Study Title: Prospective Evaluation of iCam-OCT

NCT #: not yet assigned

Date: July 28, 2026

Study Title	Prospective evaluation of iCam-OCT
Sponsor Name	Siloam Vision, Inc.
Protocol Number	SVCT-CIP-005 V04
Device Name	iCam-OCT
Study Sites	There will be two clinical sites participating in this study. 1. Oregon Health and Science University (OHSU) neonatal Intensive Care Unit (NICU), where device users will be new to the use of the device and all clinicians will be unaffiliated with the sponsor. 2. Children's Hospital Colorado Anschultz (CHCO) medical campus, where device users will be new to the use of the device and all clinicians will be unaffiliated with the sponsor.
Study Purpose	The purpose of this study is to compare the ability of ophthalmologists to assess ROP using images from the iCam-OCT compared to binocular indirect ophthalmoscopy (BIO). The results of this study will be used as part of an FDA 510(k) submission by Siloam Vision. A similar follow-up study will be conducted at the completion of this study where subjects are not dilated for the OCT imaging but are dilated afterwards for the BIO examination.
Study Endpoints	**PRIMARY ENDPOINT** • Assessment of OCT images for clinical quality and utility in neonates eligible for ROP screening compared to BIO evaluation using three independent and masked image grading experts (ophthalmologists experienced with ROP). **SECONDARY ENDPOINTS** 1. Assessment of the presence or absence of ROP between BIO and OCT image assessment through sensitivity (target > 90%) and specificity (target > 70%) determination. The presence of ROP is defined as stage 1 or worse ROP in any zone, with or without pre-plus or plus disease. 2. Determination if the eye is fully vascularized or if there is a border present between vascular and avascular areas. • In eyes with full vascularization determined by BIO, the agreement (sensitivity) of documentation of full retinal vascularization by visualization of zone III and within two-disc diameters of the ora serrata (target > 90% sensitivity and

	> 70% specificity). This assessment requires visualization of the ora serrata. • In eyes with incomplete retinal vascularization and areas of avascular retina determined by BIO, the agreement (sensitivity) of documentation of visualization of the vascular/avascular border by OCT (target > 90% sensitivity and > 70% specificity). Visibility of the ora serrata is not required for this assessment and so will not be included in the determination of the visibility of the ora serrata. **In addition to these primary and secondary endpoints, a safety assessment will be performed to determine if any adverse events occur and the nature of the adverse events (AEs) including:** • Systemic adverse events as part of the examination process, defined as nurse initiated pauses in the examination procedure. These will be observed and recorded by the study coordinator. • Ocular AEs: corneal abrasion, conjunctival irritation, ocular infection, need for topical medications. • Any other AEs.

Study Design	This is a prospective study where eligible premature infants will be enrolled (premature infants that meet ROP screening recommendation by the AAP). Parents or guardians of eligible subjects will be consented and enrolled if they agree to participate. BIO examination will be performed by an independent ROP experienced Ophthalmologist and ROP status will be determined. For the purposes of this study, eyes with "immature retina" but no ROP stage will be identified as such, but classified as "no ROP", as will eyes with fully vascularized retina. Eyes with stage 1 or worse ROP in any zone will be classified as having "any ROP"). OCT imaging on the iCam-OCT will be performed by a trained healthcare provider (can be ophthalmologist, independent nurse, technician, coordinator, etc). Imaging will follow a standardized procedure based on the training material, including attempts to visualize the vascular/avascular border (if necessary for clinical diagnosis). **PRIMARY ENDPOINT GRADING:** Anonymized and masked OCT images will be graded by three independent and experienced ROP clinicians for image quality and clinical utility (both independently). In terms of quality, the graders will be instructed on specific evaluation criteria for quality OCT scans, including brightness, focus, field of view maximization, vignetting, reference arm mal-positioning, etc). Graders will score each image for on a scale from 0-3 where scores of 0 indicate image failure with no usable clinical information, 1 indicates artifacts or technique significantly limits image quality and usable information, 2 indicates the presence of some artifacts or suboptimal image quality but minimal impact on image interpretation, and 3 indicates good image quality. In terms of utility, graders will be asked to assess whether there is clinically useful information present in the images (i.e., usefulness for helping to aid clinical decisions), such as viewing normal structures (confirming absence of pathology) or detecting pathological changes in the images (confirming pathology). Scores of 0 and 1 indicate the images provide no (0) or minimal (1) useful clinical information and are unacceptable for aiding clinical decisions while scores of 2 or 3 indicate images do provide useful clinical information for making clinical decisions and are considered acceptable for aiding clinical assessment of ROP. **SECONDARY ENDPOINT GRADING:** The graders (who are masked to the BIO findings) will document the full extend of ROP diagnosis for each eye, including zone (I-III), stage, and plus disease, if possible. These labels will be used to classify the eye as having ROP "present or not" (with the above definition) and compared to ophthalmoscopy for sensitivity/specificity. In addition, it will look at eyes with "no ROP" for documentation either of full vascularization or of immature retina

with a vascular border farther than 2-3 disc diameters from the ora serrata ("Immature retina").

PERFORMANCE GOALS:

The performance goal for the primary endpoint is that the percentage of images with an acceptable grading (scores of 2 or 3) is 85% or above for both quality and clinical utility.

Performance goals for agreement on the presence or absence of ROP are mean sensitivity and specificity of 90% and 70% respectively.

The performance goal for documentation and visualization of full vascularization out to the ora serrata is 90% mean sensitivity and 70% specificity, and the performance goal for documentation and visualization of the vascular/avascular border is 90% mean sensitivity and 70% specificity.

Sample size is based on a power calculation for a non-inferiority test based on sensitivity for detecting the presence of ROP. This results in a minimum requirement of 30 infants with ROP. In addition, for specificity comparisons, 10 infants without ROP will also be enrolled.

