COmparison of ***C***larus and ***O***ptos Ultrawide Field Imaging Systems for Geographic Atrophy (COCO-GA)

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PROTOCOL TITLE:

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REVISION HISTORY

Version #	Version Date	Summary of Changes	Consent Change?
1	21Jun2023	New	N/A
2	20Mar2023	Added descriptions for retention and sharing of data and images for future studies within DOVS and the associated confidentiality breach risk	Yes
3	06Nov2024	For participants also enrolled in Protocol 2023-1715 FPF in AMD only, a description of sharing images and data with OcuSciences, Inc. was added	Yes – Participants also enrolled in FPF in AMD only
4	03/20/2025	Increased the number of participants to be enrolled to 100	No

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STUDY OVERVIEW

Study Title:	COmparison of Clarus and Optos Ultrawide Field Imaging Systems for Geographic Atrophy (COCO-GA) Protocol
Name of Devices:	Zeiss Clarus 700 and Optos
Device Descriptions:	The Zeiss Clarus 700 (Carl Zeiss Meditec Inc., California, USA) is an ultrawide field retinal imaging system designed to cover up to 133 degrees of the retina in a single image. The technology uses both confocal imaging and true color imaging. The Clarus provides both blue and green fundus autofluorescence (FAF) images using a technology known as Broad Line Fundus Imaging (BLFI). [1] Optos (Optos PLC, Dunfermline, United Kingdom) is an ultrawide field imaging system which allows visualization of up to 200 degrees of the retina in a single image. It uses a confocal scanning laser (cSLO) and provides pseudocolor images using red and green lasers. [2]
Rationale and Aims:	Age-related macular degeneration (AMD) is a disease of the central retina and the leading cause of blindness in people over the age of 60 in the developed world, presenting a significant global concern. [3] [4] Geographic atrophy (GA) is the end stage of AMD which may lead to blindness. Autofluorescence is a common imaging technique used to measure the area of atrophic patches in the retina due to GA. Change in area of GA over time is considered a primary endpoint for clinical trials. Measurement of GA area from FAF images is usually performed at central reading centers. The most commonly used FAF imaging system is the Spectralis camera from Heidelberg (Heidelberg Engineering Inc., Heidelberg, Germany) which provides FAF images covering 30-degrees of the retina. More recent developments in ultrawide field systems such as Optos and Clarus, have allowed visualization of larger areas of the retina of more than 100 degrees. Each system uses unique technology in an effort to provide maximal coverage and clarity. The goal of this study is to compare GA area measurements from FAF images taken by standard Spectralis imaging with images taken using the Optos and Clarus ultrawide field imaging systems. Additionally, the presence and frequency of GA or other autofluorescence abnormalities outside the standard 30-degree field will be assessed.
Study Population:	Patients 50 or older with GA secondary to AMD presenting at a single center of an ophthalmic retina practice.

Study Design:

A prospective, comparative imaging study in which eligible participants will have dilated FAF imaging using Spectralis FAF as well as Optos and Zeiss Clarus ultrawide field FAF. All devices are FDA approved for fundus imaging and is consistent with their approved device labeling/instructions. Patient coded images will be evaluated at a central reading center (Wisconsin Reading Center (WRC) University of Wisconsin-Madison)

Patient Recruitment:

Patients will be recruited from clinical practices of the nine retinal physicians at a single site, the UW Eye Clinic at University Station. 75 eyes with GA will be enrolled, from 100 patients with GA in one or both eyes. Study eyes will be imaged in the comparative study of Spectralis with Optos and Clarus autofluorescence imaging. Subjects will be limited to GA area of between 1.25 mm^2 and 23 mm^2, with seventy percent of patients having GA area ranging from 2.5 mm^2 to 17.5 mm^2. GA may be subfoveal or extrafoveal with at least twenty-five percent of subjects having subfoveal atrophy. GA may be unifocal or multifocal. The presence of peripapillary atrophy will not exclude subjects from participation.

Exclusion criteria include the presence of neovascular AMD, significant media opacity precluding adequate retinal imaging, or concurrent retinal disease that could confound assessment.

Informed consent will be obtained. The goal for duration of individual participation will be 1-2 hours over one visit. All images will be paid for by the study according to a set clinical research fee schedule without any cost to the patient. Fifty dollars will be given to patients for compensation for their time.

Outcome Variables:

The performance characteristics to be assessed in this study for each device/image assessment:

Primary

- Comparison of geographic atrophy area measurements by Clarus and standard Spectralis FAF imaging.
- Comparison of geographic atrophy area measurements by Optos and standard Spectralis FAF imaging.
- Comparison of geographic atrophy area measurements by Clarus and Optos FAF imaging.

Secondary

- Prevalence of GA outside the standard 30 degrees in Clarus and Optos ultrawide field images.
- Prevalence of other autofluorescence abnormalities outside the standard 30 degrees in Clarus and Optos ultrawide field images.

Data Analysis:	Paired images obtained by all cameras will be evaluated by readers who will independently assess the area of GA using standardized image evaluation procedures. The readers are trained and certified by the WRC.
Study Sponsor:	Wisconsin Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin – Madison.

