Abbreviated Title: Pediatric Optic-to-Audio Device Study

NIH IRB #: 000414.

Version Date: October 25, 2022

Title: Pilot Study of an Optic-to-Audio Device in a Pediatric Cohort with CLN3-related conditions or Low Vision

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Investigational Agents *(if applicable)*:

Device Name:	OrCam MyEye 2
Sponsor:	Not applicable
Manufacturer:	OrCam Technologies Ltd.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

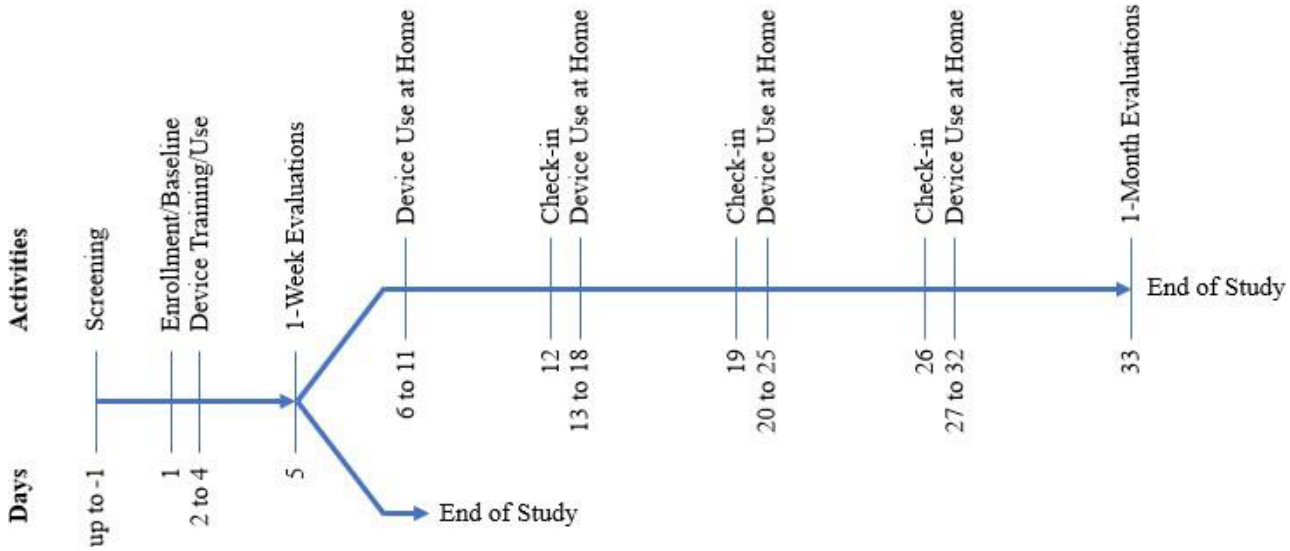
Title:	Pilot Study of an Optic-to-Audio Device in a Pediatric Cohort with CLN3-related conditions or Low Vision
Study Description:	This is a pilot study of an augmentative visual device, OrCam MyEye 2 (OrCam), in pediatric individuals with CLN3-related conditions or low vision. We hypothesize that, given the relatively simple design and operating procedure of the device, the use of the OrCam by study participants will be safe and feasible. We also hypothesize that the device will enhance their ability to obtain visually based information.
Objectives:	*Primary* Assess the safety and feasibility of OrCam use by children with CLN3 or low vision. *Secondary* Assess the effectiveness of OrCam use by children with CLN3 or low vision. *Exploratory* Assess the feasibility and effectiveness of OrCam use in CLN3 versus non-CLN3 groups. Optimize methods for assessing efficacy of visual accommodation/assistive devices for the CLN3/NCL population
Endpoints:	*Primary* 1) Adverse events during the use of OrCam. 2) Feasibility test. 3) Feasibility questionnaire. 4) Device use diary. The assessment periods will be 1 week at study site and 1 month at home. *Secondary* 1) Function test of using OrCam. 2) Ability questionnaire. *Exploratory* 1) Function test. 2) Feasibility, Ability, Applicability questionnaires.
Study Population:	30 individuals age 6-18 years with low vision (20 with CLN3-related conditions, 10 without CLN3) of any gender, demographic, geographic location who meet study eligibility criteria.
Phase:	Not applicable
Description of Sites/Facilities Enrolling Participants:	The NIH Clinical Center will be the only site enrolling participants.
Description of Study Intervention:	The study uses the OrCam MyEye 2, a 22.5-g portable, eyeglass-mounted device that converts camera-captured inputs to auditory outputs. Its advertised functions include text reading, facial recognition, and product identification. The study participants and

parents/guardians will be trained on how to use the device. Evaluations for primary and secondary endpoints will be done following 1 week and 1 month of device use.

Study Duration: 24-36 months.

Participant Duration: 1-2 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening[a,d] Up to Day -1	Enrollment Baseline Day 1	Day 2[b]	Day 3 to 4[b]	1-Week Evaluations Day 5[b]	Day 6-11[b]	Day 12[b]	Day 13-18[b]	Day 19[b]	Day 20-25[b]	Day 26[b]	Day 27-32[b]	1-Month Evaluations Day 33[b,c]
Informed consent[c]	X												
Demographics[c]	X												
Medical history[c]	X												
Physical exam[d]	X												
Vital signs[d]	X												
Ophthalmic evaluation[d]	X												
Neuropsychologic evaluation[c]	X												X[d or h]
Audiologic evaluation[d]	X												
UBDRS[c,e]	X												
Device training[c,f]		X[d]	X[d]	X[d or h]	X[d]		X[h]		X[h]		X[h]		
Device use[g]			X[d or h]	X[d or h]		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Adverse events review[c]					X[d or h]		X[h]		X[h]		X[h]		X[d or h]
Feasibility test[c,i]		X[d]			X[d]								X[d or h]
Feasibility questionnaire[c,j]					X[d or h]								X[d or h]
Function test[k]		X[l, d]			X[l, d]								X[m, d or h]
Ability questionnaire[n]		X[d]			X[d or h]								X[d or h]
Applicability questionnaire[o]		X[d]											
Quality of Life questionnaires[p]		X[d]											X[d or h]
Phlebotomy[d]	X												
Research biospecimen collection[q]	X												

[a] Screening evaluations can be done under 18-CH-0002 protocol if participant consented to co-enroll, or under this protocol. Previous evaluations/procedures within stated time frames (**Section 8.1.2**) will be accepted in lieu of repeating.

[b] +/- 2 days, except for Day 2 to 4 range may be +2 days

[c] By in-person or remote technology methods

[d] At NIH CC

[e] Only in participants with CLN3-related conditions who are not co-enrolled in study 18-CH-0002.

[f] **Appendix J** - OrCam MyEye 2 User Guide, Software Version 8.2-EN, Jan 2020.

[g] By participant for minimum of 15-30 minutes per day. If participant/parents/guardians encounter issues with device use, they may contact the study team and a video- or audioconference will be scheduled as appropriate.

[h] At home

[i] **Appendix A**. To be administered by study team to participant

[j] **Appendix B**. To be administered by study team to participant if able, and parents/guardians

[k] **Appendix C**. To be administered by study team to participants.

[l] Full Function Test done with evaluator and participant at NIH CC or partial Function Test done via remote technology (e.g., videoconferencing).

[m] Full or partial Function Test if participant cannot return to NIH CC

[n] **Appendix D**. To be administered by study team to parents/guardians

[o] **Appendix E**. To be administered by study team to parents/guardians

[p] **Appendices G - I**. To be administered by study team to participants if appropriate, and parents/guardians

[q] If not already done as part of CLN3 natural history protocol (18-CH-0002). Includes at the most: cheek swab (at home or NIH), saliva (at home or NIH), skin biopsy (at NIH), urine (at NIH)

2 INTRODUCTION

2.1 STUDY RATIONALE

CLN3 is a fatal, lysosomal disease that results in progressive neurodegeneration. It is the most common type of the 13 disorders of neuronal ceroid lipofuscinosis with incidence estimates ranging from 1/12,500 to 1/100,000 in European and USA populations. The initial clinical presentation is vision loss, resulting in legal blindness by 7-8 years of age in most individuals with classic CLN3 disease. Cognitive impairment and behavioral dysfunctions are also early presenting symptoms, followed by seizures and motor dysfunction. Current life-expectancy for affected individuals is in to the second to third decade of life.