Infants who are determined to be in the "no ROP" group by BIO but who are classified as ROP stage 1 or worse by OCT grading (considered false positive for ROP compared to the historical gold standard BIO exam) will be analyzed separately in the following ways:

1. A coordinator will review the medical records of these infants a few weeks later in their hospital course to determine if they develop stage 1 or worse ROP in the weeks following the study exam date. This follow-up assessment will address the possibility of detection of visible structural changes consistent with ROP by OCT images prior to BIO that might not meet the clinical diagnosis of stage 1.
2. We will have all 3 graders re-review these images to establish consensus on whether the OCT findings represent true stage 1 (that might have been missed by BIO) versus earlier pathologic changes (as above) consistent with immature retina with a defined vascular border.

NOTE: The management of all babies in this study will be by BIO alone (not affected by OCT). these measures are to evaluate the possibility that OCT might be, in some cases, more sensitive and specific than BIO. The other way to address this would be to subject the infant to multiple BIO exams, but this is challenging from an ethical perspective with the desire to minimize the risk and time of the study procedures.

INCLUSION CRITERIA:

The patient is an infant matching American Academy of Pediatrics (AAP) screening criteria for ROP evaluation which include:

A birth weight of <1500 g or a gestational age of ≤30 weeks; or

	A birth weight between 1500 - 2000 g or a gestational age of >30 weeks who are believed to be at risk by their attending pediatrician or neonatologist. **MAIN EXCLUSION CRITERIA:** Inability to obtain informed consent from the parent or guardian, or deemed clinically unstable for research imaging by the neonatology team.
Recruitment Approach	Parents of all eligible infants who require ROP screening in the NICU are approached for participation in this study. The study population is premature infants indicated for ROP screening.
Sample Size	This study will enroll at minimum 40 premature infants that match the AAP guidelines for ROP assessment. At least 30 of these infants should have ROP diagnosis of stage 1 or greater and at least 10 should have no ROP present. When enrollment for either group target is reached (i.e., 30 ROP or 10 without ROP), provided there are at least 20 subjects from each site, then recruitment in that group will be stopped.

Statistical Analysis Plan	For the image grading analysis by three independent expert graders, the percent of images graded as acceptable (scores of 2 and 3) will be determined for both image quality and clinical utility. Image scores will be analyzed together and separately for infants with ROP and infants without ROP. Performance goals for graded images scored as acceptable or higher are 85% or greater for both image quality and clinical utility. Image analysis for agreement between BIO ROP assessment and image grading for ROP will be calculated as sensitivity and specificity using BIO as the 'ground truth'. Performance goals for sensitivity and specificity are 90% and 70% respectively. In addition, the visibility of a fully vascularized retina by OCT in comparison to BIO will be determined as well as the presence of a vascular/avascular border. The performance goal for these structural assessment visibility tasks is 90% sensitivity and 70% specificity for each.
Study Duration	Expected study duration is approximately 3-4 months from study start.
Study Chair	J Peter Campbell, MD, MPH Chief Executive Officer, Siloam Vision, Inc. 5331 Macadam Ave, Ste 258 #1040, Portland, Oregon, 97239 Professor, School of Medicine, Oregon Health and Science University 545 SW Campus Dr, Portland, Oregon 97239 Phone: 503-494-7891 Email: peter@siloamvision.com
Sponsor	Siloam Vision 5331 Macadam Ave, Ste 258 #1040, Portland, Oregon, 97239
Study Sites	1. Doernbecher Neonatal Intensive Care Unit (OHSU) 3181 Sam Jackson Park Rd Floor 12a, Portland, OR 97239 2. https://www.cumedicine.us/location-appointment/Childrens-Hospital-Colorado-Anschutz-Medical-Campus-Aurora Children's Hospital Colorado Anschutz Medical Campus 13123 East 16th Ave, Aurora, CO 80045
Study Manager	Karyn Jonas Chief Development Officer, Siloam Vision, Inc. 5331 Macadam Ave, Ste 258 #1040, Portland, Oregon, 97239 Phone: 561-818-2161 Email: karyn@siloamvision.com
Study Safety Monitor	Benjamin Young, M.D., M.S. 545 SW Campus Drive, Portland, Oregon 97239

Principle Investigators	J Peter Campbell, MD, MPH Professor, School of Medicine, Oregon Health and Science University 545 SW Campus Dr, Portland, Oregon 97239 Phone: 503-494-7891 Emily Mccourt, MD Chief of Pediatric Ophthalmology, Vice Chair of Pediatric Ophthalmology, The Ponzio Family Chair for Pediatric Ophthalmology Children's Hospital Colorado Anschutz Medical Campus 13123 East 16th Ave, Aurora, CO 80045 720-777-1234

LIST OF ABBREVIATIONS

AAP	American Academy of Pediatrics
AE	Adverse event
ADE	Adverse device effect
BIO	Binocular indirect ophthalmoscopy
CRF	Case report form
ERNV	Epiretinal neovascularization
FDA	Food and Drug Administration
FOV	Field of View
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICROP	International Classification of ROP
IDE	Investigational Device Exemption
IFU	Indications for Use
IRB	Institutional Review Board
NICU	Neonatal intensive Care Unit
NSR	Non-significant Risk
OCT	Optical coherence tomography
OHSU	Oregon Health Sciences University
PAR	Persistent Avascular Retina
ROP	Retinopathy of Prematurity
SADE	Serious adverse device effect
SAE	Serious adverse event
SS-OCT	Swept-source optical coherence tomography
USADE	Unanticipated serious adverse device effect
UWF	Ultra-widefield
WDFI	Widefield Dilated Fundus imaging
WF	Widefield

PROTOCOL

1. PROTOCOL TITLE

Prospective evaluation of iCam-OCT

2. OBJECTIVES

The purpose of this study is to compare the ability of ophthalmologists to assess ROP using images from the iCam-OCT compared to binocular indirect ophthalmoscopy (BIO).
The results of this study will be used as part of an FDA 510k submission by Siloam Vision.