INTRODUCTION

Age-related macular degeneration (AMD) is a disease of the central retina characterized by progressive damage which may result in significant and irreversible vision loss. In 2019, it was estimated to affect 18.34 million people over the age of 40 in the United States alone, with 1.49 million people suffering from advanced stages of the disease. [5] Worldwide, the Global Burden of Disease Study estimated a nearly 70% increase in cases of blindness due to AMD between 1990 and 2020. [6]

Two distinct types of AMD exist, neovascular or "wet" AMD and non-neovascular or "dry" AMD. While these forms share similarities, neovascular AMD is differentiated by the development of choroidal neovascularization, the abnormal growth of blood vessels into the neurosensory retina. Though historically choroidal neovascularization has been a significant cause of vision loss in neovascular AMD, vast improvements have been made with the advent of intravitreal anti-vascular endothelial growth factor (VEGF) treatments. The potential for severe vision loss in non-neovascular AMD lies in the development of geographic atrophy (GA), a progressive loss of retinal pigment epithelium, photoreceptors and choriocapillaris. There are currently limited options available for the treatment of GA. [7]

Due to the potential significance of GA development, detection and monitoring for progression are vital. Fundus autofluorescence (FAF), which was first utilized in 1995, is a non-invasive imaging technique commonly used in the assessment of AMD. [8] FAF works by detecting lipofuscin, a fluorophore that accumulates in the retinal pigment epithelium (RPE) as a byproduct of the aging eye and can be an indicator of RPE health. During FAF imaging, lipofuscin absorbs light at a peak excitation wavelength of 470 nm and emits light at peak emission of 600-610 nm. This emission, or autofluorescence, is then used in analysis of lipofuscin density. [9] As GA represents the loss of retinal pigment epithelium, and thus changes in lipofuscin density, FAF has particular application in the assessment of GA.

The current gold standard in FAF is Spectralis FAF imaging from Heidelberg Engineering. Spectralis is a scanning laser ophthalmoscope which uses a blue light excitation wavelength of 488 nm and a 500 nm barrier filter to produce FAF images. Spectralis images 20-55 degrees of the retina. [9-10] By contrast, Optos is an ultrawide field imaging platform which images up to 200 degrees of the retina. [2] It uses both a green-light excitation wavelength of 532 nm and a red-light excitation wavelength of 633 nm with an emission filter of greater than 540 nm to produce FAF images. As other sources of fluorophores in the eye and the presence of cataracts may produce interference in blue FAF, green light FAF may provide an improvement in FAF imaging clarity and may be more sensitive to certain retinal changes. [9-10] Zeiss Clarus 700 is an ultrawide field imaging system with similar retinal coverage to that of Optos. It uses Broad Line Fundus Imaging to produce blue FAF images at excitation wavelengths of 435-500 nm and green FAF images at wavelengths of 500-585 nm. [11] The ability to capture both blue and green FAF images may provide the potential to maximize assessment of subtle retinal changes in AMD, while minimizing interference. Additionally, ultrawide field FAF, as seen in Optos and Clarus, may provide insight into retinal changes occurring outside the standard 30-degree images provided by Spectralis. Figure 1 summarizes device specific parameters.

Figure 1: Coverage and imaging parameters for tested devices.

Device	Field of View (degrees)	Excitation Wavelength (nm)	Emission Filter (nm)
Spectralis	30	488	500
Optos	200	532, 633	540
Clarus - Blue	133	435-500	532-650
Clarus - Green	133	500-585	630-750

Figure 2: Spectralis FAF images of a normal fundus (a) and fundus with GA (b).

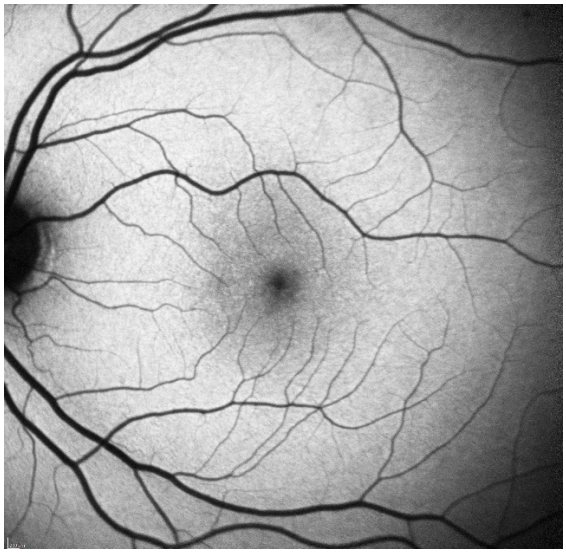
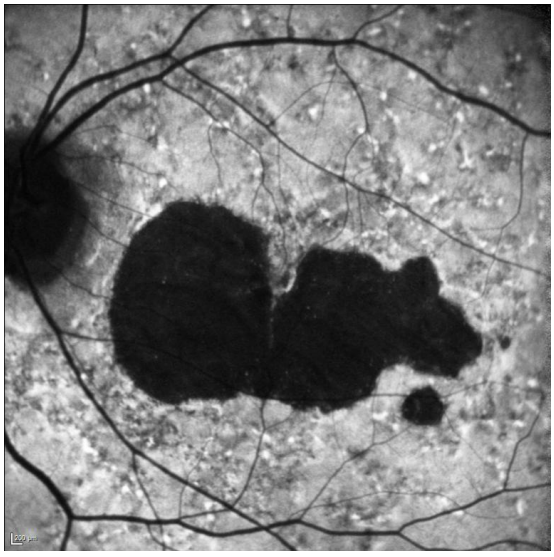
a  b 

Figure 3: Optos ultrawide field FAF images of normal fundus (a) and a fundus with GA (b).

