

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Appendix 1: Image Acceptance Criteria

Macular Cube Scans

Scans should be reviewed by the operator at the time of acquisition for acceptable quality. These considerations apply to both the CIRRUS 6000 and CIRRUS 5000 HD-OCT devices.

Criteria for Obtaining Good Quality OCT Scans

Before capturing an image, use the following criteria to ensure that it will be an acceptable image on the acquisition screen:

- The iris image should:
  - Be focused on the iris
  - Be centered on the pupil
- The LSLO image should:
  - Be sharp and clear
  - Have the scan overlay centered on the fovea for macular scans
  - Not have dark corners
- The OCT scan images should:
  - Be completely visible without missing data
  - Have uniform color or black / white density from end to end
  - Be the brightest and clearest in the Enhancement (polarization) range

Criteria for Selecting Good Quality OCT Scans

Scans should be reviewed by the operator at the time of acquisition for acceptable quality. On the Scan Quality Check screen, assess the following:

- The LSLO image should:
  - Be sharp and clear
  - Scan should be centered on the fovea or optic nerve head
  - Not have dark corners
- The OCT scan images should:
  - Be completely visible without missing data
  - Have uniform color or black / white density from end to end
  - Signal strength should be 7 or more
- The OCT en-face image should:
  - Be sharp and clear
  - Not have obvious saccades

For acceptable scans, select Save. For unacceptable scans, select Try Again. A maximum of 3 scan retries per scan type per device may be attempted. **If scans do not qualify, the reason and number of scans disqualified must be recorded on the eCRF.**

Angiography Scans

Scans should be reviewed by the operator at the time of acquisition for acceptable quality. On the Scan Quality Review screen, assess the following:

- Check that the signal strength is 6 or higher. (In the presence of cataracts and other media opacities, the best achievable signal strength may be lower than 6. The operator may save the scan based on their clinical judgement if they deem the scan to be clinically acceptable)
- Check that the focus is sharp and clear, preferably with good visibility of the branching blood vessels (see Figures A and B).
- Check that the scan overlay in the fundus image is centered on the fovea, and that it is illuminated uniformly and without dark corners (see Figures A and B).
- Ensure that there are few to no artifacts that may cast shadows on the OCT scan (see Figures C and D).
- Make sure that the scan is complete in all windows without missing data (see Figure D).
- Check for saccades. The enface image should have minimal saccades, which can be detected by discontinuities in the appearance of the blood vessels (for example, a horizontal shift of the vessel at a specific location) (see Figure E).
- The angiography enface should not contain excessive horizontal banding (see Figure E).
- Figures B-E are examples of Angiography scans over the fovea. See Figure F for an example of a scan with appropriate centering over the ONH.
- Note: If scans do not qualify, the reason and number of scans disqualified will be recorded on the CRF.

For acceptable scans, select Save. For unacceptable scans, select Try Again. A maximum of 3 scan retries per scan type per eye may be attempted. **If scans do not qualify, the reason and number of scans disqualified will be recorded on the CRF.**