3. STUDY ENDPOINTS

Primary Endpoint

- Assessment of OCT images for clinical quality and utility in neonates eligible for ROP screening compared to BIO evaluation using three independent and masked image grading experts (ophthalmologists experienced with ROP).

Secondary Endpoints

- Assessment of the presence or absence of ROP between BIO and OCT image assessment through sensitivity (target > 90%) and specificity (target > 70%) determination. The presence of ROP is defined as stage 1 or worse ROP in any zone, with or without pre-plus or plus disease.
- Determination if the eye is fully vascularized.
- In eyes with full vascularization determined by BIO, the agreement (sensitivity) of documentation of full retinal vascularization by visualization of zone III and within two-disc diameters of the ora serrata (target > 90% sensitivity and > 70% specificity). This assessment requires visualization of the ora serrata.
- In eyes with incomplete retinal vascularization and areas of avascular retina determined by BIO, the agreement (sensitivity) of documentation of visualization of the vascular/avascular border by OCT (target > 90% sensitivity and > 70% specificity). Visibility of the ora serrata is not required for this assessment and so will not be included in the determination of the visibility of the ora serrata.

In addition to these primary and secondary endpoints, a safety assessment will be performed to determine if any adverse events occur and the nature of the adverse events (AEs) including:

- Systemic adverse events as part of the examination process, defined as nurse initiated pauses in the examination procedure. These will be observed and recorded by the study coordinator.
- Ocular AEs: corneal abrasion, conjunctival irritation, ocular infection, need for topical medications.
- Any other AEs as reported by investigator or study coordinator.

4. BACKGROUND

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness.[1] With prompt diagnosis, ROP treatment can be highly effective and related blindness is nearly always avoidable.[2-4] Annually, an estimated 1–2 million are at risk for ROP, and approximately 20,000–50,000 infants suffer preventable

blindness, primarily due to missed, delayed, or incorrect ROP diagnosis, worldwide.[5,6] Part of the difficulty of proper ROP diagnosis is the ROP examination itself. The ROP examination is physiologically stressful to the neonates and put neonates at increased risk of cardiopulmonary complications[7]. It is also subjective and clinical agreement on the diagnosis and stage of disease can be poor. In one study by Biten et al. 2018, investigators compared the ability of clinicians to diagnose ROP using only a BIO clinical examination versus retinal images compared to a consensus decision based on several ophthalmologists with both information[8]. They found ophthalmoscopy and telemedicine each had similar sensitivity for zone I disease (78% vs 78%), plus disease (74% vs 79%), and type 2 ROP (stage 3, zone I, or plus disease: 86% vs 79%, but ophthalmoscopy was slightly more sensitive in identifying stage 3 disease (85% vs 73%). This study suggests diagnosis with telemedicine can be effective, but even a direct clinical examination may not be perfect with sensitivity values ranging from 74% to 86% depending on stage of pathology. An ROP examination that is fast, easy, objective, and induces less stress to the neonates would be very helpful to improve clinical practice and the standard of care for ROP assessment.

The iCam-OCT is a new imaging device specially designed for the unique clinical circumstances of ROP assessment. It is fast, easy to use, less stressful for the neonates, operates under non-mydriatic conditions, and provides high contrast retinal images with a FOV extending out into the far-periphery. The images allow clinicians to accurately, consistently, and immediately diagnosis all components of ROP, including ROP in zone III (which no other pediatric imaging devices are currently able to do). The iCam-OCT utilizes swept-source OCT technology, which is invisible to the patient, reducing discomfort. It scans at a speed of 400 kHz per second allowing a wide field of view of nearly 200 degrees in 1-2 seconds. It does not require scleral depression or long examination times, further reducing patient discomfort and stress[7].

5. Published Studies with the iCam-OCT

There have been numerous publications with several prototype iCam-OCTs, mostly with a contact imaging probe in premature neonates at risk of ROP[9-18]. In all of these studies, including imaging of more than 500 patients in more than 1700 imaging sessions, no reports of any adverse events have been reported. The images were found to be clinically helpful in guiding decisions on ROP and other pathologies in nearly all cases[9-18]. These studies document the evolution of the iCam-OCT through various iterations demonstrating its technological breakthroughs and associated clinical effectiveness for visualization and diagnosis ROP and other pediatric ocular pathologies.

The first studies were conducted around 5 years ago and these were the first to utilize a new state of the art light source (VCSEL swept-source light-source) enabling super high speeds of 400 kHz at IR wavelengths (1040 nm) and also employing a compact hand-held imaging probe to allow supine imaging on premature neonates[9,10,11]. The combination of these breakthroughs with an invisible light-source were an ideal combination for imaging premature neonates in order to assess their ocular health. The fast speed allowed short examination times, the invisible light source reduced stress during imaging, and the handheld probe allowed imaging in a supine position in the NICU. These early studies demonstrated the iCam-OCT was an ideal device for imaging premature neonates because of its ease of use, fast acquisition speed, invisible light-source and immediate en face OCT and OCTA images which improved clinical decisions and diagnosis. It was observed that helpful clinical images could be obtained in nearly all neonates very quickly and the discomfort and stress on the neonates was less

compared to retinal fundus imaging and also BIO examinations. These early studies showed clinical value in a range of pathologies beyond ROP including imaging premature infants with incontinentia pigmenti (IP), and X-linked retinoschisis (XLRS). Furthermore these investigators found this early iCam-OCT was sufficient for objective diagnosis and zone/stage/plus disease categorization, it allows for minimally-invasive longitudinal monitoring of disease progression and post-treatment course, and provides three-dimensional mapping of the vitreoretinal interface and OCT imaging over a five-week period demonstrated accumulation of neovascular tufts with progression to stage 3 ROP with extraretinal fibrovascular proliferation along the ridge[9,10,11]. (NOTE, in this way, OCT-based imaging of stage 3 may have advantages over 2D imaging of stage 3 that was found to be slightly inferior to ophthalmoscopy in a prior publication[8]).

