DRCR Retina Network

Home OCT Monitoring System: Feasibility Study

(Protocol AK)

Sponsor: Jaeb Center for Health Research (JCHR)

Version Number: 1.0
July 22, 2021

Signature Page

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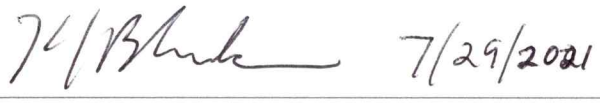
Signature/Date	 7/29/2021

KEY ROLES

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VERSION HISTORY

The following table lists versions of the protocol.

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Claire Calhoun	Cynthia Stockdale	09JUL2021	Initial

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AI	Artificial Intelligence
AMD	Age-related macular degeneration
CC	Coordinating Center
CRF	Case Report Form
E-ETDRS	Electronic-Early Treatment Diabetic Retinopathy Study
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Committee of Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
JCHR	Jaeb Center for Health Research
nAMD	Neovascular age-related macular degeneration
NOA	Notal OCT Analyzer
NVDC	Notal Vision Diagnostic Center
OCT	Optical Coherence Tomography
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SD-OCT	Spectral Domain OCT
VA	Visual Acuity

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Home OCT Monitoring System: Feasibility Study
Précis	Treatment of retinal vascular diseases with anti-VEGF therapy is a major improvement but at a very high treatment burden and cost for patients and the healthcare system. The ability to perform daily monitoring of intraretinal fluid and subretinal fluid using a home OCT system offers the opportunity to obtain a detailed assessment of fluid over time. Understanding retinal and subretinal fluid dynamics for an individual patient may allow customization of treatment that may reduce treatment burden and improve the chance for better long-term VA outcomes. In addition, daily fluid monitoring could provide a better understanding of the differences between drugs in anatomical and functional outcomes. Notal Vision has developed an OCT system for at-home use, called Home OCT system. The Home OCT system has only been used in a few, small in-clinic studies. Large studies are needed to understand the potential utility of home OCT monitoring. However, feasibility of the Home OCT system outside of the clinic must first be assessed prior to implementing monitoring in a large-scale study. This feasibility study will collect information on the logistics of the Home OCT system needed to plan a larger study and will also contribute to the evaluation of fluid patterns between in-office visits. Comparing the Home OCT scans to the SD-OCT scans performed in-office will also provide additional validation of the ability to detect fluid volumes and fluid absence/presence.
Objectives and Corresponding Outcomes	Home OCT Use Objectives • Develop and assess methods of OCT image transfer to Notal and/or the DRCR Retina Network Coordinating Center and/or the DRCR Retina Network OCT Reading Center • Develop and assess methods for transfer of files containing Notal interpretations (presence and volume of intraretinal and subretinal fluid) of OCT images to the Coordinating Center • Assess methods and timeliness of OCT image interpretation by Notal ○ Mean time between scan acquisition and fluid measurements (from the AI algorithm) becoming available on web viewer • Assess ability of clinic and Notal staff to educate patient about conducting Home OCT monitoring

PARTICIPANT AREA	DESCRIPTION
	○ Number of support telephone calls from Notal required to maintain a regular scanning schedule at home or to correct quality issues • Assess willingness of patients to participate in a program requiring home OCT monitoring ○ Proportion of participants approached by the site to enroll in study who were not interested in using the device ○ Proportion of participants approached by the site to enroll in study who were not capable of conducting Home OCT monitoring • Assess ability of patients to complete home OCT monitoring as specified in the protocol ○ Number of screen failures (participants that were sent the Home OCT device but were unable to initiate self-scanning and were required to return the device to Notal) ○ Proportion of participants who maintained regular scanning (definition TBD) and the frequency of scanning ○ Proportion of good quality scans AMD-Specific Objectives • Assess fluid dynamics ○ Gather information to contribute to the database for determining criteria for triggering an alert for a visit to the ophthalmologist ○ Review Surveillance Reports on the Notal OCT Web Viewer ○ Assess the following for intraretinal, subretinal, and total retinal fluid in the 3x3 mm area: ▪ Rate of change in fluid on Home OCT between treatments ▪ Minimum/maximum fluid volume reached between treatments ▪ Fluid presence interval between treatments ▪ Fluid-free interval between treatments ▪ Fluid regression interval between treatments ▪ Fluid increase interval between treatments ▪ Cumulative fluid presence interval over 6 months ▪ Cumulative fluid-free interval over 6 months ▪ Ratio of cumulative presence interval to cumulative free interval