Figure A. Acceptable Macular Scan

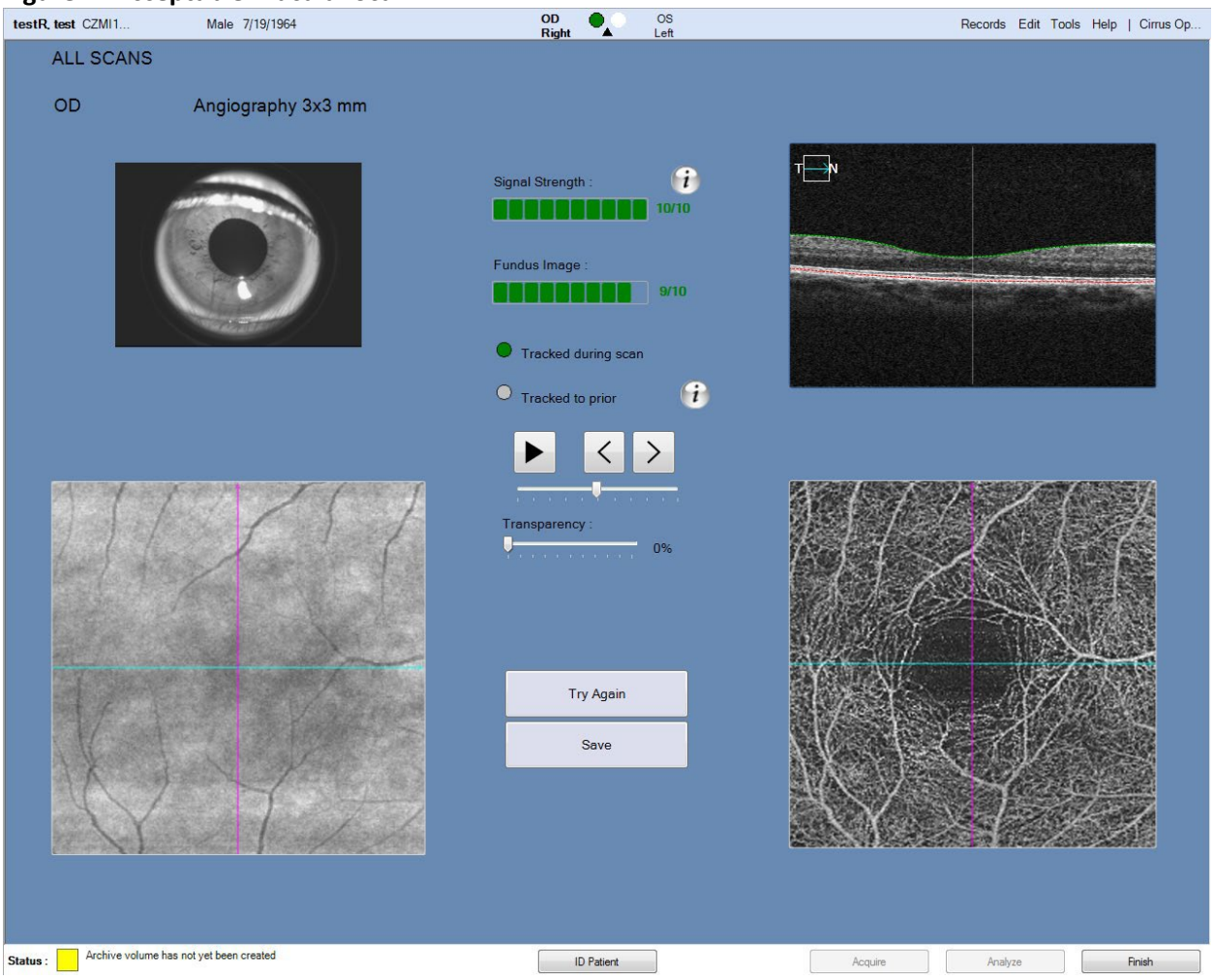


Figure B. Unacceptable Scan due to Defocus