The next breakthrough was an improvement to the lens design which provided more peripheral imaging with a widefield FOV. The FOV was increased to over 150°, the widest OCT FOV yet reported[12]. This advancement is especially important for pediatric pathologies such as ROP due to the fact the peripheral vasculature is very important to evaluate when determining the stage and severity of the pathology not to mention incidences of peripheral traction, schisis, and retinal detachments. By utilizing a contact method with this lens, an unprecedented ultra-widefield FOV was achieved capturing 197° in a single shot[13-18]. These studies were conducted on large number of premature patients and demonstrated a number of key findings including: 1) in over 425 patients imaged in over 1400 sessions, there were no adverse events, 2) over 99% of patients could be successfully imaged in less than 2 minutes (both eyes), 3) ROP stage, zone involvement, and presence of plus disease could be successfully ascertained in 95-99% of all ROP cases, 4) additional pathologies could also be detected and assessed including retinoblastomas, retinal traction and detachments, COATs disease, FEVR, and others. The prototype iCam-OCTs in these studies (refs 13-18) were very similar to the current final design of the iCam-OCT including speeds of 400kHz with swept source light source at 1040nm, with the same FOV and same basic scan patterns. The final design is essentially equivalent to the design used in these studies featuring only small incremental improvements that do not affect the clinical value or utility of the images, and provide small improvements to image quality and cost of goods. This strongly suggests the clinical findings from these prototype systems are relevant and provide substantial evidence the final iCam-OCT design is safe and effective and a useful clinical tool for assessing the ocular condition of premature neonates.

6. Device Description

The iCam-OCT is a handheld, swept-source optical coherence tomography (OCT) device suitable for pediatric use, consisted of (1) a computer, display/monitor, and OCT imaging module and (2) a handheld optical system, as shown in ***Figure 1***. It is used in contact mode as an ultra-widefield (UWF) OCT. It is indicated for use in the imaging of posterior ocular structures for pediatric patients in a clinical environment. The intended users are healthcare providers (physicians and non-physicians). The iCam-OCT uses the same OCT imaging technology as other OCT devices currently cleared on the market for the adult population. Unlike most conventional OCT devices, the iCam-OCT can be used with patients in the supine position. Compared to OCT devices currently on the market, this handheld optical system provides a more convenient and user-friendly way to image the pediatric population, especially infants or small children who are too small to fit into a conventional tabletop OCT device (current standard of care for adults), and/or who are not able to cooperate with the examination.

The iCam-OCT has undergone a series of improvements and advances over the years from its first prototype developed at OHSU over 5 years ago. The final commercial design of the iCam-OCT is a state of the art swept source OCT device with a center wavelength of 1040nm and scans at a speed of 400kHz. The depth resolution is 7 microns and the OCT scan window has a depth of 12mm. It utilizes a handheld probe to image the eye and displays en face images in real time to help guide the user when capturing images. It is a contact imaging system with an unprecedented ultra-widefield FOV of 197 degrees. It can operate under non-mydriatic conditions and each scan takes less than one second. A complete bilateral ROP examination on average takes between 1-2 minutes. This combination of technological breakthroughs provides clinical advantages especially for pediatric applications such as ROP.

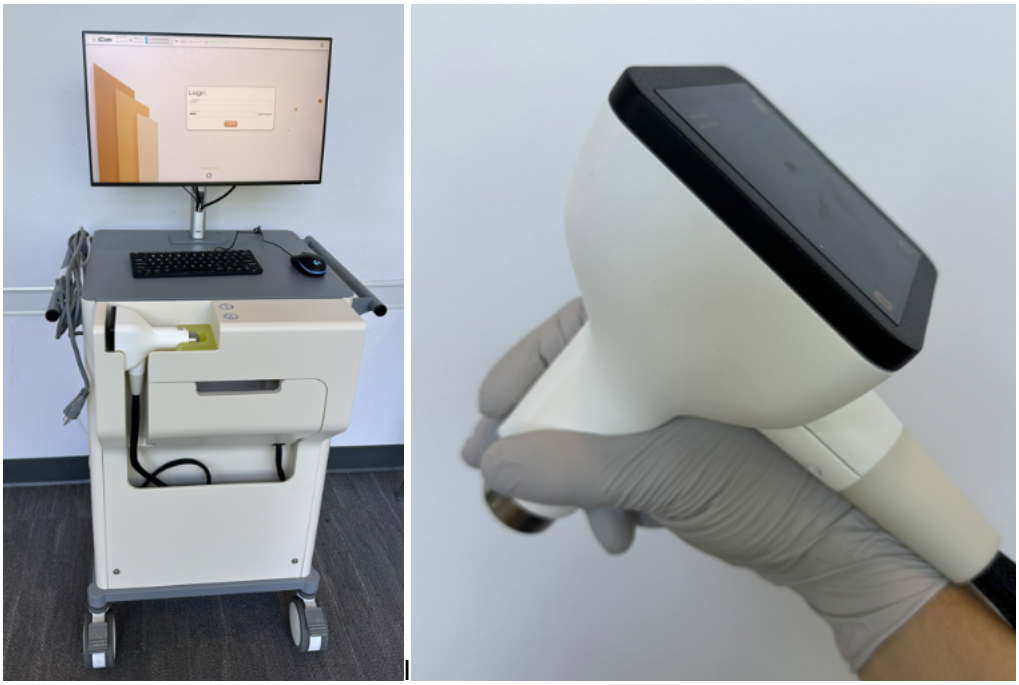


Figure 1. The iCam-OCT with portable cart and handheld imaging probe

7. INDICATIONS FOR USE

The iCam-OCT is a contact-based Swept Source Optical Coherence Tomography (SS-OCT) intended to acquire, display, and save high-resolution and ultra-widefield images of posterior ocular structures, including the peripheral retina extending to the ora serrata, in pediatric patient populations in a supine position. The images can be viewed en face and in cross-section. The device is indicated to aid in the detection, monitoring, and documentation of conditions of the posterior segment, including Zone I-III retinopathy of prematurity (ROP).