PARTICIPANT AREA	DESCRIPTION
	▪ Area under the fluid volume curve ▪ Persistent fluid yes/no ▪ Maximal weekly fluid volume increase rate [nL/week] ▪ Number of fluid recurrence events • Assessment of whether scans obtained on different days would be sufficient for home monitoring o Compare information gained on images obtained daily versus information on images 3-7 days apart. • Determine agreement of SD-OCT image interpretation by the Reading Center with interpretation of home monitoring OCT images by the Notal OCT Analyzer (NOA) AI algorithm on the days that patients are examined in their ophthalmologist's office. The agreement will be analyzed for the identification, quantification (where applicable), and localization of intraretinal and subretinal fluid
Study Design	Multi-center, prospective study
Number of Sites	3
Population	Key Inclusion Criteria: • Age ≥ 55 years • Able to read and understand English • Has cognitive capacity to provide consent and follow instructions • Participant's home has a table with a smooth, flat surface close to an outlet to support placement of the device for 6 months (device dimensions are 9.8" wide x 14.2" deep x 16.9" high) • Participant will be able to set up the Home OCT device by themselves or with assistance from others (device is 16 pounds without packaging, 17.8 pounds with packaging) • Lives in an area with adequate cell phone reception (for the Home OCT data to be properly uploaded to the cloud) • Has a telephone number (home or cell) for Notal to call and provide Home OCT assistance and reminders • Able and willing to perform daily home OCT monitoring tests for six months without interruption (such as travel of more than 14 days). • Able to perform initial self-scan in the 7 days following receipt of the Home OCT device (ships in 3-5 days) • No plans to move out of the area in the next six months • Active choroidal neovascularization (CNV) due to AMD in at least one eye in which the investigator intends to treat with anti-VEGF o AMD defined as presence of at least one large drusen in either eye (determined by investigator)

PARTICIPANT AREA	DESCRIPTION
	○ Active CNV defined as presence of intraretinal or subretinal fluid (determined by investigator) • Visual acuity of 20/20 to 20/320 (Snellen) or 24 to 88 letters (ETDRS) Key Exclusion Criteria • Previous treatment for CNV (intravitreal injection of any anti-VEGF agent, or any other AMD therapy) • Prior intravitreal injection of any anti-VEGF agent or treatment with laser for any indication • Choroidal neovascularization from ocular disease other than AMD • Dense cataract or other media opacity that would preclude adequate imaging of the macula
Sample Size	10 participants (participants can have more than one study eye)
Treatment Groups	None
Participant Duration	6 months
Protocol Overview/Synopsis	1. Informed consent will be obtained for screening. 2. Eligibility will be assessed and standard care visual acuity will be recorded. Any other visit procedures may be performed at investigator discretion. An OCT taken as part of standard care procedures in the prior 2 weeks may be used for the investigator to confirm eligibility. Data from standard care procedures will be entered on Case Report Forms, and the SD-OCT images obtained as part of standard care will be uploaded to the Coordinating Center. 3. Eligible eyes will be enrolled and the site will notify Notal Vision Diagnostic Center (NVDC) of the enrolled participant. Site staff will provide the participant with an overview and instructions for using the Home OCT device, including set-up instructions. 4. NVDC will then ship the Home OCT device system to the participant. The participant will set-up the Home OCT system by themselves or with a family member, friend, or caregiver once delivered to their house (estimated shipping time 3-5 days). Remote support is available by the NVDC via phone. 5. The first day of follow-up begins with the first successful self-imaging session with the Notal Home OCT on both eyes. Participants will perform daily Home OCT monitoring as part of the study for six months. 6. NVDC will perform monthly participant engagement calls for the duration of the home monitoring period. The first call will take place two weeks after the first test session.

PARTICIPANT AREA	DESCRIPTION
	7. Notal Vision patient engagement specialist will contact participant if they are not scanning regularly or if images are not of adequate quality. NVDC will reach out on the next business day following two consecutive days of no self-testing. Training will be repeated if images are not of adequate quality. 8. Follow-up visits will occur at time points the participant is normally seen as part of standard care. All in-person visit procedures are at investigator discretion as part of standard care. Any OCT scans obtained on the study eye(s) will be uploaded to the Coordinating Center. Data on standard care visual acuity, nAMD treatment, and participant experience with the Home OCT system will be captured on Case Report Forms. 9. At the end of 6 months the participant will return the Home OCT system to Notal using the provided box and shipping label. The participant will complete the study and can continue with their standard care visits outside the study.