The early and relatively rapid visual changes significantly impact the quality of life of individuals with CLN3. Current standard accommodative approaches for the progressive blindness, i.e., enlarged fonts, Braille, sign language, have limited applicability given the multiple disabilities associated with the neurodegeneration. Though treatment trials are in development, none specifically targets low vision. Thus, approaches to provide means for obtaining vision-related inputs are needed. Additionally, better understanding of parental goals for their child in terms of ability to perform vision-related tasks will inform the development of future accommodations. To begin addressing these knowledge gaps, this protocol will assess the safety, feasibility, and efficacy of the use of an augmentative visual device in a cohort of children and adolescents with CLN3, low vision, and intellectual disability. This protocol will further explore parental objectives for their child's function, and the potential of the device in addressing these.

Information on the use of the OrCam MyEye 2 device in the pediatric population with low vision is not available. Thus, to evaluate the feasibility and effectiveness of this device in children with low vision, and no concomitant neurodegenerative process, we will include a cohort of pediatric individuals with low vision but without a CLN3-related disorder.

2.2 BACKGROUND

CLN3 (JNCL, Batten Disease, MIM 204300) is an autosomal recessive, fatal, lysosomal disease that results in progressive neurodegeneration.[1-3] It is one of 13 disorders categorized as neuronal ceroid lipofuscinosis. In aggregate, these are considered the most common neurodegenerative disorders in children, with incidence estimates ranging from 1/12,500 to 1/100,000 in European and USA populations.[2, 4]

The disease presentation typically involves vision loss observed around pre-school years, with eventual progression to blindness within 1-3 years.[5-7] The underlying pathophysiology involves intracellular accumulation of ceroid lipofuscin materials in retinal ganglions, and possibly in photoreceptors.[8-10] This manifests on ophthalmic measures as decreased electrical responses to stimuli on electroretinogram [5, 7, 11] and thinning of the retinal cell layers on pathology and optical coherence tomography [7, 9, 12]. Neurocognitive development plateaus around 7-10 years of age and progresses to dementia starting in the early teen years.[13-15] Behavioral, psychiatric, seizure, and motor disorders are also common findings in individuals with CLN3.[1, 16] Current estimated average life expectancy is in the 20-30's.[2] There are no therapies for this devastating disorder. Therapeutic trials using gene therapy or small molecules are in the early stages of implementation.[17] Pathogenic variants in *CLN3* have also been associated with a non-syndromic phenotype that appears to affect vision only.[18, 1

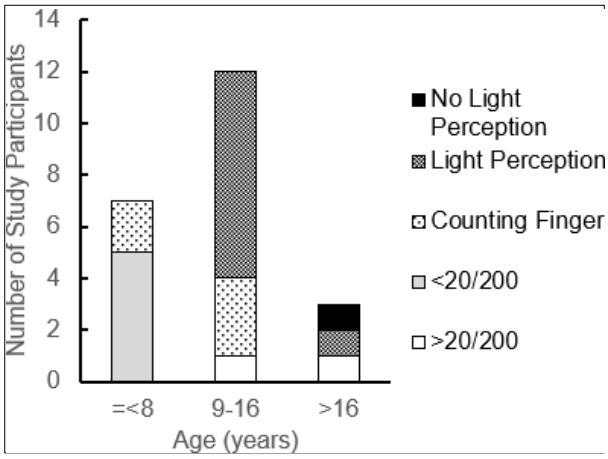


Figure 1. Visual ability of CLN3 natural history study participants (n=22).

To augment the development of biomarker discovery for application in diagnosis and therapeutic trial monitoring, we initiated a Natural History study of individuals with CLN3 (NCT03307304). The study includes extensive evaluations including ophthalmologic, neurodevelopmental, audiologic, functional visual and occupational therapy measures. Of the initial 22 study participants enrolled, all but two have vision qualifying for legal blindness status (**Figure 1**). Vineland-3 adaptive behavior composite (ABC) assessment, a parental report measure of an individual's real-world functioning with good correlation with standard IQ testing, showed that a significant number of the study participants older than 8 years of age scored in the range of intellectual disability (≤ -2 SD; **Figure 2**, left panel), with daily living skill scores also significantly below the mean standard score (**Figure 2**, right panel).

The loss of a major means of sensory input likely contributes to some of the behavior dysfunctions such as anxiety and perseveration in children with CLN3.[20] Quality of life for the affected child and family members is profoundly impacted as they adapt to the blindness and disease.[20, 21] When asked to rank in order (1=most desirable) the symptoms they would like to see being addressed by future interventions, 37% of mothers (n=19) and 47% of fathers (n=15) in the Natural History study cohort chose vision as number one.

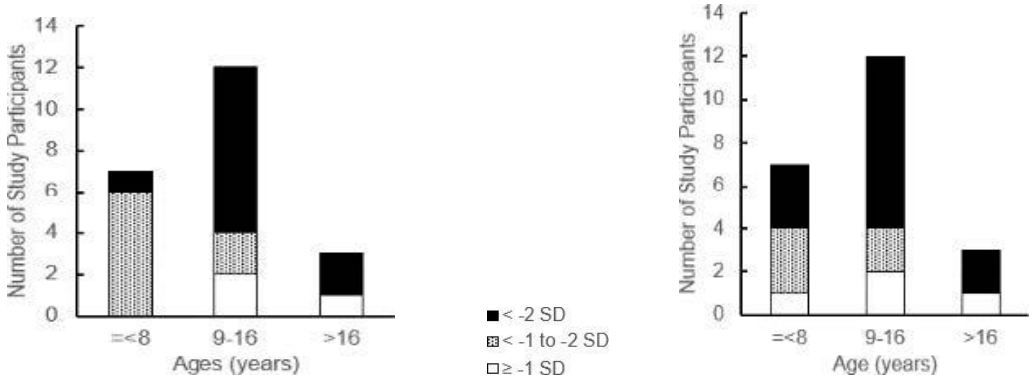


Figure 2. Adaptive behavior of CLN3 natural history study participants as measured by Vineland-3 parental interview (n=22). Left panel: Adaptive behavior composite standardized scores. Right panel: Daily Living Skill standardized sub-scores. Mean score = 100. Standard deviation (SD) = 15.

Current approaches towards therapeutic intervention for CLN3 appropriately focus on addressing neurologic or systemic symptoms. [22-24] However, these approaches have unclear impact on visual ability as information on the effectiveness of blood-retinal barrier delivery has not been published. While many of the study participants were initially started on Braille, the

concomitant intellectual disability limited them from attaining the skill level necessary for efficient use. Other alternative and augmentative modes for communication and sensory inputs such as auditory (e.g. books on tape) and tactile (e.g. textured objects) may be more applicable[21]. Study participants in the NICHD natural history cohort have preserved hearing ability and are reported by parents to maintain interests in listening to stories or movies on their electronic devices. The OrCam MyEye 2[25] is a portable, optic-to-audio assistive vision device that contains features likely applicable to the CLN3 cohort. The eyeglass-mounted device (**Figure 3**) is advertised to allow users to read text, and to identify faces, objects and colors by pointing and aiming the camera at the intended target[25]. A pilot study

Figure 3. OrCam MyEye 2. https://www.orcam.com/en/blog/category/general/, on 3/8/2020.

using the OrCam in 12 adults with low vision and intact cognition showed improved ability in reading and daily function tasks[26]. The adult study participants also found the OrCam to be easy to use and would recommend it to others with low vision. No study in children or in individuals with CLN3 is available.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Efforts will be made to reduce physical and psychological stress associated with study participation. These procedures will be explained to the individual participants and to their parents/guardians.

A. OrCam MyEye 2 Device and Use. Non-significant risks are associated with the use of the device when following the manufacturer's User Guide (**Appendix J**). The device is worn as an accessory to regular eyeglass frames. The relative proportion of the device to a pediatric participant is shown in **Appendix K**. If an individual does not have glasses, they may experience discomfort with wearing glasses for the first time. The increase in auditory inputs may be irritating. The device use acclimation process may be frustrating. These are expected to improve with repeated use.