Contraindications

Any patient with a perforating injury to the globe must not be imaged with the iCam-OCT system until the wound is repaired. In the case of an eye infection, use of the iCam-OCT must be delayed until treatment for the infection has been rendered. Any infant determined to be unstable by a neonatologist is not a candidate for imaging with the iCam-OCT.

8. Device Risk Analysis and Risk Assessment

The sponsor believes that the "Prospective evaluation of iCam-OCT" is a Non -Significant Risk study because the iCam-OCT device poses no potential light-hazard and/or risk to the retina.
Furthermore, the iCam-OCT device does not meet any of the following conditions which would make it a significant risk device:

1. Is an implant;
2. Is used in supporting or sustaining human life;
3. Is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
4. Otherwise presents a potential for serious risk to the health or welfare of a subject.

The iCam-OCT is a Class 1 laser product and conforms to the following Standards:

Standard, edition	Title
IEC 60601-1: 2005 (Third Edition)+ CORR.1:2006+CORR.2: 2007+A1:2012	Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
IEC 60601-1-2:2014+AMD1:2020	Medical electrical equipment – Part 1-2: General requirements for basic safety and essential performance; and – Collateral standard: Electromagnetic compatibility - Requirements and tests
IEC 60825-1: 2007 IEC 60825-1: 2014	Safety of laser products – Part 1: Equipment classification and requirements
ISO 15004-1:2020	Ophthalmic instruments – Fundamental requirements and test methods - Part 1: General requirements applicable to all ophthalmic instruments
ANSI Z80.36-2021	Ophthalmics - Light Hazard Protection For Ophthalmic Instruments

iCam-OCT Standards Conformance

9. Rationale for the Study

The use of a commercial OCT system specifically designed for ROP assessment that provides all the technological and clinical benefits of the iCam-OCT system has not been thoroughly evaluated previously and has not been directly compared to BIO assessment. This study will help provide clinical evidence that the iCam-OCT can be successfully used to assess ROP in premature neonates. It will also establish the clinical value of the images for aiding clinical decisions.

10. Study Design

This is a prospective study where eligible premature infants will be enrolled (premature infants that meet ROP screening recommendation by the AAP). Parents or guardians of eligible subjects will be consented and enrolled. BIO examination will be performed by an independent ROP experienced

Ophthalmologist and ROP status will be determined. Eyes with immature retina but no stage will be classified as no ROP as well as eyes with fully vascularized retina. Eyes with stage 1 or worse ROP in any zone will be classified as having ROP.
OCT imaging on the iCam-OCT will be performed by a trained healthcare provider (can be ophthalmologist, independent nurse, technician, coordinator, etc). Imaging will follow a standardized procedure based on the training material, including attempts to visualize the vascular/avascular border (if present). All imaging operators will be trained and certified according to Siloam's training and certification programs.

OCT Imaging Procedure

Parents or legal guardians will be asked if they elect to enroll their eligible neonate in the study. If they agree, they will be asked to review the study procedures and purpose as provided in the consent form and provide informed consent. Subjects will be considered enrolled after informed consents are signed by the parents or legal guardians.

The order of the BIO examination and iCam-OCT imaging will be randomized, such that each subject receives one modality before the other in a randomly assigned sequence. All patients will be dilated as part of routine clinical care prior to the first assessment.

The imaging procedure itself is as follows:

An eyelid speculum is inserted after the eye is numbed with proparacaine. The handheld probe's screen is used to directly visualize the position and centration of the camera on the surface of the eye, with the retinal reflection on the 10 Hz warp mode being used to guide the initial positioning. The user then centers the imaging on the appropriate area and captures an UWF scan (0.9) seconds. The camera automatically reverts to warp mode to allow repositioning to capture the same or another area of the retina. The user can double click at any time to obtain a "high resolution" scan (half the FOV but higher resolution as the UWF scan). Once sufficient scans have been obtained, the camera is removed and the eyelid speculum is removed.

Suggested scans to be acquired:

1. Posterior UWF image - UWF image centered on posterior pole (fovea)
2. Temporal image - UWF image with the nerve at the nasal edge of the image (if temporal vascular border not visualized on posterior image)
3. Nasal image - UWF image with the nerve at the temporal edge of the image (if nasal vascular border not visualized on posterior image)
4. Temporal ora serrata image - UWF image for visualization of the temporal ora serrata if possible, to document full vascularization (if temporal vascular border not visualized on temporal image)
5. Nasal ora serrata image - UWF image for visualization of the nasal ora serrata if possible, to document zone II or III (if not fully vascularized on temporal ora serrata image)
6. Posterior HD image (HD) - HD image centered on posterior pole (fovea)

There will be a minimum of 2 scans acquired for each subject with potentially 6 or more depending on what clinical features are visible in what scan and the stage of disease. The device operator may repeat

scans as necessary if acceptable scan quality is not obtained on the first scan. All scans will be saved, with acceptable scans marked on the CRF and excluded scans indicated on the CRF along with reasons for exclusion. Acceptable scans will be exported and uploaded into the image grader software.

All study data will be stored in an anonymous fashion and on a password protected computer. All de-identified data may be used for possible future research studies or for educational purposes.

Subjects may be withdrawn from the study at any time point for any safety reason.

If a subject is withdrawn prematurely from the study, the reason surrounding the circumstances of the withdrawal will be collected.