Chapter 1: Background Information

1.1 Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss for individuals aged 60 years or older. Activities such as reading, driving, and recognizing faces become impaired with destruction of the macula, the area responsible for sharp, fine-detail vision. Within the United States, the estimated number of people with AMD is expected to increase from about 2 million to 5.4 million within the next 30 years.[1] The global cost of visual impairment due to AMD is estimated to be $343 billion, including $255 billion in direct health care costs.[2]

AMD can be categorized as either nonexudative ('dry') or neovascular/exudative ('wet'). In nonexudative AMD, degeneration of the RPE in the foveal center leads to photoreceptor apoptosis and a loss of central vision. There is no current treatment for nonexudative AMD. In neovascular AMD, choroidal neovascularization (CNV) leads to uncontrolled growth of new blood vessels under the macula that destroys the macula.[3] Without treatment, legal blindness can occur in about 79-90% of eyes with neovascular AMD.[4]

Optical Coherence Tomography (OCT) was originally developed in 1991 as a non-invasive imaging technology to generate cross-sectional imagery of ocular tissues *in vivo*. Cross-sectional visualization of the retina has proven to be a valuable tool in the identification and assessment of structural abnormalities that are not visible with ophthalmoscopic or biomicroscopic examination. OCT has become a leading diagnostic tool in the detection, diagnosis and treatment of retinal diseases and conditions, including age-related macular degeneration (AMD), diabetic macular edema, and retina vein occlusion.

1.1.1 Current Treatment Options for Neovascular AMD

Anti-vascular endothelial growth factor (VEGF) agents have profoundly transformed the management and prognosis of neovascular AMD. Improvements in vision preservation and quality of life is often attributed to anti-VEGF agents. Clinical practice guidelines in the United States and Europe agree that anti-VEGF agents are first-line treatment for neovascular AMD due to their ability to improve visual and anatomic outcomes over other therapies such as laser photocoagulation and photodynamic therapy.[3,5-7]

Depending on the anti-VEGF agent, the FDA-approved prescribing guidelines recommend an injection every 4-12 weeks after several initial loading doses.[8,9] In practice, current anti-VEGF treatment frequency algorithms are driven primarily by the presence or absence of fluid on OCT. The frequency of OCT assessment of fluid is empirical and limited by the in-office presence required to obtain an OCT. There is a lack of information on the change in fluid between visits, such as the time to resolution of fluid with treatment and how this time may vary between anti-VEGF agents. Further, predicting the fluid-free interval and the time to recurrence is difficult given the current infrequency of fluid assessment (OCT) and the considerable variability between patients in the time to recurrent exudative disease activity.

Innovations are needed to lessen the burden of anti-VEGF injections and monitoring while still maintaining vision and treatment efficacy. One such innovation that is expected to change the treatment paradigm for neovascular AMD is the development of more advance at-home monitoring technology.

1.1.2 Notal Vision Home OCT

Notal Vision Inc. (Manassas, VA) pioneered one of the first cloud-based platforms to connect healthcare providers, Notal Vision's Diagnostic Clinic, and their patients through a personalized, remote management of ophthalmic diseases. Their first application of the cloud-based platform was ForseeHome®, an FDA-cleared diagnostic device that monitors visual changes in patients at risk of vision loss from undiagnosed neovascular AMD.[10]

The Notal Home OCT, the next application of Notal's cloud-based platform, is designed for technician-free operation in the home setting and meant to complement current disease monitoring strategies. The Notal Home OCT allows providers to monitor disease status and progression continually and identify a recurrence of fluid faster than if identified at periodic in-clinic visits. A machine learning algorithm called the Notal OCT Analyzer (NOA™) detects pathological fluid in exudative retinal diseases including wet AMD, macular edema, and retinal vein occlusions. If fluid is identified using the NOA, the Notal Home OCT then generates a report of the findings and conveys the results to the patient's treating physician. Generated metrics include intraretinal and subretinal fluid volume in a 3 mm x 3 mm field of view, minimum/maximum fluid volume reached between treatments, and intervals for presence, absence, regression, and increase of fluid.