B. Medical Evaluations. Minimal risks are associated with the physical, the Unified Batten Disease Rating Scale (UBDRS), and neuropsychologic examinations. Multiple independent evaluations may be stressful to a child or an impaired participant.

C. Ophthalmologic Evaluation.

A standard ophthalmologic exam includes dilation. Iris dilation can make participants transiently sensitive to light.

D. Audiologic Evaluation. For the hearing test the participant will wear headphones or soft foam earplugs. They will then be exposed to tones and words which vary in loudness and asked to respond to the sounds. This testing involves minimal discomfort.

Acoustic reflex measurement allows the audiologist to further examine the integrity of the acoustic reflex arc which relies on functional integrity of the middle ear system, inner ear, seventh and eighth cranial nerves and auditory pathways in the lower brainstem. For this test, very brief, somewhat loud tones are presented to each ear. In a normal-hearing ear, the stapedius muscle in the middle ear contracts in response to loud sounds presented

at levels of about 70-100 dB HL (decibels hearing level). In this test, the audiologist presents tones at these levels and determines whether there is an acoustic reflex and what level of sound is required to produce the reflex. This is a standard audiologic test.

The audiologic evaluation will include measurement of auditory evoked potentials. For this test, the participants will wear either headphones or soft, foam earplugs. Electrodes will be taped to the participants' head and the electrical response to sound will be recorded. This testing involves minimal discomfort and risk.

E. Neuropsychologic Evaluations. Participants may fatigue or get frustrated from answering many questions. Breaks will be provided to minimize these potential issues.

F. Phlebotomy. An anesthetic cream such as EMLA may be used to decrease discomfort. Infection and bruising are possible at the site of the blood draw.

G. Cheek swab/Saliva collection. The collection may be inconvenient. The cheek swab may cause temporary oozing of blood that should be minimal.

H. Urine collection. This collection may be inconvenient.

I. Skin biopsy. The biopsy may hurt. This can be minimized by administration of local anesthetics. The site may leave a faint scar. Individuals with history of excessive keloid formation will not have a skin biopsy done. Bleeding and infection are minimal risks.

J. Genetic Testing. Genetic information obtained from participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. Researchers who will have access to genetic information about the participants will take measures to maintain the confidentiality of this information. Individuals enrolled in this protocol would already have the diagnosis of CLN3-related conditions or a genetic cause of low vision, with its attendant risks of insurance and employment discrimination. If the underlying genetic cause for the low vision is not known and it is applicable to identify, then the participant will be referred to protocol "Evaluation of Patients with Genetic Disorders" (16-CH-0103). To the fullest extent possible, the investigators will not disclose to third parties any information about the participants without their expressed consent.

K. Sample confidentiality. Specimens not being used for clinical care or standard clinical tests which are sent to various laboratories will have identifiers removed and be coded. This code and clinical data will be maintained on password protected computers and in locked offices.

L. Psychological Harms. This protocol may reveal unexpected medical findings. If these medical findings can be evaluated and treated at the NIH-CC we will provide short term care for these findings. For any unanticipated medical findings that result in psychological stress, the medical team will provide counseling and support to the participant and the parents/guardians. If needed, the medical team can be reached by letter, phone, and email to address other uncertainties.

M. Risk to Family Relationships. This protocol is not likely to reveal unexpected family relationships such as adoption or misplaced paternity. If these issues do arise, we will not mention them to the participant or family members unless the issue is of clinical significance for the participant. Every attempt will be made to uphold the objective of privacy and participant autonomy.

2.3.2 Known Potential Benefits

This is a feasibility study of using the OrCam by children with CLN3 or low vision. No previous study of this device in this population has been done, thus information on known potential benefits are limited to the following:

1) The device provides an approach to augment visual inputs by translating these into auditory inputs, a sensory system apparently unaffected in children with CLN3 or low vision.
2) In adults with low vision, the device improves their ability to read text and recognize products[26]. It is advertised to improve the ability to recognize faces, colors, and report dates and times. These are functions integral in basic daily life tasks.
3) Appropriate use of the device may allow children with CLN3 or low vision to regain independence in some basic daily tasks and decrease care burden for family members.

2.3.3 Assessment of Potential Risks and Benefits

This protocol provides an intervention with the potential for benefits. The risk of the intervention, use of OrCam, is minimal. The research evaluations (Ophthalmology, Neuropsychologic, Audiology) are required to determine eligibility and carry minimal risks. The research evaluations (UBDRS, collection of biospecimens, genetic testing) add to the general understanding of the natural history of CLN3. For the non-CLN3 cohort the collection of biospecimens and genetic testing will serve as important pediatric control samples. These proposed procedures carry minimal risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess: a) safety and b) feasibility of using OrCam MyEye 2 by children with CLN3 or low vision.	a) Adverse events b) Feasibility test, Feasibility questionnaire, and Device use diary (see Section **9.4.2**) *The assessment periods will be 1 week at study site and 1 month at home.*	a) Collection of adverse event data is a standard method for evaluating safety in clinical trials. b) No validated, standardized tool is available to evaluate the feasibility of augmentative communication devices such as the OrCam. We modified the feasibility questionnaire used in an adult study [26] to provide appropriate adaptation for the pediatric cohort.
Secondary		
To assess the efficacy of using the OrCam by	1) Function Test – Efficacy Scores (see Section **9.4.3**)	No validated, standardized tool is available to evaluate the efficacy of augmentative communication

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
children with CLN3 or low vision.	2) Ability questionnaire (see Section **9.4.3**) *The assessment periods will be 1 week at study site and 1 month at home.*	devices such as the OrCam. We developed a Function Test based on the device's advertised functions, our observations of the pediatric cohort in the Natural History study, and the one used in an adult study [26], to provide age and ability appropriate assessments.
Exploratory		
1) To compare the feasibility and efficacy of using the device between the CLN3 and non-CLN3 groups. 2) To optimize methods for assessing efficacy of visual accommodation/assistive devices for the CLN3/NCL population 3) To characterize parental objectives relating to vision-based functions for a child with CLN3 4) To assess unanticipated adaptive functions of using the OrCam. 5) To discover biochemical markers relevant to disease	1) Function test – Feasibility Scores, Feasibility, Ability, Applicability questionnaires 2) Function test – Feasibility Scores, Neuropsychologic evaluation (1-month), Feasibility, Ability, Applicability questionnaires 3) Ability, Applicability, Quality of Life questionnaires 4) Device use diary 5) Samples collection to complement Natural History	1) Individuals with CLN3 also have neurocognitive disability, whereas the non-CLN3 may not. These evaluations would provide perspectives on differences in the two groups. 2) Participants' and caregivers' perspective will be important towards informing future development of studies and interventions for visual function in the CLN3 cohort . 3) Collection of biospecimens will allow increase in numbers and statistical power for the biomarker discovery

4 STUDY DESIGN

4.1 OVERALL DESIGN

Individuals with CLN3 are anticipated to have vision loss and intellectual disability, but with preserved auditory function. We hypothesize that **an auditory-based assistive technology with a simple operating procedure, such as the OrCam, will be safe and feasible for use in a pediatric population, including those with CLN3, and will enhance their ability to obtain visually based information**. We propose a pilot study of 20 study participants to evaluate the safety, feasibility, and efficacy of using the OrCam in a cohort of the CLN3 pediatric population. Since no information is available on the safety, feasibility and efficacy of the OrCam in the

pediatric population, we also propose enrolling 10 pediatric participants with low vision from non-CLN3-related causes. The primary and secondary objectives will be assessed using data from all 30 participants.

In this 2-cohort (CLN3 and non-CLN3), open-label, single-center study, we aim to determine:

1) the safety and feasibility
2) the potential clinical efficacy

of the use of OrCam in children, including individuals with CLN3.