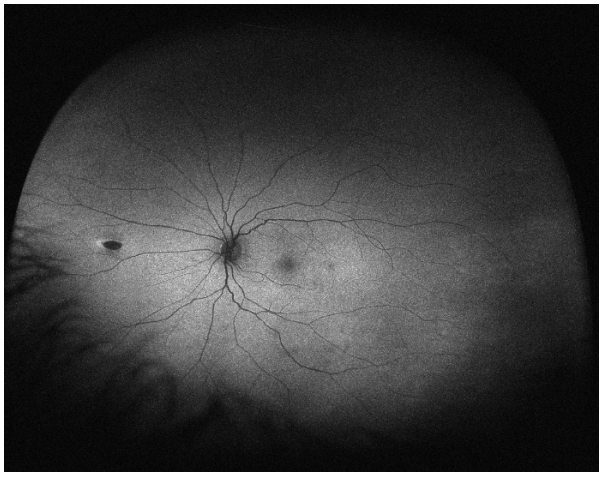
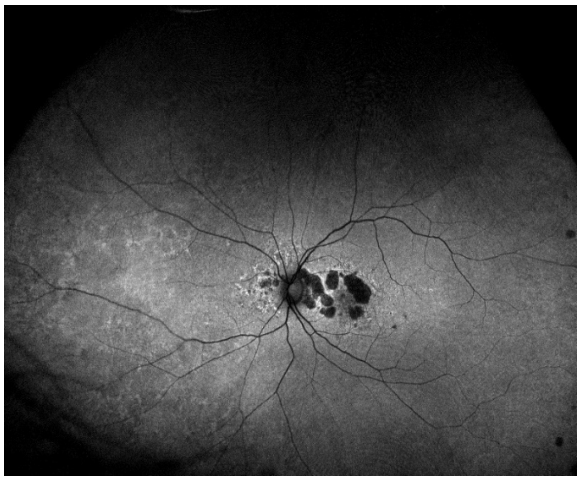
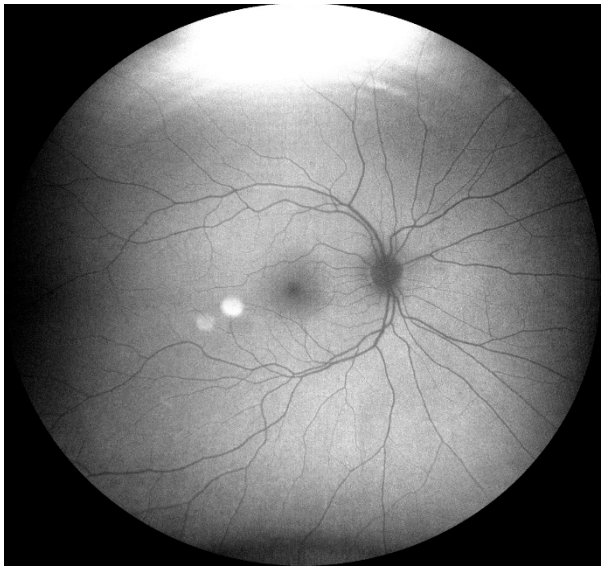
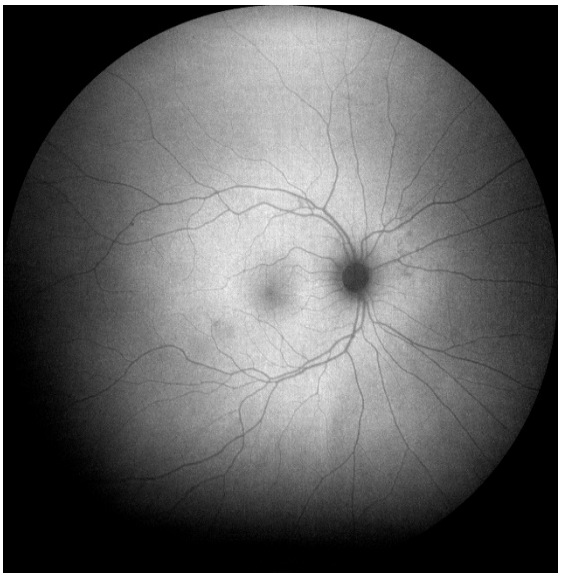
a  b 

Figure 4: Clarus 700 ultrawide field blue-FAF image (a) and green-FAF image (b) of a normal fundus.

a  b 

The proposed study, as outlined below, will involve imaging eyes from participants with GA due to AMD using standard Spectralis FAF, Optos ultrawide field FAF, and both blue and green ultrawide field FAF with Zeiss Clarus 700. Patient coded paired images of each eye will be provided to a reading center for analysis, including measurement of geographic atrophy area.