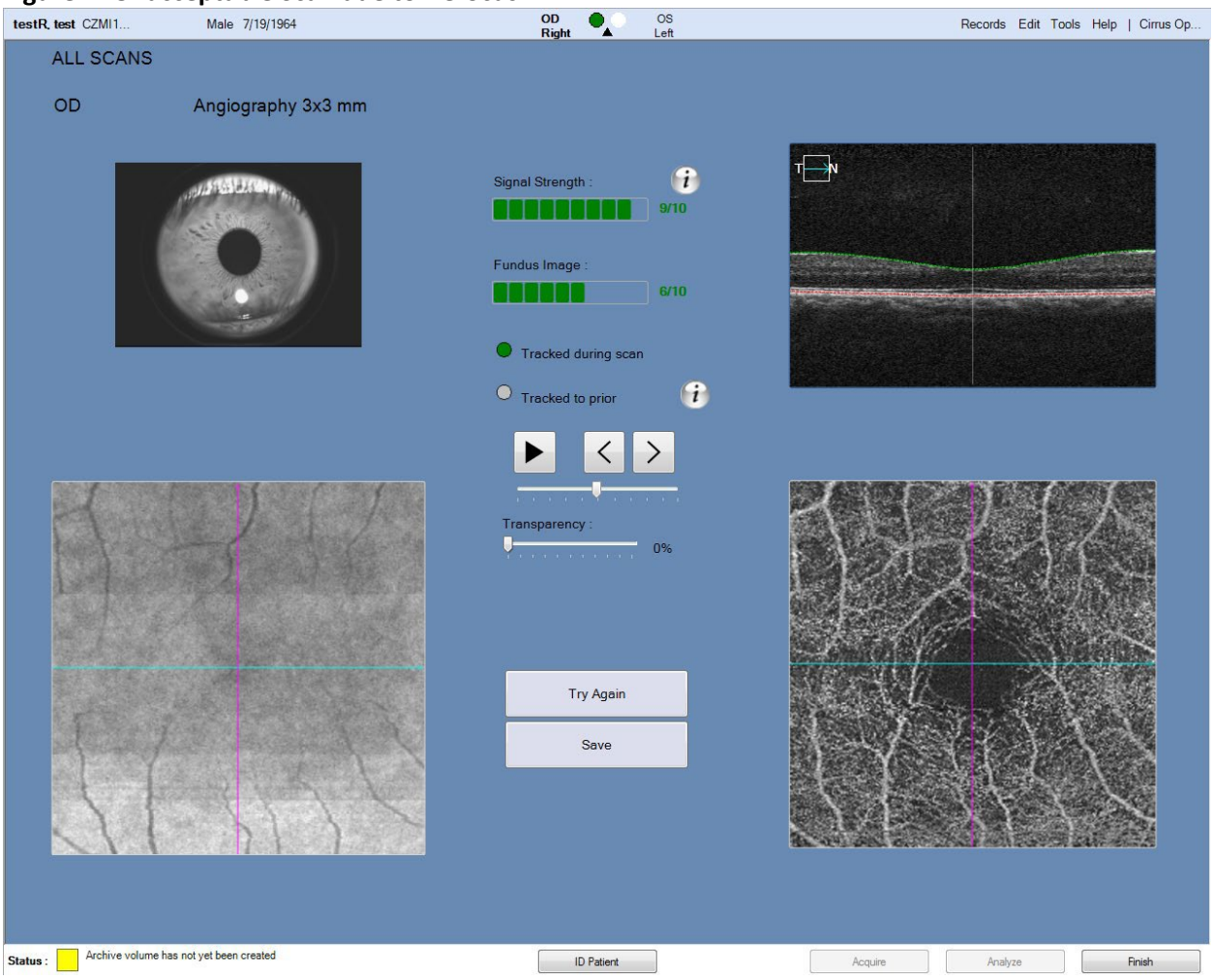


Figure C. Unacceptable Scan due to Shadows (Decentered Pupil)