4.2 Scientific Rationale for Study Design

Currently, there is no device similar to the OrCam available or in accepted use for individuals with CLN3. In addition, there is also no data available on the use of this device in children with low vision. Thus, a combined cohort of pediatric participants with and without CLN3-related disorders will optimize recruitment potential, and provide preliminary information for evaluation of feasibility and efficacy in pediatrics, and specifically in individuals with CLN3-related conditions. To assess efficacy, we will use the study participants' baseline data as controls. This option encompasses the least number of confounding factors for a cohort of small size.

In the CLN3 natural history study (18-CH-0002), accrual rate averages at 8-10 per year. Not all of these individuals will meet the eligibility criteria for this proposed study. However, we anticipate, based on experience with interventional trials of other rare diseases, that families hesitant to participate in an observational study would be more open to participating in an interventional study. Given these considerations, we anticipate an accrual rate of 5 participants per year and a reasonable potential to enroll 20 CLN3 participants over 2-3 years. We have also discussed potential eligible participants with local Ophthalmology groups (Howard University, Johns Hopkins, NEI), and the anticipated number for pediatric individuals with low vision and not CLN3-related condition is estimated to be in the same range. We plan to screen up to 50 participants.

4.3 Justification for Dose

Not applicable.

5 0-STUDY POPULATION

5.1 Inclusion Criteria

To participate in the screening portion of this study, an individual must meet all of the following criteria:

1. Has a diagnosis or suspected diagnosis of any genetically based condition causing low vision to the level specified in criteria 2.
   If the genetic condition is CLN3-related, the individual must have <u>one</u> of the following:
   a. Two *CLN3* pathogenic variants,
   b. One *CLN3* pathogenic variant AND
      i) clinical presentation suggestive of CLN3, OR
      ii) characteristic electron microscopy (EM) findings (such as curvilinear body, fingerprint profile, granular osmiophilic deposits).
2. Has an estimated visual acuity in the better seeing eye < 20/200, without the use of an assistive or augmentative device.
3. Is between 6 to 18 years of age.

To participate in the intervention/device use portion of this study, an individual must meet the above screening criteria and the following criteria:

Has an appropriate cognitive developmental ability to participate based on Investigators' screening assessment.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Has any of the following auditory dysfunctions: non-reversible or non-correctable hearing loss, tinnitus that is chronic or occurring daily, auditory hallucinations that occur daily.
2. Uses an optic-to-audio assistive device at the time or within 3 months of screening and enrollment.
3. Is unable to travel to the NIH because of medical condition for required in-person portions of the study.
4. Is unable to comply with or have medical conditions that would potentially increase the risk of participation.

5.3 INCLUSION OF VULNERABLE PARTICIPANTS

5.3.1 Participation of NIH Staff or family members of study team members

Family members of NIH staff or of individuals on the study team may be enrolled in this study if meeting the study entry criteria. Neither participation nor refusal to participate as a subject in the research will have an effect, either beneficial or adverse, on the participant's family member's employment or position at NIH.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable an unidentifiable manner.

The NIH Information Sheet on NIH Staff Research Participation will be made available. Please see section **10.1.3** for consent of NIH Staff.

5.3.2 Participation of children and cognitively impaired children

CLN3 is a disease with typical onset in childhood. For age- and visual severity level-appropriate comparisons, individuals with low vision but not CLN3 will also be children. The procedures included in the protocol are reasonably commensurate with those that children with CLN3 or low vision would encounter in their expected medical care. Participants may benefit directly from the use of the OrCam. We will follow procedures outlined in **Section 10.1 Informed Consent Process** for consenting children.

5.4 INCLUSION OF PREGNANT WOMEN, FETUSES OR NEONATES

Not applicable.

5.5 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to wear the OrCam device, attached to an eyeglass frame (**Appendices I** and **J**), for a minimum of 30 minutes each day while performing device-supported activities.

5.6 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a temporary or reversible deficit in hearing ability may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.7 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from the current 18-CH-0002 CLN3 Natural History protocol, through patient and professional organizations, at conferences, and through other healthcare providers. Study participants and parents/guardians may also contact the study team directly. We will also distribute information of this protocol through the NIH OPR, posting on clinicaltrials.gov, postings on social media websites, and referencing of this study website in presentations on CLN3-related topics. We plan to screen up to 50 participants for the duration of the study and enroll 5-10 per year for a total accrual goal of 30 participants.

5.7.1 Costs

All study-related procedures and interventions done at the NIH CC will be provided at no charge. If the study participants must be referred to an outside facility for further evaluations and treatments, the medical cost associated with these interventions will be covered by the participants' primary insurance.

5.7.2 Compensation

Coverage for travel, lodging, and food will be provided per NICHD's guideline.

Table 1. Time-based calculations for proposed compensation to participants in protocol 000414. (Reference: **Policy 302**)

	$	Screening	Baseline/ Training	1-Week	1-Month (in-person)	1-Month (remote)
		16 hours	12 hours	8 hours	3 hours	2 hours
Outpatient – 1st hour ($)	20	40	40	20	20	20

Outpatient Time – Per Additional Hour ($)	10	140	100	70	20	10
Escort Fee – Per Outpatient Visit ($)	20	40	40	20	20	0
Time Totals ($)		220	180	110	60	30

Based on the above calculations, the compensation scheme would be as below for each future enrolled participant. For incomplete participations, the compensation amount will be prorated based on the number of hours participated.

1. $220 for completing the Screening evaluations.
2. $180 for completing the Baseline and Training visits.
3. $110 for completing the 1-Week visit.
4. $60 for completing the 1-Month visit *in-person*, or $30 for completing the 1-Month visit *remotely*.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS(S) ADMINISTRATION

6.1.1 Study Intervention Description

OrCam MyEye 2 is an FDA class 1 device (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/rl.cfm?lid=397540&lpcd=HPG). The main components include a 13 megapixels camera, a 3.7V DC (nominal 320mAH) battery, and ancillary charging and glass-mounting supplies. The OrCam MyEye 2 is available in only one size that has dimensions of 76x21x14.9 mm, and weighs 22.5 g. Additional visual and descriptions of the device, its set-up and functions are provided in **Appendices I-K**. The use of the OrCam in this study will be according to the manufacturer's specifications. The device is not intended as an implant and does not present potential for serious risk to the health, safety, or welfare of a subject. Due to its risk profile, the device should be considered a non-significant risk device.

Participants will be trained and asked to use the device for at least 30 minutes daily as indicated in the **Schedules of Activities**. All participants meeting eligibility criteria will enroll in the 1-week study and be exposed to the device use for 5 days. Participants may enter the additional 1-month study if parents/guardians/participants endorse desire to continue using the device at home.

6.1.2 Dosing and Administration

Not applicable.

6.1.2.1 Dose Escalation

6.1.2.2 Dose Limiting Toxicity

Not applicable.

6.1.2.3 Dose Modifications

Not applicable.

6.1.2.4 Drug Administration

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Handling and use of the device must follow the manufacturer's recommendation as described in the User Guide.

6.2.1 Acquisition and Accountability

An OrCam MyEye 2 device will be provided to participants for the duration of the study. The device must be returned in the appropriate postage-paid packaging provided by the study team following the end of study assessments.

6.2.2 Formulation, Appearance, Packaging, and Labeling

OrCam MyEye 2 is manufactured by OrCam Technologies Ltd.

6.2.3 Product Storage and Stability

Device handling and storage is as described in the User Guide.

6.2.4 Preparation

Device assembly and use instructions are as described in the User Guide.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is an open-label study. Participation in the 1-month extension is on a voluntary basis.

6.4 STUDY INTERVENTION COMPLIANCE

Participants or parents/guardians will complete a Device Use Diary (**Appendix F**) in either paper or web-based format. The use log will be cross-checked with the participants/parents/ guardians by a study team member daily for the 1-week study, and at weekly adverse events review contacts for the 1-month study.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from daily use of the OrCam does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Feasibility questionnaire (if participant has completed device training)
- Ability and Applicability questionnaires
- Adverse events
- Quality of Life questionnaires

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Completion of study intervention
- Disease progression which requires discontinuation of the study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Prior to removal from study, effort will be made to have all participants complete a safety evaluation approximately 1 week following the last use of study device.