In one prior study, Notal Vision demonstrated that 90% of 196 elderly AMD patients with VA >20/400 were able to self-operate the Notal Home OCT system in clinic and capture analyzable images in clinic following a short two-minute tutorial. The majority of participants (>60%) reported the self-scan method was quick and easy to understand and complete, and that the headrest was comfortable and easy to use.[11]

In another study, the accuracy of the NOA to detect presence/absence of fluid (on Home OCT scans obtained in clinic) was compared to that of three retina specialists. When tested using 142 cube scans, the accuracy of the NOA vs. retina specialists (with 95% confidence interval) was 91%±7%, sensitivity was 92%±6%, and specificity was 91%±6% for detecting fluid presence. In another study, the agreement between NOA vs. human grading for both fluid presence and quantity was assessed among 211 scans obtained at-home over 1 month by four individuals with nAMD. The NOA and human determination of presence of fluid agreed in 94.7% of cases. From a subset of 24 scans with fluid, the correlation coefficient for NOA vs. human fluid volume measurements was 0.996 and mean absolute difference was 1.5 nL (correlation for interhuman agreement was 0.995 with mean absolute difference of 1.2 nL).[12] The Notal Home OCT system may prove to be a valuable tool in clinical applications given the feasibility of automated delineation of retinal contours.[13]

1.2 Rationale

Treatment of retinal vascular diseases with anti-VEGF therapy is a major improvement but at a very high treatment burden and cost for patients and the healthcare system. The ability to perform daily monitoring of intraretinal fluid and subretinal fluid using a home OCT system offers the opportunity to obtain a detailed assessment of fluid over time. Understanding retinal and subretinal fluid dynamics for an individual patient may allow customization of treatment that may reduce treatment burden and improve the chance for better long-term VA outcomes. In addition, daily fluid monitoring could provide a better understanding of the differences between drugs in anatomical and functional outcomes.

Notal Vision has developed an OCT system for at-home use, called Home OCT system. The Home OCT system has only been used in a few, small in-clinic studies. Large studies are needed to understand the potential utility of home OCT monitoring. However, feasibility of the Home OCT system outside of the clinic must first be assessed prior to implementing monitoring in a large-scale study. This feasibility study will collect information on the logistics of the Home OCT system needed to plan a larger study and will also contribute to the evaluation of fluid patterns between in-office visits. Comparing the Home OCT scans to the SD-OCT scans performed in-office will also provide additional validation of the ability to detect fluid volumes and fluid absence/presence.

1.3 Study Design

This study is an observational feasibility study of eyes with neovascular AMD monitored for fluid using the Home OCT monitoring system from Notal. Participants in this study will continue with their standard of care treatment for nAMD and will perform daily Home OCT monitoring using the Notal system for six months without on-site supervision at home.

1.4 Study Objectives

The objective of this study is to assess feasibility and use of Home OCT. The specific outcomes for each objective below are detailed in Chapter 6.

Home OCT Use Objectives

- Develop and assess methods of OCT image transfer to Notal and/or the DRCR Retina Network Coordinating Center and/or the DRCR Retina Network OCT Reading Center
- Develop and assess methods for transfer of files containing Notal interpretations (presence and volume of intraretinal and subretinal fluid) of OCT images to the Coordinating Center
- Assess methods and timeliness of OCT image interpretation by Notal
- Assess ability of clinic and Notal staff to educate patient about conducting Home OCT monitoring
- Assess willingness of patients to participate in a program requiring home OCT monitoring

- Assess ability of patients to complete home OCT monitoring as specified in the protocol

AMD-Specific Objectives

- Assess fluid dynamics
- Assessment of whether scans obtained on different days would be sufficient for home monitoring
- Determine agreement of SD-OCT image interpretation by the Reading Center with interpretation of home monitoring OCT images by the Notal OCT Analyzer (NOA) AI algorithm on the days that patients are examined in their ophthalmologist's office.

1.5 Potential Risks of the Study

1.5.1 Known Potential Risks Related to Common Procedures

Many of the procedures in this study are part of daily ophthalmologic practice in the United States and pose few if any known risks.

1.5.2 Risks Related to Home OCT

The risks related to Home OCT include eye strain or tiredness and headache. There is also the risk for bodily injury if the device is not used according to manufacturer instructions.

Because the Notal Home OCT device is investigational, all of its side effects may not be known. There may be rare and unknown side effects.

1.5.3 Risks Related to Confidentiality

The risk of disclosure of protected health information is very small. Efforts are taken to ensure that this does not occur, in compliance with HIPAA.

1.5.4 Risk Assessment

The protocol risk assessment for this study has been categorized as no greater than minimal risk.