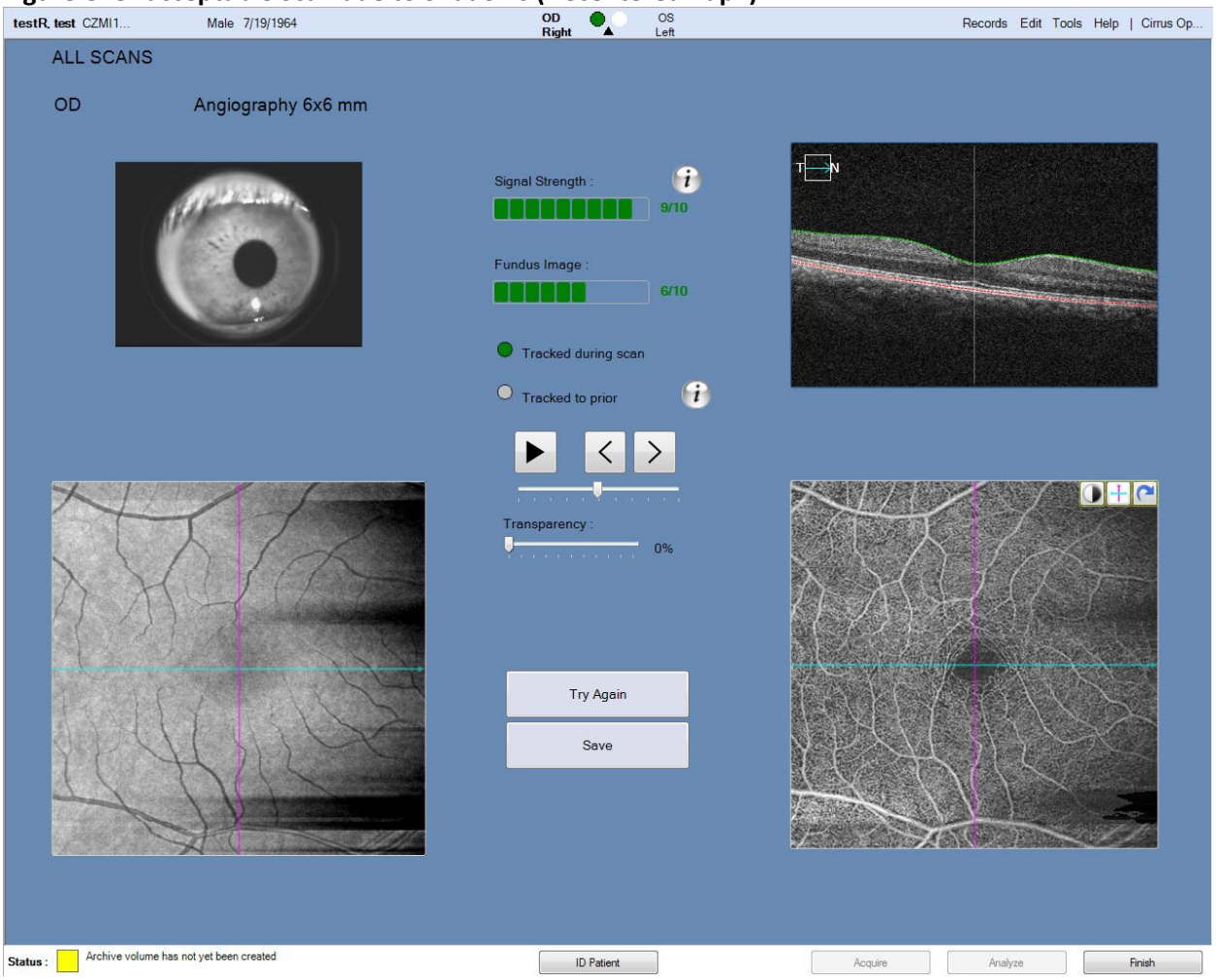


Figure D. Unacceptable Scan due to Shadows (Floaters)