STUDY OBJECTIVES

A. Purpose

The purpose of this study is to compare measurements of GA area between standard Spectralis FAF imaging, Optos ultrawide field FAF and Zeiss Clarus 700 ultrawide field FAF. Analysis of the following endpoints will estimate how the Clarus functions in comparison to Optos ultrawide field FAF and standard Spectralis FAF.

B. Outcome Variables/Endpoints:

Accuracy of geographic area measurement, as determined by assessing images produced by the test devices and by the control device, according to standardized image evaluation forms (see Appendix A).

Primary:

1. Comparison of geographic atrophy area measurements by Clarus with standard Spectralis imaging.
2. Comparison of geographic atrophy area measurements by Optos with standard Spectralis imaging.
3. Comparison of geographic atrophy area measurements between Clarus and Optos.

Secondary

1. Prevalence of atrophy outside the standard 30 degrees in Clarus and Optos ultrawide field images.
2. Prevalence of other autofluorescence abnormalities outside the standard 30 degrees in Clarus and Optos ultrawide field images.

STUDY POPULATION AND PARTICIPANT SELECTION

A. Number of Participants

We will assess 75 eyes. We expect to acquire the 75 eligible eye from 100 participants. Patients from vulnerable populations (e.g. children, pregnant persons, prisoners, persons with impaired decision-making capacity) will be excluded. The study will provide a comparative assessment of images taken on each of the three technologies outlined.

Statistical Justification: The sample size calculation is based upon intergrader agreement in measurement of GA area in mm^2 using Spectralis FAF. Using internal data, mean difference in GA area between 2 graders was 0.36 mm^2 (CI, -1.03 to 1.75) among 47 eyes.

With a power of 0.95, alpha 0.05 and effect size of 0.5, the sample size is calculated as 60 eyes with GA. Additional assumptions include that half the participants will have bilateral GA meeting inclusion criteria and 20% data loss due to image quality [12].

Based on the above assumptions, a sample size of 75 eyes from 100 participants will allow adequate sample size to compare measurement of GA between the 3 devices.

B. Participant Selection

1. Inclusion Criteria

Eligible participants must meet all the following inclusion criteria:

1. 50 years or older and may be either male or female and may be of any race.
2. Established diagnosis of GA due to AMD.
3. GA characteristics: GA area of between 1.25 mm^2 and 23 mm^2, with seventy percent of eyes having GA area ranging from 2.5 mm^2 to 17.5 mm^2. GA may be unifocal or multifocal. GA may be subfoveal or extrafoveal, with twenty-five percent of eyes having subfoveal GA. The presence of concurrent peripapillary atrophy will not exclude subjects from participation.
4. Willing to participate as evidenced by signing the written informed consent.

2. Exclusion Criteria

Eligible participants must not meet any of the following exclusion criteria:

1. Unable to tolerate ophthalmic imaging.
2. Presence of neovascular AMD on OCT as confirmed by an ophthalmologist.
3. Presence of significant media opacity preventing adequate retinal imaging.
4. Presence of concurrent retinal disease which may confound assessment.

C. Participation Details (Risks, Compensation, Results)

Participation in this study poses minimal to no risk to subjects.

Imaging Devices: FDA-approved ophthalmic imaging systems will be used in this study. These are all standard imaging devices commonly encountered during a routine eye exam and pose no risk to the subject. Sensitive participants may experience some discomfort or light sensitivity due to imaging. This should be mild and brief.

Pupillary Dilation: It is expected that most participants will enroll and complete the study on the same day as their clinical appointment. Pupillary dilation is a standard procedure of a clinical appointment and will not need to be repeated if performed on the same day. If a participant chooses to complete the study on a different day, Phenylephrine hydrochloride (2.5%) and Tropicamide (1%) will be used to dilate the pupil of the participant's eye. Dilation of the pupil is necessary to obtain quality imaging of the back of the eye.

A concern about the use of these drugs is that they can precipitate acute angle closure in a very small percentage of patients (~1:20,000). This would result in a painful eye, blurry vision, and possibly nausea. In addition, a small proportion of the population can develop conjunctivitis in response to topically applied eye drops. This is a benign condition that is self-limited upon discontinuing the drops and will either spontaneously resolve in one to three days without treatment or can be treated with mild anti-inflammatory medications if needed.

To minimize the risk of an acute angle closure event, we will ascertain whether a subject has previously had their eyes dilated or not. Successful previous dilation eliminates the prospective risk of an acute angle closure event. Fortunately, subjects who are susceptible to this problem can be identified by an ophthalmic exam prior to administering the drug. Before beginning this study, every subject will be examined to ensure they are not susceptible to such an acute angle closure event. The exam will be administered under the supervision of an ophthalmologist at the UW Health Eye Clinics. We may use a slit lamp or a pen light test to check for the presence of an open angle. In addition, we will carefully instruct the subject that if they experience any of the symptoms (painful eye, blurry vision, and possibly nausea) to let us know right away.

To minimize the risk of conjunctivitis associated with pupillary dilation, personnel administering drops will wear gloves prior to handling and administering the eye drops.

Confidentiality Breach: There is a risk that patient information could be unintentionally shared with others (e.g. an unlawful data breach). To minimize this risk strict adherence to the IRB protocol will be maintained.