Although the Home OCT is an investigational device, it can be considered a non-significant risk device due to the following criteria:

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

- The device complies with the safety and EMC standards for lasers and ophthalmic instruments.
- It uses the standard 840 nm wavelength and its total power is less than 1 Milliwatt.

1.6 General Considerations

The study is being conducted in compliance with the policies described in the DRCR Retina Network policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

When feasible, data will be directly collected in electronic case report forms, which will be considered the source data.

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Approximately ten participants are expected to be enrolled into the follow-up phase. Recruitment will end once ten participants have successfully initiated the Home OCT system as part of the study. Screened participants who are unable to successfully initiate the Home OCT system within 7 days will be replaced. Additional participants may be recruited if necessary if participant withdrawal affects the ability to assess outcome measures. No more than 5 additional participants would be enrolled.

Study participants will be recruited at three clinical centers in the United States. All eligible participants will be included without regard to gender, race, or ethnicity. It is expected that each participating site will enroll at least one participant in the study, otherwise there is no restriction on number of participants to be enrolled by each site toward the overall recruitment goal. If each clinical center enrolls at least 2 participant every month, enrollment will be complete in approximately 2 months.

Clinical centers will complete a screening log that will record the number of new nAMD patients seen during the recruitment period and whether and why the participants did/did not enroll in the study. This information will help plan for a future, larger study.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, written informed consent will be obtained.

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form (ICF) to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the informed consent form has been signed.

2.2 Participant Inclusion Criteria

2.2.1 Individual-Level Criteria

Inclusion

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age ≥ 55 years
2. At least one eye meets the study eye criteria listed below

3. Able and willing to provide informed consent
4. Has cognitive capacity to provide consent and follow instructions.
5. In good general health (e.g. participant does not have a medical condition that would preclude ability to complete 6 months of OCT monitoring in the opinion of the investigator)
6. Able to read and understand English
7. Participant's home has a table with a smooth, flat surface close to an outlet to support placement of the device for 6 months (device dimensions are 9.8" wide x 14.2" deep x 16.9" high)
8. Participant will be able to set up the Home OCT device by themselves or with assistance from others in their household (device is 16 pounds without packaging, 17.8 pounds with packaging)
9. Lives in an area with adequate cell phone reception (for the Home OCT data to be properly uploaded to the cloud)
10. Has a telephone number (home or cell) for Notal to call and provide Home OCT assistance and reminders
11. Able and willing to perform daily home OCT monitoring tests for six months without interruption (such as travel of more than 14 days).
12. Able to perform initial self-scan in the 7 days following receipt of the Home OCT device (ships in 3-5 days)
13. No plans to move out of the area in the next six months
14. Will not receive any other drug or device that is not FDA-approved during the course of the study

2.2.2 Study Eye Criteria

To be eligible, the study participant must have at least one eye meeting all of the inclusion criteria and none of the exclusion criteria listed below. A participant may have two study eyes. The eligibility criteria for a study eye are as follows.

Study Eye Inclusion

a. Active choroidal neovascularization (CNV) due to AMD in which the investigator intends to treat with anti-VEGF
    - AMD defined as presence of at least one large drusen in either eye (determined by investigator)
    - Active CNV defined as presence of intraretinal or subretinal fluid (determined by investigator)
b. Visual acuity of 20/20 to 20/320 (Snellen) or 24 to 88 letters (ETDRS)

Study Eye Exclusion

c. Previous treatment for CNV (intravitreal injection of any anti-VEGF agent, or any other AMD therapy).
d. Prior intravitreal injection of any anti-VEGF agent or with laser for any indication
e. Choroidal neovascularization from ocular disease other than AMD
f. Dense cataract or other media opacity that would preclude adequate imaging of the macula

2.2.3 Non-Study Eye

There are no eligibility or exclusion criteria with respect to the non-study eye.

2.3 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history and performance of a physical examination by study personnel if needed to screen for exclusionary medical conditions. Medical history needed for eligibility assessment will be obtained by medical charts if available at the enrolling site; otherwise, it will be self-reported by the participant.

2.3.1 Baseline Testing Procedures

The following clinical information is needed to confirm eligibility and/or serve as baseline measures.

- If a procedure has been performed as part of usual care and provides sufficient information to complete case report form data collection, then it does not need to be repeated specifically for the study if it was performed within the defined time windows specified below.