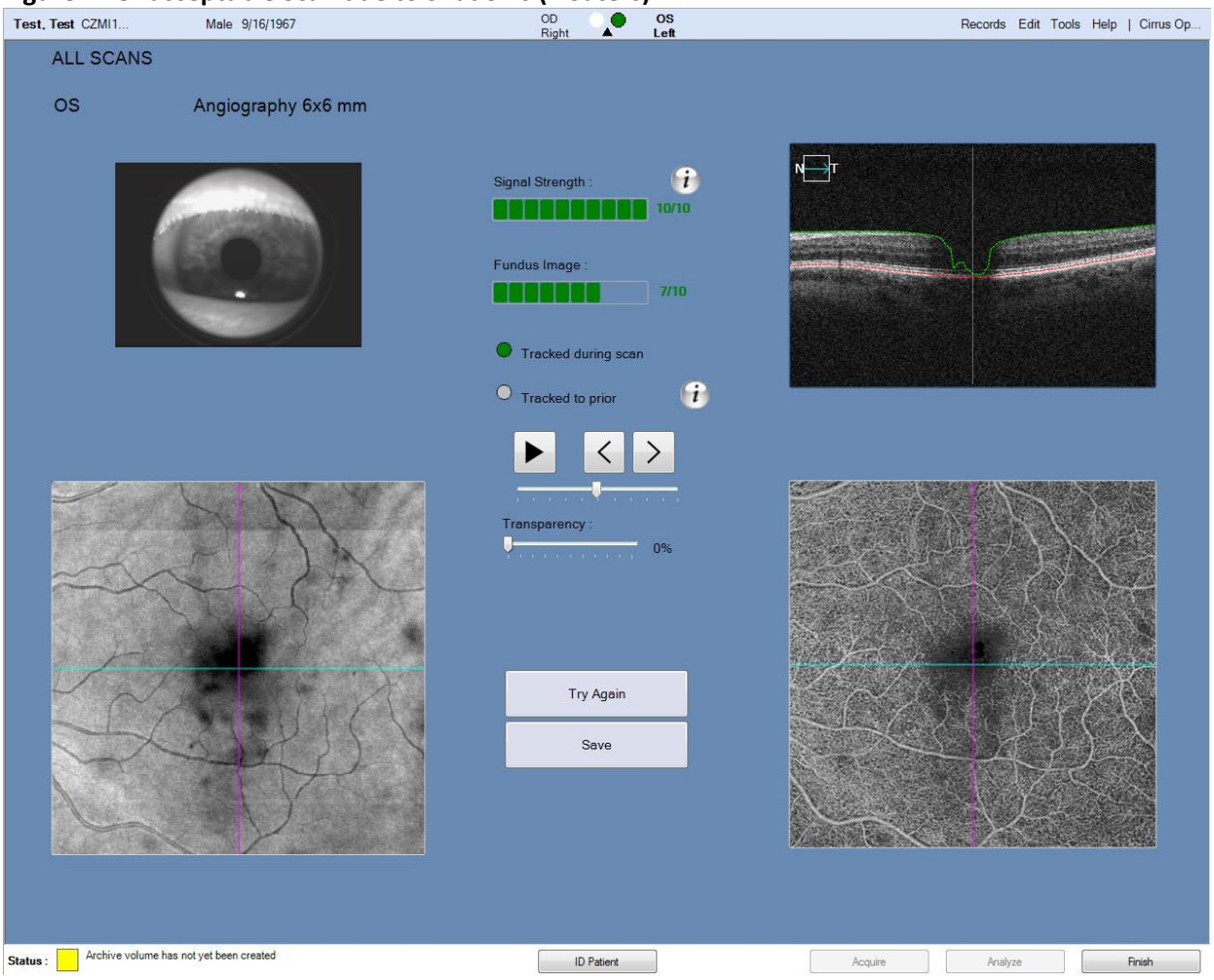
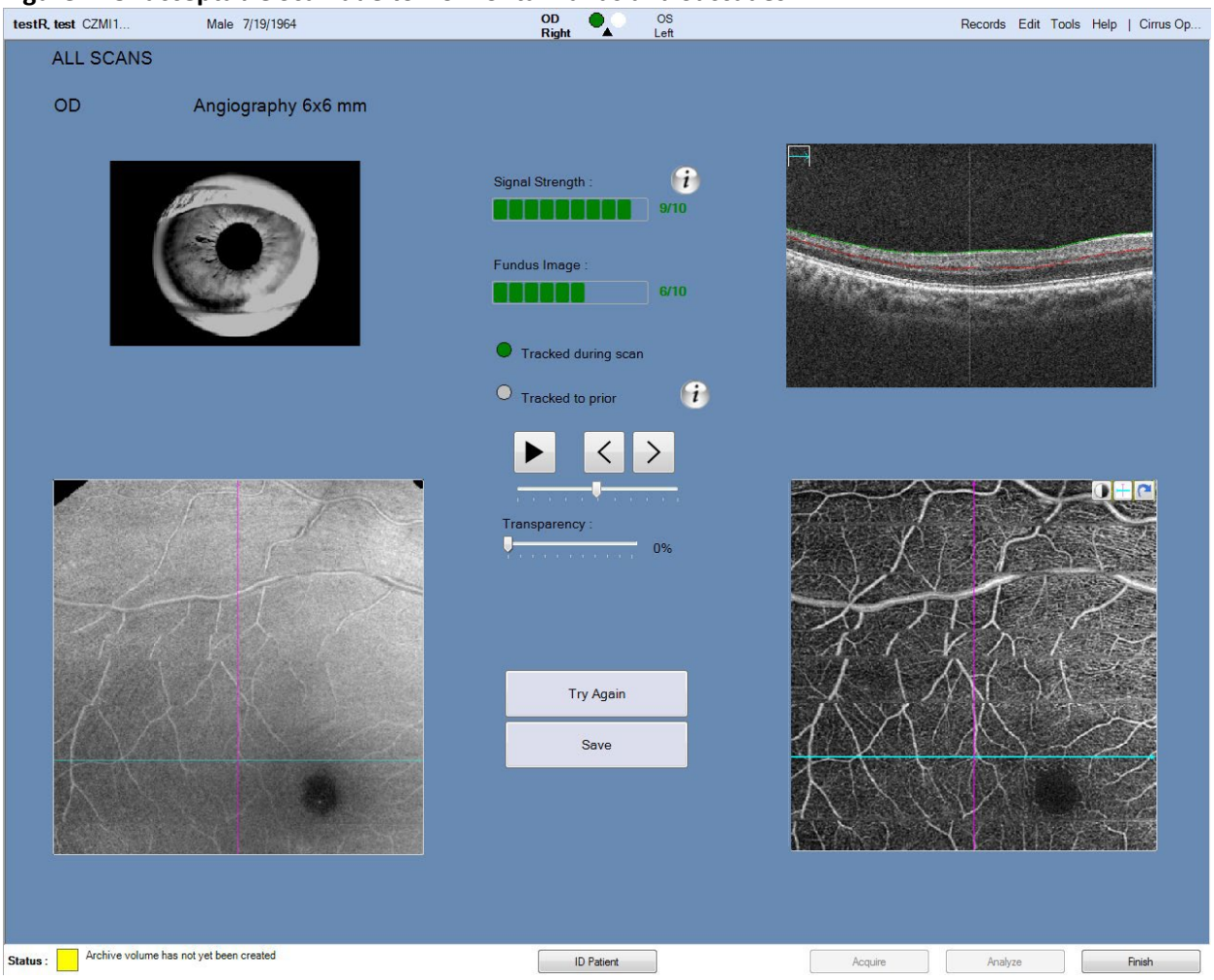
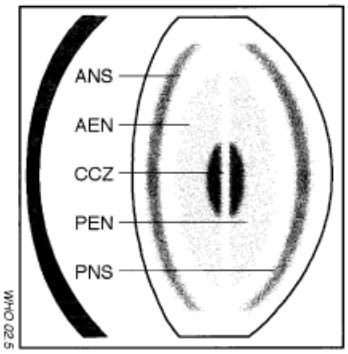