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant has completed the study follow-up period
- Death
- Screen Failure

The reason for participant discontinuation or withdrawal from the study will be recorded on the Discontinuation/Withdrawal Case Report Form (CRF). Participants who sign the informed consent form but do not receive the study intervention, i.e. the activities on enrollment/baseline

day, may be replaced. Participants who sign the informed consent form, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two weekly scheduled check-in calls and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to present for a required study appointment:

- The site will attempt to contact the participant within +/- 2 days of the scheduled appointment and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

8.1.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of existing photographs or videos.
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

To determine CLN3 disease status, we will review medical or research records evaluations done for diagnostic purposes. If this information is not available from the CLN3 Natural History protocol 18-CH-0002, we will request them via written or verbal query. If genetic sequencing has not been done, it can be done under this protocol as part of the screening evaluations or under protocol 18-CH-0002.

8.1.2 Screening activities performed after a consent for screening has been signed

Screening procedures as listed in the Schedule of Activities will be done on-site at the NIH CC to determine study eligibility. Results of the below evaluations within the time frame and from sources indicated in **Table 2** will be reviewed by the corresponding collaborating specialists and

accepted for purpose of determining eligibility as applicable. All other procedures listed in the Schedule of Activities for the screening visit can be done within 6 months of study enrolment.

Table 2. Types of evaluations and results acceptable for use in determining study eligibility.

Procedures	Acceptable	
	Time prior to enrolment	Route
Ophthalmology	within 3-4 months	18-CH-0002; NEI protocols (e.g. 08-EI-0102, 13-EI-0049, 15-EI-0128)
Neuropsychologic	within 6 months	18-CH-0002; outside or NIH records
Audiology	within 3-4 months	18-CH-0002; outside or NIH records

1. **Ophthalmologic Evaluation.** We will collaborate with the NEI team to obtain an age-appropriate eye examination in study participants, with documentation of best uncorrected and corrected visual acuity. The evaluations will be adjusted based on applicability of available records as listed in **Table 2**. No sedation will be used under this protocol.

2. **Neuropsychologic Evaluation.** We will assess cognitive function in study participants, by using clinical judgment based on age and/or developmental level, to prioritize use of the following instruments, if possible:

   A Wechsler IQ test

   Wechsler Preschool and Primary Scale of Intelligence, 4th edition for children ranging from 2.6-3.11 and 4.0-7.7, or

   Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) for 6 to 16 years of age, or

   Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV) for individuals over age 16 will be the preference.

   The *Wechsler Abbreviated Scale of Intelligence-Second Edition,* or *the Wechsler Nonverbal Scale of Ability (WNSA)* will be used when necessary.

   Further for younger individuals or those with significant cognitive impairments, the following tests will be used:

   Mullen Scales of Early Learning (MSEL). The Mullen Scales of Early Learning is a standardized developmental test for children birth to 5 years, 8 months. The measure consists of five scales: Gross Motor, Visual Reception, Fine Motor, Receptive Language, and Expressive Language; all scales with the exception of the Gross Motor scale provide an estimate of developmental functioning, the Early Learning Composite.

   For assessment of adaptive behavior, *The Vineland Adaptive Behavior Scales*, Third Edition, based on parent interview, will be employed. This may be done by methods that

do not require in-person meetings (such as via a phone call) to provide adaptability to the protocol and to maximize ability to collect meaningful longitudinal data.

Other neuropsychological assessments that may be used include:

Wide Range Assessment of Memory and Learning, 2nd edition (WRAML-2) for individuals 5 – 90 years of age

Clinical Evaluation of Language Fundamentals, 5th edition (CELF-5) for individuals 5-21 years of age

Participants, legal guardians and informants will be allowed to take parent/informant and self-report measures on the day of the testing appointment, and return them by self-addressed, stamped envelope if they are not able to complete them on the day of the evaluation. The self-reported measures may also be completed via a web-based format. The evaluations will be adjusted based on applicability of available records as listed in **Table 2**. It is anticipated that parent interview and completion of the parent report forms will take approximately 1 to 1.5 hours.

3. **Audiologic evaluation**. An audiologic evaluation may include behavioral assessment of pure-tone and speech thresholds, and word recognition ability using test techniques appropriate for age and condition. Physiologic measures that do not require a behavioral response will be used to evaluate middle ear function (tympanometry), acoustic reflex thresholds, and cochlear function (otoacoustic emissions). The auditory evoked potentials will be used to assess functional integrity of the auditory nerve and auditory central nervous system pathways. This evaluation takes approximately 2 hours, and will be adjusted based on applicability of available records as listed in **Table 2**.

8.2 EFFICACY ASSESSMENTS

The specific timing of procedures/evaluations to be done at each study visit are captured in **Section 1.3, Schedule of Activities.** Direct evaluations (e.g., Function test) at Screening, Enrollment Baseline Day 1, Device Training Day 2, and 1-Week Evaluations Day 5 visits will be done onsite at the NIH CC. Non-direct evaluations (e.g., surveys and questionnaires) and evaluations on other study days can be done onsite or at home. Non-direct evaluations may be completed using paper or web-based format.

8.2.1 Clinical Evaluations

1. **Function Test.** The study participants will be asked to complete tasks relating to device-supported daily activities (**Appendix C**). These include identification of printed words (e.g., books, documents, menus, labels, signs) and identification of faces and colors.
   At Days 1 (baseline) and 5 (1-week evaluation), the Function Test will be done in its entirety via face-to-face encounters. A sub-group of the Function Test items may be done via the use of remote technologies (e.g., videoconferencing). At the 1-month evaluation, if the study participants are able to come to the NIH the Function Test will be done as on Days 1 and 5. If study participants are not able to come for an in-person visit, the sub-group of the Function Test items will be done remotely.
2. **Ability and Applicability Questionnaires**. Parents/Guardians will complete questionnaires of their child's ability to accomplish the tasks in the Function Test without help, and their ratings of how important it would be for their child to accomplish these

tasks without help. (**Appendices D, E**). The questionnaires may be completed using paper or web-based format.

3. **Neuropsychologic Evaluation.** We will assess adaptive behavior using *The Vineland Adaptive Behavior Scales*, Third Edition, Daily Living Scale, based on parent interview. This may be done by methods that do not require in-person meetings (such as via a phone call) to provide adaptability to the protocol and to maximize ability to collect meaningful longitudinal data.
4. **Quality of Life Questionnaires**. Parents/Guardians will complete age-appropriate PedEyeQ[27], PROMIS[28], and Low Vision QOL[29] questionnaires (**Appendices G - I**). The questionnaires may be completed using paper or web-based format.

8.2.2 Biospecimen Evaluations

Not applicable. Biological specimen collected will be for future research use and not for efficacy assessment.

8.2.3 Correlative Studies for Research/Pharmacokinetic Studies

Not applicable.

8.2.4 Samples for Genetic/Genomic Analysis

8.2.4.1 Description of the scope of genetic/genomic analysis

DNA may be obtained for CLN3 genotyping and stored for future molecular analysis of other genes that may influence the CLN3 phenotype. DNA will be obtained from blood, buccal swab, or saliva. Exome/genome or other forms of next-generation sequencing may be performed.

DNA analysis is not restricted to standard DNA sequencing. For example, methylation patterns may be studied, or new technologies applied. Any mutation analysis reported to the participant or participant's family will be confirmed in a CLIA approved laboratory.

RNA analysis may be performed. This analysis is not limited to mRNA but may include other RNAs such as miRNA and ncRNA.

8.2.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Data or biomaterials will be shared with collaborating research groups or laboratories at the NIH or outside the NIH. The data will be anonymized using a unique code generated for each study participant using cryptographic methods that cannot be reversed. Collaborating sites may use the same methods to generate the unique code. Thus, participants common to collaborating sites can be linked by the unique identifier. However, participants who have not been seen at a collaborating site will remain unknown (de-identified).

The protocols at the NIH and other sites will describe the coding mechanism described above and allow for data sharing with outside institutions. The collaborating institutions will have IRB oversight for their activities with identifiable data and samples. The Consent forms will inform the study participants that their coded data and samples will be shared with institutions who may be able to re-identify them.