Primary endpoint grading:
Anonymized and masked OCT images will be graded by three independent and experienced ROP clinicians for image quality and clinical utility (both independently).
In terms of quality, the graders will be instructed on specific evaluation criteria for quality OCT scans, including brightness, focus, field of view maximization, vignetting, reference arm mal-positioning, etc). Graders will score each image for on a scale from 0-3 where scores of 0 indicate image failure with no usable clinical information, 1 indicates artifacts or technique significantly limits image quality and usable information, 2 indicates the presence of some artifacts or suboptimal image quality but minimal impact on image interpretation, and 3 indicates good image quality.
In terms of utility, graders will be asked to assess whether there is clinically useful information present in the images (i.e., usefulness for helping to aid clinical decisions), such as viewing normal structures (confirming absence of pathology) or detecting pathological changes in the images (confirming pathology). Scores of 0 and 1 indicate the images provide no (0) or minimal (1) useful clinical information and are unacceptable for aiding clinical decisions while scores of 2 or 3 indicate images do provide useful clinical information for making clinical decisions and are considered acceptable for aiding clinical assessment of ROP.
Secondary endpoint grading:
The graders (who are masked to the BIO findings) will document the full extent of ROP diagnosis for each eye, including zone (I-III), stage, and plus disease, if possible. These labels will be used to classify the eye as having ROP “present or not” (with the above definition) and compared to ophthalmoscopy for sensitivity/specificity. In addition, it will look at eyes with “no ROP” for documentation either of full vascularization or of immature retina with a vascular border farther than 2-3 disc diameters from the ora serrata (“Immature retina”).

11. PERFORMANCE GOALS:

The performance goal for the primary endpoint is that the percentage of images with an acceptable grading (scores of 2 or 3) is 85% or above for both quality and clinical utility.
Performance goals for agreement on the presence or absence of ROP are mean sensitivity and specificity of 90% and 70% respectively.
The performance goal for documentation and visualization of full vascularization out to the ora serrata is 90% mean sensitivity and 70% specificity, and the performance goal for documentation and visualization of the vascular/avascular border is 90% mean sensitivity and 70% specificity.

Infants who are determined to be in the “no ROP” group by BIO but who are classified as ROP stage 1 or worse by OCT grading (considered false positive for ROP compared to the historical gold standard BIO exam) will be analyzed separately in the following ways:

1. A coordinator will review the medical records of these infants a few weeks later in their hospital course to determine if they develop stage 1 or worse ROP in the weeks following the study exam date. This follow-up assessment will address the possibility of detection of visible structural changes consistent with ROP by OCT images prior to BIO that might not meet the clinical diagnosis of stage 1.
2. We will have all 3 graders re-review these images to establish consensus on whether the OCT findings represent true stage 1 (that might have been missed by BIO) versus earlier pathologic changes (as above) consistent with immature retina with a defined vascular border.

NOTE: The management of all babies in this study will be by BIO alone (not affected by OCT). These measures are to evaluate the possibility that OCT might be, in some cases, more sensitive and specific than BIO. The other way to address this would be to subject the infant to multiple BIO exams, but this is challenging from an ethical perspective with the desire to minimize the risk and time of the study procedures.

12. SAMPLE SIZE:

The sample size calculations were made based on the performance goal for sensitivity for a statistically significant non-inferiority test (sensitivity is non-inferior or better than clinical BIO sensitivity-Gold Standard). The assumed BIO sensitivity used in the calculations was 85% based on the study by Biten et. al. 2018[8]. These calculations also assume a lower margin of error of 0.05 as not being clinically significant. With n=30 and device sensitivity of around 95%, the power is 80%, suggesting 30 is the appropriate sample size (see Figure 2 below). This sample size calculation is for sensitivity as this is the key performance metric under consideration (i.e., clinically more meaningful and relevant for ROP assessment). In addition to the 30 ROP patients to be enrolled, this study will also enroll 10 premature neonates without ROP to assess specificity as well.

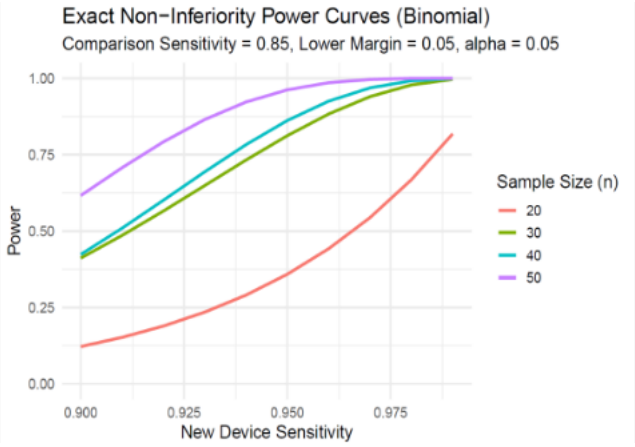


Figure 2. Power analysis for various sample sizes based on non-inferiority test for a comparison sensitivity of 85% and a lower margin of error at 5%.

13. STUDY POPULATION

This study will enroll approximately 40 premature babies that match the AAP screening guidelines for ROP assessment (described below). At least 30 of these infants should have ROP diagnosis of stage 1 or greater and at least 10 should have no ROP present.

Inclusion criteria: The patient is an infant matching American Academy of Pediatrics (AAP) screening criteria for ROP evaluation which include:

- A birth weight of <1500 g or a gestational age of ≤30 weeks; or
- A birth weight between 1500 - 2000 g or a gestational age of >30 weeks who are believed to be at risk by their attending pediatrician or neonatologist.

Main exclusion criteria: Inability to obtain informed consent from the parent or guardian, or deemed clinically unstable for research imaging by the neonatology team.

Patient Recruitment: Eligible patients from the NICU will be approached for recruitment. Patients may have been previously diagnosed and examined in the past and may be under observation and management. New patients may also be enrolled. This will ensure a wide range of possible disease severity may be enrolled. Parents of all eligible infants who require ROP screening in the NICU are approached for participation in this study. The study population is premature infants indicated for ROP screening.