For Participants Enrolled in Protocol 2023-1715 FPF in AMD Only: To minimize the risk of a breach of confidentiality, only coded images and data will be shared. The images and data will be transferred to OcuSciences using one of the UW-Madison Office of Compliance Approved Tools for Exchanging and Storing PHI (e.g., Globus). Images and data will be shared, used, and maintained in compliance with the approved Data Transfer and Use Agreement (DTUA) between the UW-Madison study team and OcuSciences.

No potential direct benefits to participants are expected.

Participants will be given fifty dollars for compensation for their time. All imaging procedures will be paid for through the study. No economic burden to participants is expected.

Participants will not be informed of the results of the study. Unexpected results or abnormal findings which are inconsistent with clinical picture may be shared with participants through the managing ophthalmologist.

STUDY DESIGN

A. Study Design:

This study is a single site pilot comparative imaging study in which enrolled participants will undergo dilated fundus exam as per standard of care. Study images will be obtained using Optos ultrawide field FAF and both blue and green ultrawide field FAF with Zeiss Clarus. AF imaging will also be performed on the Spectralis as it is currently the gold standard. The goal will be to obtain all images in 60-75 minutes over one visit. All images will be recorded in digital format and stored in a computer at the site in the instrument computer software. Images will be assessed, and area of geographic atrophy measured independently by two experienced readers.

B. Enrollment of Participant into the Study:

Participants will be recruited at a regular UW Health - Eye clinic visit by the clinician responsible for their care. Participants will be recruited based on information contained in their private/protected records (e.g., medical records – a diagnosis of GA due to AMD with certain characteristics) that has been reviewed by the clinician. The clinician will make initial contact with potential participants. Interested patients would be referred by the clinician to a study team member for consent discussion. Written informed consent will be obtained from each study participant prior to enrollment into the study. After obtaining a signed informed consent form, a unique identification number (code) will be assigned to the

participant. This participant's identity will be masked from the ophthalmologist and the readers and will be securely maintained by the study coordinator until completion of the study.

Participants will have diagnosed GA secondary to AMD in one or both eyes. Atrophy may be unifocal or multifocal. Atrophy may be subfoveal or extrafoveal, with at least twenty-five percent of eyes having subfoveal GA. Area of geographic atrophy will be limited to between 1.25 mm^2 and 23 mm^2, with seventy percent of eyes having GA area between 2.5 mm^2 and 17.5 mm^2. These criteria are based on standard inclusion criteria used for clinical trials. A custom developed algorithm will be used to measure area of GA in real time to ensure that inclusion criteria for area and stratification requirements are met.

C. Imaging Procedure:

Retinal (back of the eye) images of one or both eyes of each participant will be acquired by experienced ophthalmic photographers. All images will be acquired by photographers in the Clinical Eye Research Unit (CERU). The images will be acquired following pupillary dilation, which could occur as part of the participant's regular clinical visit or at a separate research visit. If a participant chooses to complete the study on a different day, Phenylephrine hydrochloride (2.5%) and Tropicamide (1%) will be used to dilate the pupil of the participant's eye. Dilation of the pupil is necessary to obtain quality imaging of the back of the eye.

The participant will place their chin on the chinrest and head against the headrest for each device. The ophthalmic photographer will provide instructions/guidance as needed. The participant will be asked to focus on a target. Once the photographer has good alignment, a series of images will be taken with varying light intensities. This process will be completed for one or both eyes on all 3 devices. The total duration of the imaging procedures will vary based on if one or 2 eyes are being imaged and cooperation (e.g. fixation, light sensitivity) of each participant. It is estimated that the imaging procedure could take up to 2 hours for both eyes. If imaging 2 eyes, the imaging procedure on each device is estimated to take 15 minutes on the Clarus, 15 minutes on the Optos, and 40 minutes on the Spectralis. This includes set-up (such as instructions, adjustment of participant head position and maneuvering of camera by the operator) but not the 30-minute break between the devices. If only 1 eye is being imaged, the duration should be cut in half.

Pupillary Dilation (occurring at regular clinic visit or at research-only visit (after consent) → Optos FAF → Clarus green FAF → Clarus blue FAF → 30-minute break → Spectralis FAF + OCT

Retinal photoreceptor bleaching is a known phenomenon following FAF. As this normal and transient effect may confound subsequent retinal imaging, care will be taken in order of acquisition using the above protocol [13].

D. Image Evaluation:

Coded images are transferred to the reading center via sFTP within the WRC network. Images are stored in secure servers at the WRC for grader access. The readers/graders will be trained by the WRC ophthalmologists in the data-collection format. The readers/graders are certified in GA assessment. All WRC graders go through a rigorous certification program with continuous quality control, and all participate in multiple phase 3 trials grading a large volume of images.

The images will be displayed in digital format, one-at-a-time on each reader's calibrated monitor. Images from all three devices will be evaluated in a common display software, so the graders will not be masked to image type. However, the sets of images will not be evaluated at the same time; grading will be separated by time. We propose that the images be separated so that there is a gap of at least 2 days before other images of the same participant are reviewed by a grader. Data will be captured in electronic case report forms based on the grading questions listed in appendix A.

If for any image there is disagreement between the measure of GA area of greater than ten percent between the two readers, a third senior reader will need to adjudicate. The adjudicator independently reviews the images and then, with access to both graders' evaluation of GA area, arbitrates between the two grades.