1. Self-reported demographics (date of birth, sex, race, and ethnicity)
2. Standard care visual acuity testing in study eye *(within prior 21 days)*
    - If visual acuity in the non-study eye is available, it will also be collected.
3. Spectral-Domain OCT (SD-OCT) using Zeiss Cirrus or Heidelberg Spectralis in the study eye *(within prior 14 days)*
    - An OCT scan obtained as part of standard care may be used for the investigator to confirm AMD eligibility**.** OCT scans must be sent to the Coordinating Center.
4. Ocular examination in the study eye to screen for exclusionary medical conditions *(within prior 21 days)*
    - An exam is not required specifically for the study; standard care procedure is expected to provide sufficient information to complete case report form data collection and eligibility assessment.

Participants will receive a general overview (including a description of the device and a review of the Notal Home OCT set-up guide) of the self-operation of the Notal Home OCT by trained study personnel.

2.4 Enrollment and Home OCT Device Assignment and Delivery

Once an eligible participant is enrolled, the clinical site will notify Notal Vision Diagnostic Center (NVDC) via a secure file-sharing platform and will provide participant contact and shipping information (detailed in the Informed Consent Form). A Notal Home OCT device is then assigned to the participant. NVDC will contact the participant to confirm shipping address and review self-imaging instructions. NVDC will then ship the device (and return shipment supplies) to the participant's home (estimated shipping time 3-5 days). The device will be

delivered to the participant's home, with confirmation from the delivery service sent back to the NVDC.

2.4.1 Initial Set-Up

The participant will be asked to set-up the Home OCT system by themselves or with a family member, friend, or caregiver once delivered to their house. Remote support is available by the NVDC via phone during standard business hours of 8am - 6pm EST, if needed.

The subject will be asked to follow the steps detailed in the Set-up Guide included in the box:

1. Open the box and remove the Notal Home OCT.
2. Place the Notal Home OCT on a flat, sturdy surface such as a table or desk close to an electric outlet.
3. Connect the power supply to the device.
4. Connect the device to the electric outlet.
5. Turn on the device.
6. Adjust volume.
7. Touch the screen to start the video tutorial and calibration session.

NVDC will contact participant if no transmission is received within one business day from Home OCT device delivery. If a participant is unable to initiate daily Home OCT testing (e.g. the eye cannot calibrate during 7 separate attempts or the participant fails to test 7 consecutive days), the participant may be asked to discontinue self-imaging and return the device to the NVDC. If the device is returned due to non-compliance, the participant will be dropped from the study and considered a screen failure.

2.5 Screen Failures

Participants who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion. A Final Status Form will be completed, and the reason for screen failure will be noted.

Chapter 3: Follow-Up Visits and Testing

3.1 Home Monitoring

3.1.1 Daily Home OCT Monitoring

The first day of follow-up begins with the first successful self-imaging session with the Notal Home OCT on both eyes. Participants will be asked to perform daily Home OCT monitoring as part of the study for six months.

NVDC will perform monthly participant engagement calls for the duration of the home monitoring period. The first call will take place two weeks after the first test session.

Notal Vision patient engagement specialist will contact the participant if they are not scanning regularly or if images are not of adequate quality. NVDC will reach out on the next business day following two consecutive days of no self-testing. Training will be repeated if images are not of adequate quality. Participants can be withdrawn from the study due to noncompliance with self-imaging requirements.

At the end of 6 months, the participant will be contacted by Notal Vision and asked to discontinue daily monitoring and return the Home OCT system as soon as they are able. Notal Vision will provide a box and shipping label for the return shipment. The participant will complete the study and can continue with their standard care visits outside the study.

3.1.2 Data Upload and Processing

The data collected during the use of the Notal Home OCT device will be automatically transmitted through a cellular connection to the Notal Health Cloud for storage, processing, and backup. The Notal OCT Analyzer (NOA) artificial intelligence algorithm then processes the scans to identify and quantify any fluid present. The Home OCT scans and fluid data are then shown in the Home OCT Web Viewer. Only the DRCR Retina Network Coordinating Center will have access to the Home OCT Web Viewer during this study.

3.2 Study Visits

3.2.1 Study Visits and Procedures

Follow-up visits will occur at time points the participant is normally seen as part of standard care. All visit procedures are at investigator discretion as part of standard care. Standard care procedures will provide sufficient information to complete case report form data collection. Any OCT scans obtained on the study eye(s) will be uploaded to the Coordinating Center. Data on standard care visual acuity, nAMD treatment, and participant experience with the Home OCT system will be captured on Case Report Forms.