14. SAFETY MONITORING

14.1 Definition of Adverse Events (AEs) and Serious Adverse Events (SAEs)

There are low risks of corneal abrasion, subconjunctival hemorrhage, or infection from the examination procedure with contact-based camera (these risks also occur with standard of care indirect ophthalmoscopy with scleral depression or FDA cleared contact ROP cameras). All ROP examinations carry the risk of apnea or bradycardia because the infants are medically fragile from being premature and requiring intensive care monitoring.

14.2 Relationship of AE to Device

The risks of adverse events occurring during retinal imaging conducted in this study are similar to routine retinal examinations and in fact may be less because the imaging is performed without a bright light which can be more stressful to infants. Imaging during an ROP examination is considered minimal risk.

14.3 AE/SAE Reporting Timelines

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made. All AE/SAEs will be reported to the IRB within 5 days of the event. All adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, imaging test, or other means will be recorded in the

spreadsheet set up for recording and maintaining a log of any adverse events. Cumulative adverse event data are annually tabulated for review.

14.4 Data Safety Monitoring Plan

The study team has designated Dr. Benjamin Young (545 SW Campus Drive, Portland, OR 97239) as the investigator that will monitor the study participants and data for safety. Dr. Young is an IRB approved co-investigator on this project and is a specialist in retinal and vitreous disease and surgery. Dr. Young shares duties with Dr. Campbell in performing weekly routine ROP exams at OHSU NICU. Dr. Young will oversee the study process, and interact with the study participants to evaluate for any unexpected adverse events. Dr. Young does not have any conflict of interest (other than the academic publications resulting from this research) in this technology.

15. Statistical Analysis Plan

All diagnostic performance measures use the eye as the unit of analysis, with grades assigned to the OCT image set acquired for each eye. Each eye is graded independently by three masked graders; sensitivity and specificity relative to BIO are therefore computed separately for each grader, and each endpoint is summarized as the mean of the three grader-level estimates, reported alongside the individual values.

Three families of endpoints we be assessed against pre-specified performance goals:

- Image grading: the percentage of image sets graded acceptable (score 2 or 3) for image quality and for clinical utility, analyzed across all infants and separately for those with and without ROP. Goal: ≥85% scored as acceptable for each.
- Presence or absence of ROP: sensitivity and specificity of OCT-based grading as compared to BIO. Goal: 90% sensitivity and 70% specificity.
- Vascularization: documentation of full retinal vascularization and of the vascular/avascular border as compared to BIO. Goals: 90% sensitivity and 70% specificity.

Two supportive analyses will be conducted. First, discordance between OCT and BIO classifications will be tabulated in a 2x2 paired table per grader and assessed with an exact McNemar's test for asymmetry. Second, consistent with the sample-size framework (Section 12), OCT sensitivity for the presence of ROP will be tested for non-inferiority against a fixed comparator of 85% (lower margin 5%, one-sided alpha = 0.05). This 85% is the assumed BIO sensitivity from Biten et al. 2018; because BIO is the reference standard in this study, its sensitivity cannot be estimated from these data. Thus, 85% functions as a fixed literature-derived benchmark rather than a within-study measurement. To be clear, the test asks whether OCT-based agreement with BIO meets or exceeds that external benchmark, not whether OCT is non-inferior to concurrent BIO exam. It is run separately for each grader, with non-inferiority concluded when the lower confidence bound for OCT sensitivity exceeds the threshold for all three.

Eyes classified as "no ROP" by BIO but ROP stage 1 or worse by OCT (false positives against the BIO reference standard) will be examined two ways: (1) a coordinator reviews each infant's subsequent hospital course to determine whether stage 1 or worse ROP develops in the following weeks, addressing whether OCT may have detected structural changes ahead of BIO; and (2) all three graders re-review the images to reach consensus on whether the findings represent true stage 1 potentially missed by BIO versus immature retina with a defined vascular border.

NOTE: The management of all babies in this study will be directed by BIO alone (not affected by OCT). These analyses assess only the possibility that OCT is, in some cases, more sensitive and specific than BIO. Repeated BIO examinations, the alternative means of adjudication, would be to subject the infant to multiple BIO exams, but this is challenging from an ethical perspective given the desire to minimize risk and time of the study procedures.

16. DEVICE DISPOSITION

All investigational devices will be uniquely identified and tracked by serial number. Devices will be shipped to study sites under controlled conditions and receipt will be documented. Each site will maintain device accountability logs, including assignment, use, and maintenance records. Devices will be stored and handled per manufacturer specifications. Any device malfunctions or damage will be reported to the sponsor and documented. At study completion, all devices will be returned per sponsor instructions and the sponsor will ensure any identifiable data is returned to the site. A final reconciliation will be performed to ensure full accountability.