After double reads are performed on all images and adjudication is complete, the data will be locked. In case of adjudication, the adjudicators data will be considered final. In cases where adjudication was not required, the first graders record will be considered final. A comparison of final GA area as measured on Spectralis, Optos, and Clarus images will be performed. Images with different GA area measurements between the two devices will be reviewed by the principal investigator and the grading team to document possible reasons for differences. No data will be modified during this reason documentation process.

Participants will have research OCT images collected for independent confirmation of absence of neovascular AMD. All data will be collected in an Excel spreadsheet stored in WRC secure servers.

E. Data Analysis:

GA area measurements between Spectralis FAF and within the 30-degree region of Clarus and Optos will be compared using Bland Altman Plots. Mean difference and 95% confidence intervals will be documented. Intergrader agreement within each modality will also be compared.

In addition, area of GA and detection of abnormal FAF regions outside the 30-degree region of Clarus and Optos will also be compared. The percentage of ungradable images within each device will also be analyzed.

INFORMED CONSENT

Patients will be individually approached and introduced to the study by their clinician. Interested patients would be referred by the clinician to a study team member for consent discussion. Written informed consent will be obtained from each study participant prior to enrollment into the study. A member of the study team will obtain informed consent in an exam room at the UW Health – University Station Eye Clinic. The consent process will be conducted face to face and in person. As the recruitment process could occur during a clinical visit, the waiting period available between informing the prospective participant and obtaining the consent could be minimal. As such, participants who need additional time to consider the study, may return for a separate research visit. The study will be discussed at appropriate language level and all questions will be answered, with the study physician ensuring that the potential participant understands the information. Participants will be encouraged to ask any questions throughout the consent process and study participation. The study team will follow HRP-090 - SOP - Informed Consent Process for Research. A written informed consent must be signed

and dated by the participant, and the investigator and/or designee obtaining the consent. HRP-091 - SOP - Written Documentation of Consent will be followed in obtaining written consent.

The signed informed consent will be retained with the study records at the site. It is the responsibility of the study personnel to assure that informed consent is obtained from each participant in accordance with GCP guidelines. Participants will be given a copy of the informed consent document.

Participants may withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a participant if, in his or her clinical judgment, it is in the best interest of the participant or if the participant cannot comply with the protocol. Attempt should be made to complete any examinations and the sponsor must be notified of all withdrawals.

Waiver of Signed Consent - For Participants Enrolled in Protocol 2023-1715 FPF in AMD Only
We are requesting a waiver of signed consent to obtain consent to share coded images and related-data with OcuSciences, Inc., the manufacturer of the investigational camera used in Protocol 2023-1715 FPF in AMD (see Study Documentation, section D. Data Sharing). We will obtain consent verbally via telephone call using an IRB-approved telephone script. Verbally obtained informed consent will be documented on the telephone script and in the electronic medical record. If participants provide verbal consent, we will mail each participant an IRB-approved information letter that contains the description of the image and data sharing information. We feel the waiver of signed consent is appropriate for this instance because the study is non-significant risk and the details of the change are easily conveyed via telephone conversation. Additionally, there is only one clinic visit for this study. Due to participants' age (50 or older) and possible vision impairment due to AMD/GA, it is impractical to ask participants to return to clinic to complete written consent

PROTECTING THE PRIVACY OF PARTICIPANTS

To ensure the privacy interests of participants, procedures will be performed in a private area where others cannot observe procedures or overhear conversation between participants and the research team. All members of the study team are up to date on institutional HIPAA training and are authorized to access necessary records as allowed by the legal medical record holder. No information which could pose legal or reputational risks to participants will be collected.

ADVERSE EVENT REPORTING

An adverse event is any symptom, sign, illness, or experience, which develops or worsens during the course of the study, which is considered device or procedure related. Any adverse event occurring during the study that is related to the study device and/or procedure will be considered to be an adverse event and will be recorded.

The study team will work to identify potential problems during the initial visit and participants will be asked about any issues at this time. Data will be monitored for problems at time of analysis and investigators will review the data as necessary, addressing any issues on an on-going basis.

The study physician will record the adverse experience(s) and will provide the date and time of onset, severity, the relationship to study procedure, the date of resolution (or the fact that the event

continues), the action taken, and the outcome of the adverse experience. A causality assessment will be made for every adverse experience.

A. Recording

The Investigator will monitor each participant closely for the development of adverse events and record all such events. Whenever possible, the Investigator should group together, into a single term, signs and symptoms that constitute a single diagnosis.

B. Follow up

All adverse events should be followed up in accordance with good clinical practice.

C. Severity

Adverse events should be graded for severity and noted in the description of the event. A severity category of mild, moderate, or severe, as defined below, should be determined and entered on the AE form.

- Mild – causing no limitation of usual activities.
- Moderate – causing some limitation of usual activities.
- Severe – causing inability to carry out usual activities.