Biomaterials may be used in multi-omic studies to identify potential biomarkers correlating to CLN3 disease and progression. Biomaterials sent to groups outside of the NIH may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). Outside laboratories may be

provided with coded or anonymized demographic, phenotypic and genotypic data necessary to fully interpret the experimental results. For biomaterials sent to groups outside of the NIH appropriate Material Transfer Agreements will be obtained.

Coded or anonymized data may be submitted to NIH-designated repositories (such as DASH) or databases per NIH data sharing policy. Repositories receiving data from this protocol may be open- or restricted-access.

8.2.4.3 Management of Results

Participants will be contacted if a clinically actionable gene variant is discovered on research testing. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. Participants will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory. A provider on the study team with training or practice experience in genetics will discuss the results with the participants.

This is the only time during the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

8.2.4.4 Genetic counseling

Genetic counseling and discussion of results will be done by a provider on the study team with training or practice experience in genetics.

8.3 SAFETY AND OTHER ASSESSMENTS

The specific timing of procedures/evaluations to be done at each study visit are captured in **Section 1.3, Schedule of Activities**. Direct evaluations (e.g., Device training, Feasibility test) at Screening, Enrollment Baseline Day 1 and 1-Week Evaluations Day 5 visits will be done onsite at the NIH CC. Non-direct evaluations (e.g., surveys and questionnaires) and evaluations on other study days can be done onsite or at home.

1. **Medical History and Physical Exam.** A medical history and physical exam will be obtained. For CLN3 participants, medical history will ascertain information that is being collected as part of a national CLN3 registry (https://rarediseases.info.nih.gov/diseases/5897/neuronal-ceroid-lipofuscinosis-3). Participation in the registry is not a requirement and caretakers or participants will be given the option of having medical information submitted to the registry. The history forms contain common data elements recommended for rare diseases research. Parents and participants may also be asked what elements of the disease are clinically relevant to them, in order to obtain insight into pertinent outcome measures in designing future therapeutic trials. Information from outside records or NIH visits, and from reports by participants and family members will be collected and reviewed.
2. **Anthropomorphic Measures and Clinical Photography.** Anthropomorphic measures including weight, length/height, and head circumference will be obtained at each visit.
3. **Feasibility Questionnaire**. Participants/parents/guardians will be asked to complete a questionnaire relating to their experience using the OrCam device (**Appendix B**). The questionnaire can be completed on paper or web-based format at the time points indicated in the **Schedule of Activities**.

4. **Device Training**. A study team member will provide verbal instructions to participant and parents/guardians on the assembly, set-up, and use of the OrCam. The instructions will be based on the User Guide (**Appendix J**). At the end of the training session, understanding of how to use the device will be documented by the trainer.
5. **Device Use Diary**. As described in **Section 6.4 Study Intervention Compliance**.
6. **Adverse Events Review.** A study team member will contact the family at the times indicated in the Schedule of Activities to collect information on adverse events relating to the use of OrCam MyEye 2. During this interaction, study team member will also review the Device Use Diary with the family and provide assistance to trouble shoot any issue relating to the use of the device.
7. **Clinical Staging.** For CLN3 participants not co-enrolled in protocol 18-CH-0002, clinical staging will be performed using the Unified Batten Disease Rating Scale (UBDRS). The UBDRS was developed to provide a tool to quantify physical, behavioral and functional aspects of juvenile neuronal ceroid lipofuscinosis [30]. Data from the ophthalmological, neurological, neurocognitive and speech evaluations will be integrated to obtain a UBDRS score for each participant. This tool has been shown to be a reliable instrument [30] and has been utilized in a retrospective evaluation of flupirtine [31] and prospectively for mycophenolate mofetil (https://clinicaltrials.gov/ct2/show/NCT01399047?term=CLN3&rank=2)
8. **Biomaterials Collection.** To complement the CLN3 Natural History (18-CH-0002) protocol's objective to identify biochemical markers, biospecimens will be collected from CLN3 participants who are not co-enrolled in 18-CH-0002. Participants will be consented for broad use and future research on the collected biomaterials. The method of analysis for biomarker discovery is not specified. Applicable technologies include but are not limited to proteomics, lipidomics, expression analysis, gene/exome/genome/transcriptome sequencing, metabolomics, and multi-analytes profiling. Subcomponents of a sample, such as exosomes, may be isolated and studied. Comparisons will be made to age similar control samples, made up in part by those collected from the non-CLN3 participants in this study. Since the function of CLN3 protein is incompletely understood, the objectives for biomarker discoveries are broad and may include those such as identifications of compounds in the plasma or urine whose level correlate with disease progression or with future therapeutic interventions.

   Collected cells may be used to produce cellular derivatives such as lymphoblasts, immortalized cell lines, or induced pluripotent stem cells. Coded samples will be maintained in the NICHD Biorepository and will be made available to collaborating laboratories with appropriate IRB and MTA clearance.

   Biomaterials collected as part of this study will include the following:

   -blood (such as serum, EDTA plasma and heparin plasma)
   -urine
   -DNA for CLN3 genotyping, modifier gene analysis or exome/genome sequencing
   -dried blood spots on newborn screening cards
   -peripheral mononuclear cells
   -cheek swabs/scrapings
   -saliva

-skin biopsy (3mm or smaller)

Although efforts will be made to obtain as complete a collection as possible, since these samples are collected for discovery research and not for safety monitoring not obtaining a specific sample will not be considered a protocol deviation. Except for blood-related samples, all other biomaterials will only be collected if not already done so under protocol 18-CH-0002.

Identified biospecimens obtained at outside institutions corresponding to study participants already enrolled in the study may be acquired under this protocol. These samples could be obtained secondary to clinical procedures (such as surgical specimens, clinical blood testing, or autopsy) or obtained as part of another ongoing clinical trial. Study participants will be consented to allow for the identifiable samples to be sent to NIH. These samples will be treated the same as a research specimen that was collected at the NIH Clinical Center. Unless needed for an ongoing experiment or requiring specific storage conditions other than -80 degrees Celsius, samples will be coded and stored in the NICHD Biorepository.

9. **Phlebotomy**. We anticipate collecting a maximum of 80 mL (5-6 tablespoons) of blood per participant. If more than one blood collections are needed (e.g., because of severe hemolysis) we will not exceed the 5 ml/kg/day, or 9.5 mL/kg over any 8-week period limits. Nursing staff will monitor blood-drawing volumes.
10. **Cheek swabbing/scraping and saliva collection**. We will use commercially available kits and follow the manufacturer's instructions.
11. **Skin biopsy**. A local anesthetic may be applied prior to the procedure. A 2-3 mm punch biopsy of the skin will be removed using sterile technique, and the wound will be dressed.
12. **Urine collection**. We may use a urine cup or toilet hat to collect urine. Participants will not be catheterized for this study.
13. **Outside records.** Under this protocol we may collect non-NIH Clinical Center outside records such as medical and research corresponding to participants or family members of participants. Typically, these records will be provided directly by the participant/guardian. A release of records request signed by the participant/guardian will be used if obtaining records from other health care providers. Information from these records may be incorporated into study databases. These records and personal identifying information will be maintained confidentially.
14. **Future Research**. Biomaterials, records, and data collected as part of this protocol may be used for future research not specifically specified in this protocol by both NIH and non-NIH investigators. Samples sent to outside laboratories will be coded, unless a standard clinical test is being performed. Materials Transfer Agreements will be obtained as applicable for samples sent to collaborators.
15. **Return of results and community engagement**. Participants will have access to all clinical testing and evaluation results through the NIH Clinical Center Portal. Protocol status is reviewed with participating families. Research results will be presented to the disease community via presentations or updates to the family support groups. Copies of publications related to this research will also be made available to the family support groups. The trial will be registered on clinicaltrials.gov and results will be posted per standard requirements.