REFERENCES

1. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of neonates at risk and implications for control. Early Hum Dev. 2008;84(2):77-82.
2. Hartnett ME, Penn JS. Mechanisms and Management of Retinopathy of Prematurity. N Engl J Med. 2012;367(26):2515-2526.
3. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Arch Ophthal. 1988;106(4):471-479.
4. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthal. 2003;121(12):1684-1694.
5. Reynolds JD, Dobson V, Quinn GE, et al. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthal. 2002;120(11):1470- 1476.
6. Gilbert C, Malik ANJ, Nahar N, et al. Epidemiology of ROP update - Africa is the new frontier. Semin Perinatol. 2019;43(6):317-322.
7. Mangalesh S, Sarin N, McGeehan B, et al. Preterm infant stress during handheld optical coherence tomography versus binocular indirect ophthalmoscopy examination for retinopathy of prematurity. Journal of American Association for Pediatric Ophthalmology and Strabismus {JAAPOS}. 2021;25(4):e64.
8. Biten H, Redd TK, Moleta C, Campbell JP, Ostmo S, Jonas K, Chan RVP, Chiang MF; Imaging & Informatics in Retinopathy of Prematurity (ROP) Research Consortium. Diagnostic Accuracy of Ophthalmoscopy vs Telemedicine in Examinations for Retinopathy of Prematurity. JAMA Ophthalmol. 2018 May 1;136(5):498-504. doi: 10.1001/jamaophthalmol.2018.0649. PMID: 29621387; PMCID: PMC6036899.
9. Ni S, Wei X, Ng R, Ostmo S, Chiang MF, Huang D, Jia Y, Campbell JP, Jian Y. High-speed and widefield handheld swept-source OCT angiography with a VCSEL light source. Biomed Opt Express. 2021 May 20;12(6):3553-3570. doi: 10.1364/BOE.425411. PMID: 34221678; PMCID: PMC8221946.
10. Nguyen TP, Ni S, Khan S, Wei X, Ostmo S, Chiang MF, Jia Y, Huang D, Jian Y, Campbell JP. Advantages of Widefield Optical Coherence Tomography in the Diagnosis of Retinopathy of Prematurity. Front Pediatr. 2022 Jan 18;9:797684. doi: 10.3389/fped.2021.797684. PMID: 35118032; PMCID: PMC8806029.
11. 6. Scruggs BA, Ni S, Nguyen TP, Ostmo S, Chiang MF, Jia Y, Huang D, Jian Y, Campbell JP. Peripheral OCT Assisted by Scleral Depression in Retinopathy of Prematurity. Ophthalmol Sci. 2022 Mar;2(1):100094. doi: 10.1016/j.xops.2021.100094. Epub 2022 Jan 11. PMID: 35128508; PMCID: PMC8813034.
12. Ni S, Nguyen TP, Ng R, Khan S, Ostmo S, Jia Y, Chiang MF, Huang D, Peter Campbell J, Jian Y. 105° field of view non-contact handheld swept-source optical coherence tomography. Opt Lett. 2021 Dec 1;46(23):5878-5881. doi: 10.1364/OL.443672. PMID: 34851913; PMCID: PMC10443941.
13. Nguyen TP, Ni S, Liang G, Khan S, Wei X, Skalet A, Ostmo S, Chiang MF, Jia Y, Huang D, Jian Y, Campbell JP. Widefield Optical Coherence Tomography in Pediatric Retina: A Case Series of Intraoperative Applications Using a Prototype Handheld Device. Front Med (Lausanne). 2022 Jul 4;9:860371. doi: 10.3389/fmed.2022.860371. PMID: 35860728; PMCID: PMC9289179.

14. Nguyen TP, Ni S, Ostmo S, Rajagopalan A, Coyner AS, Woodward M, Chiang MF, Jia Y, Huang D, Campbell JP, Jian Y. Association of Optical Coherence Tomography-Measured Fibrovascular Ridge Thickness and Clinical Disease Stage in Retinopathy of Prematurity. JAMA Ophthalmol. 2022 Oct 13;140(11):1121–7. doi: 10.1001/jamaophthalmol.2022.4173. Epub ahead of print. PMID: 36227622; PMCID: PMC9562098.
15. Ni S, Nguyen TP, Ng R, Woodward M, Ostmo S, Jia Y, Chiang MF, Huang D, Skalet AH, Campbell JP, Jian Y. Panretinal Optical Coherence Tomography. IEEE Trans Med Imaging. 2023 Nov;42(11):3219-3228. doi: 10.1109/TMI.2023.3278269. Epub 2023 Oct 27. PMID: 37216244; PMCID: PMC10615839.
16. Ni S, Liang GB, Ng R, Ostmo S, Jia Y, Chiang MF, Huang D, Skalet AH, Young BK, Campbell JP, Jian Y. Panretinal handheld OCT angiography for pediatric retinal imaging. Biomed Opt Express. 2024 Apr 29;15(5):3412-3424. doi: 10.1364/BOE.520739. PMID: 38855676; PMCID: PMC11161374.
17. Burt SS, Woodward M, Ni S, Jackson J, Coyner AS, Ostmo SR, Liang G, Bayhaqi Y, Jia Y, Huang D, Chiang MF, Young BK, Jian Y, Campbell JP. Isolated Retinal Neovascularization in Retinopathy of Prematurity: Clinical Associations and Prognostic Implications. Ophthalmol Retina. 2024 Oct;8(10):1021-1028. doi: 10.1016/j.oret.2024.04.025. Epub 2024 May 11. PMID: 38735640; PMCID: PMC11446652.
18. Roti EV, Ni S, Bayhaqi Y, Ostmo SR, Burt SS, Woodward MK, Jackson JD, Coyner AS, Chiang MF, Huang D, Campbell JP, Jian Y, Young BK. Ultra-Widefield Optical Coherence Tomography Beyond the Ora Serrata in Retinopathy of Prematurity. JAMA Ophthalmol. 2025 Feb 1;143(2):165-170. doi: 10.1001/jamaophthalmol.2024.5533. PMID: 39724290; PMCID: PMC11843357

REVISION HISTORY

Revision	Change Description	Author/Editor	Date
V01	Initial Released	M. Sinai	December 17, 2025
V02	• Updated study site addresses, PI information, and study manager. • Updated recruitment criteria to include ≤ 30 weeks and to at a minimum 40 subjects. • Included a follow up study with undilated imaging exams. • Added device disposition.	K. Jonas	March 27, 2026
V03	Updated sample size to include recruitment of 20 at each site.	K. Jonas	June 12, 2026
V04	• Removed ISO 15004-2:2007 • Updated ANSI Z80.36 to 2021 • Added description for randomization of BIO exam and imaging exam • Updated SAP	K. Jonas	See latest approval date

APPROVED BY

Role	Name	Title	Date	Signature
Study Chair	J Peter Campbell	CEO, Siloam Vision, Inc	07/28/2026 00:03:07	**sign-p86-i52325-b20260728000307613**