Figure E. Unacceptable Scan due to Horizontal Bands and Saccades



Note: This example scan is decentered from the fovea

Appendix 2: WHO simplified cataract grading system[3]



ANS: Anterior Nuclear Shell

AEN: Anterior Embryonal Shell

CCZ: Central Clear Zone

PEN: Posterior Embryonal Shell

PNS: Posterior Nuclear Shell

Fig.1
Image of a lens with the "grading region", as shown for early nuclear cataract, including the anterior and posterior nuclear shells, the embryonal nuclei and the central clear zone.

The **WHO/PBD NUC standards** represent increasing opacification from standards 1 to 3.

The examiner assigns a severity grade by **comparing** the degree of opacification in the slit lamp appearance of the grading region with the **standard photographs**. Grades are assigned as follows :

(i) Grade NUC-0: Less than the NUC-1 STD

(ii) Grade NUC-1: Equal to or greater than the NUC-STD 1 but less than the NUC-STD 2

(iii) Grade NUC-2: Equal to or greater than the NUC-STD 2 but less than the NUC-STD 3

(iv) Grade NUC-3: Equal to or greater than the NUC-STD 3

(v) Grade NUC-9: Cannot grade

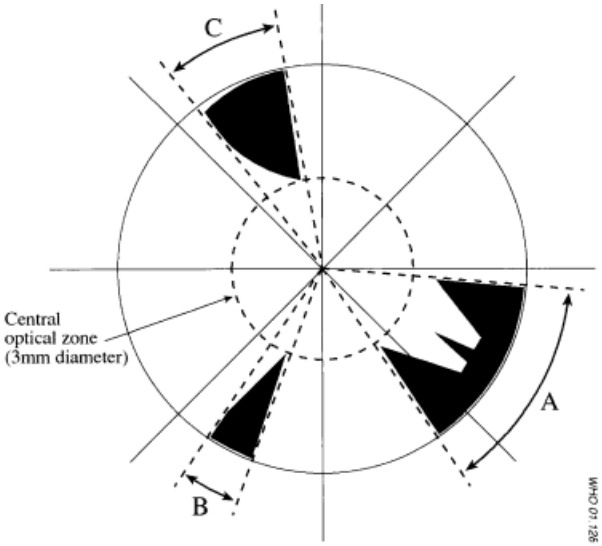


Fig.7
For ease of grading, the circumference can be divided into octants ("eighths") by first dividing the pupillary aperture into quadrants with the imaginary lines between 6 and 12, and between 3 and 9 o'clock. A quadrant can then be halved to create one-eighth segments

The examiner will determine the circumferential extent of discrete cortical opacities (COR) seen on retroillumination. In cases of a dispersed cortical cataract (with several non-contiguous spoke- or ring-like opacities), all of the opacities should be **aggregated** for the purposes of grading circumferential extent (Fig. 7):

Grade COR-0: Cataract involves less than one eighth of the circumference.

Grade COR-1: If cataract involves one eighth, but less than a quarter, of the circumference.

Grade COR-2: If cataract involves a quarter, but less than half, of the circumference.

Grade COR-3: If cataract involves half or more of the circumference.

Grade 9: Cannot grade

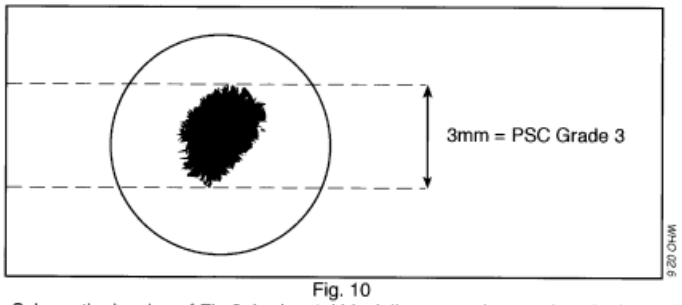


Fig. 10
Schematic drawing of Fig.9, horizontal black lines superimposed on the image to show the extent of the PSC

The PSC definitions are as follows, measured in the **vertical** dimension:

Grade 0:	Less than 1 mm
Grade PSC-1:	Equal to or greater than 1.0 mm, but less than 2.0 mm ("case")
Grade PSC-2:	Equal to or greater than 2.0, but less than 3.0 mm ("progression which may require surgery")
Grade PSC-3:	Equal to or greater than 3.0 mm ("usually requires surgery")
Grade 9:	Cannot grade