The concept for this study arose from parental responses from the CLN3 natural history study. When asked to rank in order (1=most desirable) the symptoms they would like to see being addressed by future interventions, 37% of mothers (n=19) and 47% of fathers (n=15) chose vision as number one. A family of a child with CLN3 brought the OrCam MyEye 2 device to the study team's attention, and their observations on its use has been incorporated into the study design.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 Expectedness

The Principal Investigator or designated study team member will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. As CLN3 is a neurodegenerative, multisystemic disease, progression or new onset of symptoms may be part of the disease process and unrelated to the intervention. Problems listed in **Table 2** will not be reported to the IRB as adverse events unless increase in frequency is noted.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

A designated study team member will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4.5 Adverse Event Reporting

The Principal Investigator and designated study team members are responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, and IRB requirements. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than 7 days after the PI first learns of the event.

Deaths will be reported to the Clinical Director within 7 days after the PI first learns of the event.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

Table 2. Adverse events associated with CLN3

Category		Adverse Event
HEENT	**Eyes**	Low vision/blindness; abnormal movements (nystagmus); photophobia; visual hallucination
	Ears	Auditory hallucination; abnormalities in Behavioral Hearing and ABR tests
	Oromotor/ Speech	Dysphagia; drooling; dysarthria

Cardiovascular		Sinus arrythmias; prolonged ECG intervals; elevated BNP
Hematology		Decreased serum iron, % saturation
Endocrinology		Abnormal TSH; low vitamin D
Musculoskeletal		Abnormal gait; falls; scoliosis; in-toeing; abnormal muscle tone; tremors
Neurological		Brain atrophy; seizures; cognitive impairment; memory impairment; sleep disruption; fatigue
Psychiatric/Behavioral		Irritability; aggression; perseveration; anxiety; mood instability

ABR: auditory brainstem response. BNP: pro-brain natriuretic peptide. ECG: electrocardiogram. HEENT: head, eyes, ears, nose, throat. TSH: thyroid stimulating hormone

8.4.6 Serious Adverse Event Reporting

The study investigator shall report the event to the reviewing Institutional Review Board (IRB) IC's designee and as soon as possible, but in no event later than 7 calendar days after the investigator first learns of the effect.

8.4.7 Events of Special Interest

Not applicable.

8.4.8 Reporting of Pregnancy

Not applicable.

8.5 UNANTICIPATED PROBLEMS

8.5.1 Definition of Unanticipated Problems (UP)

Any 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 Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- 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); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

8.5.3 NIH Intramural IRB Reporting of IND Safety Reports

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

- Primary Endpoint(s): The primary endpoint of this study is to assess the safety and feasibility of using the OrCam device pediatric individuals with low vision. Assessment of safety will be made by evaluating summary statistics of Adverse events/ Unanticipated problems, Feasibility test, Feasibility questionnaire, and Device use diary in all 30 enrolled participants. We hypothesize that *use of the device will be safe and feasible in pediatric individuals with CLN3*.
- Secondary Endpoint(s): We hypothesize that the *use of OrCam MyEye 2 will enhance the participants' function on visual related tasks as measured by performance on the Function Test, and the Ability and Applicability questionnaires*.

9.2 SAMPLE SIZE DETERMINATION

Since no prior research or data are available and these measures are developed specifically for this pediatric population with multiple disabilities, power calculation is not able to be determined. The study in 12 neurologically intact adults reported a mean improvement of 70% in performance over baseline on the Function Test. We anticipate that the improvement will be lower given the age and comorbidities in the CLN3 cohort, thus propose a total enrolment of 30 pediatric participants. As outlined in **Section 4.2 Scientific Rationale for Study Design**, we anticipate being able to recruit 5 CLN3 and 5 non-CLN3 participants with low vision in one year.

A major purpose of this trial is to obtain pilot data on feasibility and potential functional outcome measures that appears to improve with device use. The pilot data will inform power calculations for a subsequent trial focused on establishing device intervention efficacy.

9.3 POPULATIONS FOR ANALYSES

9.3.1 Evaluable for toxicity

All participants will be evaluable for adverse events from the time of their first use of the OrCam.

9.3.2 Evaluable for objective response

Only those participants who have used the device for at least 3 days and have completed the Feasibility and Efficacy evaluations both before and after device use will be considered evaluable for response.

9.3.3 Evaluable Non-Target Disease Response

Not applicable.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

For comparisons of before and after device intervention in the same participant and correlation calculations, statistical significance will be determined by corresponding parametric (e.g., paired t-test and Pearson correlation) or non-parametric (Wilcoxon Rank sum test and Spearman correlation) methods. A p value < 0.05 will be considered significant and between 0.05 and 0.10 will be considered a trend. Multiple comparisons will be corrected by appropriate post-hoc analysis.

9.4.2 Analysis of the Primary Endpoints

Adverse events and Device use diary data will be provided using descriptive statistics.

Feasibility Test

Data analysis. Participants' scores will be the sum of items 1 to 5 and will range from 0 to 5. Analysis will consist of summary descriptive statistics (mean, standard deviation, median, proportion of participants at each score level). No formal statistical tests will be conducted. Interpretation of results will be rule-based.

Rules for data interpretation. Device use is feasible if at baseline, 1-week, or 1-month 50% or more of total number of participants score 3 or greater out of 5.

Feasibility Questionnaire

Data analysis. Participants' scores will be the sum of items 1 to 11 and will range from 0 to 11. Analysis will consist of summary descriptive statistics (mean, standard deviation, median, proportion of participants at each score level). No formal statistical tests will be conducted. Interpretation of results will be rule-based.

Rules for data interpretation. Device use is feasible if at 1-week or 1-month 50% or more of total number of participants score 6 or greater out of 11.

9.4.3 Analysis of the Secondary Endpoint(s)

Function Test – Efficacy Scores

Data analysis. Participants' scores will be the sum of items 1 to 7 combining levels a & b and will range from 0 to 14, and the mean duration to complete each task. Analysis will consist of change in scores and mean duration to complete each task from baseline to 1 week and 1 month). No formal statistical tests will be conducted. Interpretation of results will be rule-based.

Rules for data interpretation. Device use is efficacious if at 1-week or 1-month compared to baseline:

- 25% or more of total number of participants increased score by at least 30%
- 25% or more of total number of participants decreased time by at least 30%

Below are some simulations of the power of a paired-sample test for change from baseline, using a sample size of 10 participants. This provides a sense of the possible characteristics of the data and for justifying the sample size.

<u>Simulations for tasks-completed scores</u>

Each simulation study used 1000 replications with N = 10. For each replication, baseline and post-baseline sets of scores were randomly generated. Means, standard deviations, and paired-samples t-tests of difference scores (Post-baseline – Baseline)

were computed. Power was computed by the percent of replications (out of 1000) with t-test p-values less than or equal to 0.05. Baselines were generated by randomly selecting, with replication, scores from 0 to 5 with equal probability, 1/6. The baseline range matched the baseline values reported in the adult study. Post-baseline scores included a specified number of baseline cases randomly selected without replacement to improve by 30% (Baseline x 1.30). Cases with baseline values = 0 were excluded from random selection since percentage change from 0 is undefined.

Simulation 1. Based on the decision rule of 25% of total participants, 3 cases (rounded up since 25% of N= 10 is 2.5) were randomly selected to improve 30% from baseline and the other 7 cases did not improve. *Results: power = proportion of 1000 p-values <= 0.05 = 0.37.*

Simulation 2. 3 cases randomly selected to improve 30% and 7 cases improved by 1 point. *Results: power = proportion of 1000 p-values <= 0.05 = 1.0.*

Simulation 3. 4 cases randomly selected to improve 30% and 6 cases did not improve. *Results: power = proportion of 1000 p-values <= 0.05 = 0.95.*

Simulation 4. 4 cases randomly selected to improve 30%, 6 cases improved by 1. *Results: power = proportion of 1000 p-values <= 0.05 = 1.0.*

Simulation 5. 2 cases randomly selected to improve 30% and 8 cases did not improve. *Results: power = proportion of 1000 p-values <= 0.05 = 0.00.*

Simulation 6. 2 cases randomly selected to improve 30%, 8 cases improved by 1. *Results: power = proportion of 1000 p-values <= 0.05 = 1.0.*

Simulations with baseline values 1 to 5, # cases improving 30%: 2 to 5; # cases improving by 1: 0 to 3; # cases no improvement: 4 to 8. (For any simulation run, # cases improving 30% + #cases improving by 1 + # cases not improving = 10). *Results:* These simulations correct for the problem that percentage improvement is undefined when baseline = 0. When stipulating that percentage improvement is 30% for as few as 2 or 3 cases, power is greater than .99 when only 1 to 3 other randomly selected cases improve by 1 from baseline. Power will be higher if participants' scores improve more than 1 over baseline.