3.3 Treatment for nAMD in the Study Eye

Participants will receive standard care treatment for their nAMD at investigator discretion. Information on treatment regimen and anti-VEGF agents will be collected on the Case Report Forms. Treatment decisions are based on the investigator's usual care pattern and the investigator does not receive any data about the readings from the home monitoring system.

3.4 Treatment for Other Conditions in the Study Eye

If a condition other than nAMD develops during follow-up requiring treatment, it is at investigator discretion.

3.5 Treatment in the Non-Study Eye

Treatment in the non-study eye is at investigator discretion.

Chapter 4: Unanticipated Problem and Adverse Event Reporting

4.1 Unanticipated Problems

Site investigators will promptly report to the Coordinating Center (CC) all unanticipated problems meeting the criteria below. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

The CC also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur at the CC or at another participating entity such as a laboratory.

4.2 Adverse Events

As a no greater than minimal risk study, adverse events will not be collected in this study. The Case Report Forms will ask about occurrence of specific safety events of interest during the study.

4.3 Independent Safety Oversight

Because all in-office procedures in this study are performed as part of standard care, and because the Home OCT device is considered a non-significant risk device, there will be no formal review of protocol and materials or independent monitoring of adverse events by a Data and Safety Monitoring Committee (DSMC).

Chapter 5: Miscellaneous Considerations

5.1 Participant Compensation

Participant compensation will be specified in the informed consent form.

5.2 Participant Withdrawal

Participation in the study is voluntary and a participant may withdraw at any time. If a study participant is considering withdrawal from the study, the principal investigator should personally speak to the individual about the reasons and every effort should be made to accommodate him or her.

The goal for the study is to have as few losses to follow-up as possible. The Coordinating Center will assist in the tracking of study participants who cannot be contacted by the site. The Coordinating Center will be responsible for classifying a study participant as lost to follow-up.

For participants who withdraw, their data will be used up until the time of withdrawal.

5.3 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL.

The Coordinating Center will be provided with contact information for each study participant. Permission to obtain such information will be included in the Informed Consent Form. The contact information may be maintained in a secure database and will be maintained separately from the study data.

Phone contact from the Coordinating Center will be made with each study participant in the first month after enrollment. Additional phone contacts from the Coordinating Center will be made, if necessary to facilitate the completion of study requirements. A participant-oriented newsletter and a study logo item may be sent once.

5.4 Discontinuation of Study

The study may be discontinued by the Executive Committee prior to the preplanned completion of follow-up for all study participants.

Chapter 6: Statistical Considerations

6.1 Statistical and Analytical Plan

The approach to sample size and statistical analyses are summarized below. The analysis plan synopsis in this chapter contains the framework of the anticipated analysis. A Statistical Analysis Plan will provide more detail on the analyses for each outcome.

6.2 Sample Size

This study will enroll 10 participants from 3 sites. This was chosen as a convenience sample based on the number of Home OCT devices available at the desired study startup date.

6.3 Objectives and Associated Outcome Measures

Home OCT Use Objectives and Associated Outcomes

- Develop and assess methods of OCT image transfer to Notal and/or the DRCR Retina Network Coordinating Center and/or the DRCR Retina Network OCT Reading Center
- Develop and assess methods for transfer of files containing Notal interpretations (presence and volume of intraretinal and subretinal fluid) of OCT images to the Coordinating Center
- Assess methods and timeliness of OCT image interpretation by Notal
    - Mean time between scan acquisition and fluid measurements (from the AI algorithm) becoming available on web viewer
- Assess ability of clinic and Notal staff to educate patient about conducting Home OCT monitoring
    - Number of support telephone calls from Notal required to maintain a regular scanning schedule at-home or to correct quality issues
- Assess willingness of patients to participate in a program requiring home OCT monitoring
    - Proportion of participants approached by the site to enroll in study who were not interested in using the device
    - Proportion of participants approached by the site to enroll in study who were not capable of conducting Home OCT monitoring
- Assess ability of patients to complete home OCT monitoring as specified in the protocol
    - Number of screen failures (participants that were sent the Home OCT device but were unable to initiate self-scanning and were required to return the device to Notal)
    - Proportion of participants who maintained regular scanning (definition TBD) and the frequency of scanning
    - Proportion of good quality scans