D. Relationship

The study physician will be asked to document his/her opinion of the relationship of the event to the study treatment as follows

- None – the event can be readily explained by the participant's underlying medical condition or concomitant therapy and no relationship exists between the study treatment and the event. In this event, an alternative etiology should be indicated.
- Unlikely – the temporal relationship between the event and the administration of the study treatment is uncertain and it is likely that the event can be explained by the participant's medical condition or other therapies.
- Possible – there is some temporal relationship between the event and the administration of the study treatment, and the event is unlikely to be explained by the participant's medical condition or other therapies.
- Probable – the temporal relationship is compelling between the administration of the study treatment and the event cannot be explained by the participant's medical condition or other therapies.

All adverse events will be reviewed by the enrolling investigator who will document with clinical collaborators' opinions (if necessary) regarding the relationship of the event to the study assessment.

E. Serious Adverse Event

Definition: A serious adverse event (SAE) includes any adverse reaction that:

- is fatal or immediately life threatening,
- results in permanent impairment of a body function or permanent damage to the body structure,
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, or
- in the opinion of the investigator, present a significant hazard to the participant.

Any serious adverse event, including death due to any cause, which occurs during this study, must be reported promptly.

- All SAEs require telephone notification and written SAE report within 24 hours to the Medical Monitor.
- All SAEs must be reported to the IRB immediately.

The responsible investigator must determine whether the seriousness of the event warrants removal of any participant from the study. He/she should, in any case, institute appropriate diagnostic and therapeutic measures and keep the participant under observation for as long as is medically indicated.

STUDY DOCUMENTATION

A. Regulatory Documentation for Study Initiation

The following documents must be prepared prior to the initiation of the study:

- Approved Clinical Study Protocol.
- Sample of the Informed Consent to be used.
- Signed copy of the approval notice from the IRB.

B. Data Collection from Medical Record/Participant

We will collect the required demographic and clinical information, as described by this protocol and the variables to be analyzed. The investigator or a designee will be properly trained.

The study coordinator will maintain a paper log of the subjects enrolled (key linking medical record number to a unique study code) in a secured locked location used for other clinical trial documents. A separate data collection sheet will be maintained electronically on a secure, departmental server, which is backed up on a regular basis (Department of Ophthalmology & Visual Sciences). The coded data collection sheet will contain private health information pulled from the subject's medical record. This information will include: Date of Visit, Age, Gender, Visual Acuity and Lens Status (phakic or pseudophakic). Any adverse events will also be listed on the data collection form (if applicable).

C. Maintenance and Retention of Records

All study documentation is to be kept in a secure and safe place throughout the study. Once the study is completed, the records will be maintained according to Policy UW-4032 Data Stewardship, Access, and Retention.

D. Data Sharing

For Participants Enrolled in Protocol 2023-1715 FPF in AMD Only:
Data will be shared with the DOVS staff conducting protocol 2023-1715. Data will be stored and maintained on a secure, department server.

OCT and FAF images and data will also be shared with the device manufacturer, OcuSciences, Inc., to be used as a reference to better understand, evaluate, and refine the FPF image analysis software. The images and data will be coded before they are provided to OcuSciences. The images and data will be transferred to OcuSciences using one of the UW-Madison Office of Compliance Approved Tools for Exchanging and Storing PHI (e.g., Globus). Images and data will be shared, used, and maintained in compliance with the approved Data Transfer and Use Agreement (DTUA) between the UW-Madison study team and OcuSciences.

D. Retention for Future Research

Data and images from this study may be shared with DOVS investigators conducting similar research studies (e.g., studies comparing images taken with other imaging modalities). Participants will be provided with the option to share data and images for future during the consent discussion. Participant consent must be obtained before any images or data are shared. Participants will also be notified that they may withdraw their consent at any time and withdrawing will not affect their medical care or participation in this study. Data and images will be stored on secure DOVS servers and will only be shared with DOVS study team members.