Based on these simulations, a test of efficacy using a paired-samples t-test with N = 10 would be adequately powered provided that post-baseline scores are likely to improve from baseline. Whether or not a sample of 10 is large enough to make conclusions about different characteristics of the sample group is not addressed.

Ability Questionnaire

Data analysis. Proportions of participants with scores 3 or greater in all items from 1-12. No formal statistical tests will be conducted. Interpretation of results will be rule-based.

Rules for data interpretation. Device use is efficacious if there is a 25% increase in the proportion of participants scoring 3 or greater in all items at 1-week or 1-month as compared to baseline.

9.4.4 Safety Analyses

As described in Section **9.4.2**.

9.4.5 Baseline Descriptive Statistics

Baseline demographics, ophthalmic, neurodevelopmental and auditory data will be summarized using descriptive statistics or qualitatively as applicable.

9.4.6 Planned Interim Analyses

No interim analysis is planned for this pilot study. However, the Principal Investigator and designated study team members will be continually monitoring the feasibility and safety of the use of the OrCam and may terminate this study at any time for safety or administrative reasons.

9.4.7 Sub-Group Analyses

Analyses of the sub-groups will be as described in Sections 9.4.2 and 9.4.3.

9.4.8 Tabulation of individual Participant Data

Not applicable.

9.4.9 Exploratory Analyses

We will compare the feasibility and efficacy of the OrCam use in the CLN3 versus non-CLN3 groups. We will evaluate data collected on unanticipated use (uses identified by participants and not an advertised feature) of OrCam MyEye 2 and correlation of use feasibility and ability to measures of disease status (e.g., disease severity, neuropsychologic ability, etc.) using summary statistics. Exploratory analyses of clinical and biochemical markers may be done under protocol 18-CH-0002.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 Consent/Assent Procedures and Documentation

The informed consent document will be provided as a physical or electronic document to the participant or consent designee as applicable for review prior to consenting. A designated study investigator will carefully explain in terms suited to their comprehension the purposes, procedures, and tests involved in this study, and the associated risks, discomfort, and benefits. To minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator prior to signing. A signed informed consent document will be obtained prior to any research activities taking place.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remotely, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators will view individual copies of the approved consent document either on paper or on screens at their respective locations; the same screen or paper document may be used when both the investigator and the participant are co-located but this is not required. When required, the witness signature will be obtained similarly as

described for the investigator and participant below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document and made part of the participant's NIH record. The process for documenting signatures on an electronic document is described below.

When a hand signature on an electronic document is used for the documentation of consent, this study will use the following electronic platforms to obtain the required signatures:

- Adobe Acrobat platform (which is 21 CFR Part 11 compliant); or
- iMedConsent platform (which is 21 CFR Part 11 compliant)

Both the investigator and the participant will sign the electronic document using a finger, stylus, or mouse. Electronic signatures (i.e., the "signature" is digitally generated) will not be used.

We will obtain written informed consent from the parents /guardian(s) who accompany the child to the NIH Clinical Center (CC). If the parents are divorced and share custody, we will obtain consent from both parents. If the second parent is unable to attend the visit, the second parent will be consented via telephone or other NIH approved remote platforms as described above An individual who is not associated with the protocol must witness the signature of the absent parent/guardian on the consent form. According to 45 CFR

46.408 when one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child, the permission of one parent suffices. Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts, and benefits of participation. Verbal assent will be obtained as appropriate for children ages 6-10. Children under the age of 18, but who are age > 10 years will be asked to sign an age-appropriate assent form. Children under the age of 6 years are not eligible for enrolment. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. If applicable, children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

10.1.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require that consent be obtained from the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained.

If reconsent is not feasible, we request waiver of informed consent to continue to use data and/or specimens for those individuals who become lost to follow up or who have been taken off study prior to reaching the age of majority.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
    a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The research could not practicably be carried out without the waiver or alteration.

a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.

(3) As the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

a. Though the purpose of future studies cannot yet be known, they often involve the correlation of clinical outcomes and clinical interventions with laboratory studies. Such information would be unavailable if access to medical record numbers was unavailable.

(4) The waiver or alteration will not adversely affect the rights and welfare of the subjects.

a. Retention of these samples or data does not affect the welfare of subjects.

(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

10.1.3 We only request a waiver of consent for those subjects who have been lost to follow-up or who have been taken off study prior to reaching the age of majority. Considerations for Consent of NIH staff, or family members of study team members

Consent for NIH staff or family members of study team members will be obtained as detailed above with following additional protections:

Consent will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service to minimize the risk of undue pressure on the staff member.

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological 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 PI/study team, or responsible party.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), and/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) and pharmacy records 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 or Institutional policies requirement. To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (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.

10.4 Future use of Stored Specimens and Data

See **Sections 8.3.14, Safety and Other Assessments, Future Research; 10.3, Confidentiality and Privacy;** and **10.8, Data Handling and Record Keeping**, for further information on future use of study records and specimens.

10.5 Safety Oversight

The research team will be responsible for monitoring adverse events, participant safety, and participant tolerability. Regular, typically weekly, meetings will be held by the research staff to review status of all participants, potential issues, and possible adverse events. The study is not blinded, of relatively short duration, and involves a small number of participants that can be adequately assessed through simple comparison, thus a DSMC is not required. It will be monitored by random audits by the NICHD Office of the Clinical Director as specified in the NICHD SOP for Intramural Clinical Protocol Monitoring.

10.6 Clinical Monitoring

The research team and Medical Monitor will be responsible for monitoring for participant safety. This protocol will be monitored by random audits by the NICHD Office of the Clinical Director as specified in the NICHD SOP (5.25.12).

10.7 Quality Assurance and Quality Control

The NICHD Quality Assurance Program will perform random audits annually on at least 10%

of actively accruing NICHD protocols (policy: https://science.nichd.nih.gov/confluence/display/ocd/Protocol+Navigation). Study procedures will be subject to audits to ensure compliance with the protocol and applicable regulatory requirements consistent with the NICHD quality assurance program plan. Audit visits results will be reported to the Principal Investigator for further reporting as appropriate.

10.8 Data Handling and Record Keeping

10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff under the supervision of PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. Participants may enter responses directly in a web-based format such as the NICHD CTDB Clinical Trial Survey System (CTSS), which allows participants to respond either remotely or at the Clinical Center to their assigned self-reported questionnaires/eCRFs. These eCRFs are considered as the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into CTDB, a 21 CFR Part 11-compliant data capture system provided by NICHD. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the formal discontinuation of clinical development of the study intervention, and as per the NIH Intramural Records Retention Schedule.

10.9 Protocol Deviations and Non-Compliance

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to NICHD Program Official. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare, or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.10 PUBLICATION AND DATA SHARING POLICY

10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting the PI or NICHD.

10.10.2 Genomic Data Sharing Plan

Not applicable.

10.11 COLLABORATIVE AGREEMENTS

Not applicable.

10.11.1 Agreement Type

Not applicable.

10.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the device manufacturer, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NICHD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ERG	Electroretinogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LVQOL	Low Vision Quality-Of-Life Questionnaire
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UBDRS	Unified Batten Disease Rating Scale
UP	Unanticipated Problem
US	United States

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APPENDICES

Appendix A. Feasibility Test

Appendix B. Feasibility Questionnaire

Appendix C. Function Test

Appendix D. Ability Questionnaire

Appendix E. Applicability Questionnaire

Appendix F. Device Use Diary

Appendix G. PedEyeQ Questionnaire

Appendix H. PROMIS QoL Questionnaires

Appendix I. LVQOL Questionnaire

Appendix J. OrCam MyEye 2 User Guide

Appendix K. Pediatric User Pictures

Appendix L. Device Determination Information