AMD-Specific Objectives and Associated Outcomes

- Assess fluid dynamics
    - Gather information to contribute to the database for determining criteria for triggering an alert for a visit to the ophthalmologist
        - Notal Vision is developing a Home OCT Web Viewer feature in which ophthalmologists can set certain criteria to be alerted when the NOA measures fluid above the specified threshold. The Home OCT scans and NOA-generated fluid parameters from this study will be pooled with data from other clinical trials into a single database. This database will be used to develop the feature for various alert criteria and thresholds to be set.
    - Review Surveillance Reports on the Notal OCT Web Viewer
    - Assess the following for intraretinal, subretinal, and total retinal fluid in the 3x3 mm area:
        - Rate of change in fluid on Home OCT between anti-VEGF injections for nAMD (hereby referred to as treatments)
        - Minimum/maximum fluid volume reached between treatments
        - Fluid presence interval between treatments
        - Fluid-free interval between treatments
        - Fluid regression interval between treatments
        - Fluid increase interval between treatments
        - Cumulative fluid presence interval over 6 months
        - Cumulative fluid-free interval over 6 months
        - Ratio of cumulative presence interval to cumulative free interval
        - Area under the fluid volume curve
        - Persistent fluid yes/no
        - Maximal weekly fluid volume increase rate [nL/week]
        - Number of fluid recurrence events
- Assessment of whether scans obtained on different days would be sufficient for home monitoring
    - Tabulate summary statistics for the rate of change in fluid on OCT according to the following timeframes: Daily, every 3 days, weekly, monthly.
- Determine agreement of SD-OCT image interpretation by the Reading Center with interpretation of home monitoring OCT images by the Notal OCT Analyzer (NOA) AI algorithm on the days patients are examined in their ophthalmologist's office.
    - Tabulate concordance between the Reading Center grade and the NOA grade for presence of fluid at the foveal center for intraretinal fluid, subretinal fluid, and either intraretinal or subretinal fluid.
    - The agreement between the Reading Center grade and the NOA grade for quantity of fluid at the foveal center will be determined by assessing the correlation between the two grades and producing summary statistics for the difference between the two grades. Only subretinal fluid will be assessed, as intraretinal fluid cannot be accurately measured by the Reading Center.

- The agreement between the Reading Center grade and the NOA grade for central subfield thickness will be determined by assessing the correlation between the two grades and producing summary statistics for the difference between the two grades.

6.4 Analysis of Quantifiable Outcome Measures

Summary statistics and tabulations will be produced for the above outcomes where appropriate. Other outcomes are tests of logistics for a future trial.

6.5 Safety Analyses

The frequency of each of the following events will be tabulated:

- Eye strain
- Headache
- Injury from the device (and type of injury)

6.6 Protocol Adherence and Retention

Protocol deviations and summary statistics for the number of standard care visits completed in the 6 months of follow-up will be tabulated.

6.7 Baseline Descriptive Statistics

Baseline characteristics will be tabulated and summary statistics appropriate to the distribution will be reported.

Chapter 7: Data Collection and Monitoring

7.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (eCRFs). When data are directly collected in eCRFs, this will be considered the source data. For any data points for which the eCRF is not considered source, the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

7.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 3 years following the NIH grant cycle for which the last visit was completed (expected December 31, 2026). These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the JCHR, if applicable. It is the responsibility of JCHR to inform the investigator when study documents no longer need to be retained.

7.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable.

Consistent with the Integrated Addendum to ICH E6 (R2), a risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Elements of the RBM plan may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of IRB coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- Communications with site staff
- Quality control reports
- Management of noncompliance

- Documenting monitoring activities

CC representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

7.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site principal investigator (PI) and study staff delegated to study responsibilities are responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 8: Ethics/Protection of Human Participants

8.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 Code of Federal Regulations (CFR) Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

8.2 Institutional Review Boards

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

8.3 Informed Consent Process

8.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, the sponsor(s) and their agents. This confidentiality is extended to cover testing of biologic samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The CC, other authorized vendors or representatives of the sponsor, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the

investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DRCR Retina Network coordinating center, located at the Jaeb Center for Health Research in Tampa, Florida. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the DRCR Retina Network coordinating center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DRCR Retina Network coordinating center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

8.3.3 Future Use of Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. After the study is completed, the de-identified, archived data will be made publicly available, for use by other researches including those outside of the study. In addition, OCT scans will be made publicly available. These images of the retina are considered identifiable information but are only identifiable if they can be matched to a database that already includes retinal images for identification purposes (directly identifiable information will be removed). Permission to make data and OCT scans publicly available will be included in the informed consent.

Chapter 9: References

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