REFERENCES

1. Chen A, Dang S, Chung MM, Ramchandran RS, Bessette AP, DiLoreto DA, Kleinman DM, Sridhar J, Wykoff CC, Kuriyan AE. *Quantitative Comparison of Fundus Images by 2 Ultra-Widefield Fundus Cameras*. Ophthalmol Retina. 2021 May;5(5):450-457. doi: 10.1016/j.oret.2020.08.017. Epub 2020 Aug 29. PMID: 32866664; PMCID: PMC8501635.
2. Matsui, Yoshitsugu, et al. *Comparisons of Effective Fields of Two Ultra-Widefield Ophthalmoscopes, Optos 200Tx and Clarus 500*. BioMed Research International 2019 (2019): 7. ProQuest. Web. 1 June 2023.
3. Wan Ling Wong, Xinyi Su, Xiang Li, Chui Ming G Cheung, Ronald Klein, Ching-Yu Cheng, Tien Yin Wong. *Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis*. The Lancet Global Health, Volume 2, Issue 2, 2014, Pages e106-e116,ISSN 2214-109X.
4. Robyn H Guymer, Thomas G Campbell. *Age-related macular degeneration*. The Lancet, Volume 401, Issue 10386, 2023, Pages 1459-1472. ISSN 0140-6736.
5. Rein DB, Wittenborn JS, Burke-Conte Z, Gulia R, Robalik T, Ehrlich JR, Lundeen EA, Flaxman AD. *Prevalence of Age-Related Macular Degeneration in the US in 2019*. JAMA Ophthalmol. 2022 Dec 1;140(12):1202-1208. doi: 10.1001/jamaophthalmol.2022.4401. PMID: 36326752; PMCID: PMC9634594.
6. *GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study*. Lancet Glob Health. 2021 Feb;9(2):e144-e160. doi: 10.1016/S2214-109X(20)30489-7. Epub 2020 Dec 1. Erratum in: Lancet Glob Health. 2021 Apr;9(4):e408. PMID: 33275949; PMCID: PMC7820391.
7. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. *Age-related macular degeneration*. Lancet. 2012 May 5;379(9827):1728-38. doi: 10.1016/S0140-6736(12)60282-7. PMID: 22559899.
8. Delori FC, Dorey CK, Staurenghi G, Arend O, Goger DG, Weiter JJ*. In vivo fluorescence of the ocular fundus exhibits retinal pigment epithelium lipofuscin characteristics*. Invest Ophthalmol Vis Sci. 1995 Mar;36(3):718-29. PMID: 7890502.
9. Yung M, Klufas MA, Sarraf D. *Clinical applications of fundus autofluorescence in retinal disease*. Int J Retina Vitreous. 2016 Apr 8;2:12. doi: 10.1186/s40942-016-0035-x. PMID: 27847630; PMCID: PMC5088473.
10. Xu, A., Chen, C. *Clinical application of ultra-widefield fundus autofluorescence*. Int Ophthalmol 41, 727–741 (2021).
11. Caril Zeiss Meditec, Inc. *Zeiss Clarus 500 Introduces Broad Line Fundus Imaging For Autofluorescence*. Zeiss.com, 2017, https://www.zeiss.com/meditec/en/products/retinal-cameras/clarus-700/zeiss-clarus-700-specifications.html#white-paper.
12. Fleckenstein M, Adrion C, Schmitz-Valckenberg S, Göbel AP, Bindewald-Wittich A, Scholl HP, Mansmann U, Holz FG; FAM Study Group. *Concordance of disease progression in bilateral geographic atrophy due to AMD*. Invest Ophthalmol Vis Sci. 2010 Feb;51(2):637-42. doi: 10.1167/iovs.09-3547. Epub 2009 Sep 24. Erratum in: Invest Ophthalmol Vis Sci. 2010 Mar;51(3):1800. PMID: 19797219.
13. Breazzano, Mark P., et al. *Photopigment Bleaching Phenomenon with Scanning Laser Ophthalmoscopy and Fluorescein Angiography*. Ophthalmic Surgery, Lasers & Imaging Retina 50.9 (2019): 590-2. ProQuest. Web. 1 June 2023.

APPENDIX A

Grading Form

FAF/FP Questions	Available Response	Dependency	Description
FAF/FP Confidence Score			
Confidence Score	CS1: High confidence CS2: Adequate confidence CS3: Inadequate confidence Not Applicable	If CS1, Reason defaults to 'Not Applicable'.	CS1 indicates grading confidence is high with no significant problem caused by image quality CS2 indicates grading confidence is adequate but suboptimal, image quality noticeably interfered CS3 indicates grading confidence is inadequate to determine major disease parameters
Confidence Score Reason	Technical Patient Both Unknown Not Applicable	If Confidence Score is CS1, Reason defaults to 'Not Applicable'.	If CS2 or CS3, Reason is selected.
FAF/FP Morphology			
Decreased autofluorescence within field 2	Absent Questionable Definite, Cannot Grade Not Applicable	If answered "definite', area question, presence of pattern in the junctional zone, and focality of decreased FAF are enabled. If Absent, Questionable, Cannot Grade or Not Applicable, area question, presence of pattern in the junctional zone and	Decreased FAF should be ≥ I2 (250 µm) at the smallest diameter.

		focatlity of decreased FAF are disabled.	
Area and proximity of decreased autofluorescence within field 2	Area Size (0.01-41.00 mm^2) Perimeter (0-100000 mm) Distance to Fovea (0-3.6 mm) Cannot Grade Not Applicable	If Not applicable or Cannot Grade is chosen, the area, perimeter, and distance to fovea will not be provided	Area of Decreased FAF by planimetry. Perimeter length of Decreased FAF, and Distance of the Decreased FAF to the center of the fovea are generated as answers to this question. Not applicable indicates no Decreased FAF, cannot grade indicates Decreased FAF cannot be measured.
Decreased autofluorescence outside of field 2 (Applicable for Optos and Clarus only)	Absent Questionable Definite Cannot Grade Not Applicable		Abnormal autofluorescence pattern including halo surrounding GA. When GA is absent, presence of pattern is not applicable
Area and proximity of decreased autofluorescence outside of field 2 (Applicable for Optos and Clarus only)	Area Size (0.01-41.00 mm^2) Perimeter (0-100000 mm) Distance to Fovea (0-3.6 mm) Cannot Grade Not Applicable		When GA is absent, focality of decreased autofluorescence is not applicable
Background autofluorescence	Absent Questionable Definite, non-reticular pattern Definite, reticular pattern Cannot Grade Not Applicable		Any irregularity in the normal FAF, such as the presence of a grainy, mottled, speckled or reticular pattern is considered background FAF.
FAF Comments			
General comments needed	Yes No	If yes, “General comments detail” is enabled.	

General comments detail	[Free Text]	Default disabled	Comments deemed to add value to the grading information