SickKids
THE HOSPITAL FOR SICK CHILDREN

Visual rehabilitation in a pediatric population of patients with homonymous hemianopia: a pilot study on virtual-reality stimulation

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate (an) immediate hazard(s) to the trial participants.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Name of Principal Investigator (Print): _____

Signature of Principal Investigator: _____ Date:
<DD Month YYYY>

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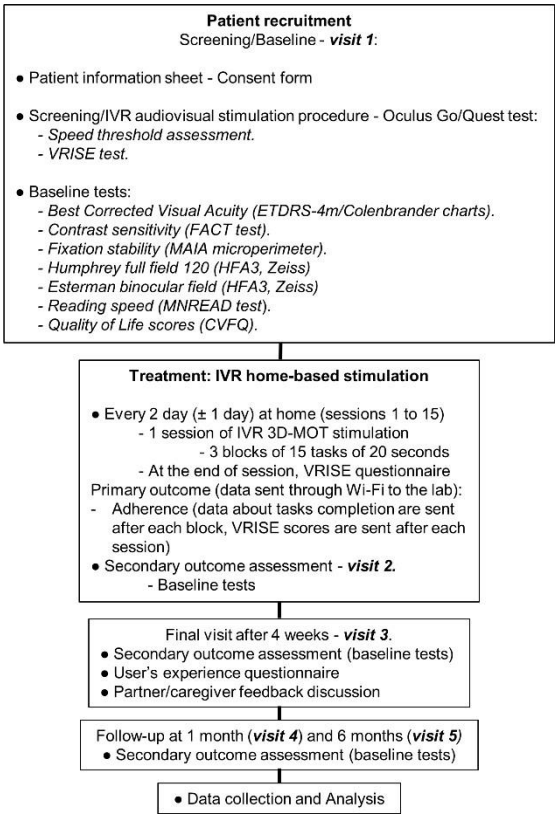
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Visual rehabilitation in a pediatric population of patients with homonymous hemianopia: a pilot study on virtual-reality stimulation.**
Study Description:	Pilot, Open label, Non-randomized study to assess the feasibility of home-based audiovisual immersive virtual-reality stimulation in pediatric patients with homonymous hemianopia.
Objectives:	Primary Objective: Feasibility Secondary Objective: Visual acuity, reading speed, field of vision, quality of life.
Endpoints:	Primary Endpoint: Completion of the home-based audiovisual virtual-reality stimulation procedure (15 sessions).
Study Population:	Male and female patients > 8 years-old with diagnosed homonymous hemianopsia with no prior visual rehabilitation interventions. A total of 10 patients (5 with chiasmatic lesions and 5 with lesions outside of the optic chiasma)
Phase:	Pilot Study
Description of Study Intervention:	Home-based audiovisual immersive virtual-reality stimulation (15 minutes every 2 day for 4 weeks)
Study Duration:	2 years
Participant Duration:	7 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Inclusion	Baseline	Treatment															Follow-up	
Day	**0**	**0**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**14**	**15**	**17**	**19**	**21**	**23**	**25**	**27**	**28**	**58**	**200**
Visit #		**1**								**2**								**3**	**4**	**5**
Fixation stability		X								X								X	X	X
BCVA		X								X								X	X	X
Contrast sensitivity		X								X								X	X	X
MNREAD test		X								X								X	X	X
CVFQ		X								X								X	X	X
Humphrey Full Field 120		X																X	X	X
Esterman binocular		X																X	X	X
VRISE	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
IVR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

2 INTRODUCTION

2.1 STUDY RATIONALE

Central nervous system tumors are the second most common malignancies in childhood[1]. A brain tumor and its treatment can affect the visual system at different levels, from the optic nerves (through compression or infiltration), to sub-cortical structures such as the superior colliculus (SC) and lateral geniculate nuclei (LGN) to optic tracts, optic radiations and visual cortices[1,2]. Children with brain tumors can present visual impairments like decreased visual acuity and contrast sensitivity, loss of color vision, and visual field loss such as hemianopias[1–3]. Hemianopia patients present difficulties in detecting stimuli in the defective visual field and show defective scanning and exploration[4]. Moreover, they show a rotation and compression of the auditory space leading to imprecise localization of sound across both hemispaces[5]. Hemianopia patients naturally develop oculo-motor strategies to compensate for visual field loss, but visual rehabilitation procedure must still be developed to optimize/improve visual perception in the blind field. Several studies demonstrated that hemianopia patients could improve visual perception in the damaged hemifield after a stimulation procedure where auditory and visual stimuli were temporally and spatially correlated[6,7]. Such

audiovisual stimulation programs induce a functional and anatomical reorganization of the visual connectivity in sub-cortical and cortical structures over time[8–10].

The current strategies rely on a significant workload, over 30 hours of audiovisual stimulation using static, spatially and temporally coherent stimuli displayed on large screens/panels in a clinical setting. These strategies require frequent visits to the clinic impeding the patients' adherence and compliance and increasing the burden of disease. We seek to develop an audiovisual stimulation procedure using immersive virtual-reality (IVR) in head-mounted display (HMD). This is an emerging and very promising visual rehabilitation approach using high-technology devices[11–15]. It is developed to provide sensory stimulation with better ecological validity due to virtual-reality, greater flexibility due to home-based programs and improved efficiency due to patient-tailored protocols[11,12]. IVR is a versatile technology, allowing its potential use for the rehabilitation of a variety of low-vision conditions. There are currently limited practical results whether this technology is suitable for low-vision patients to use at home and if it can be deployed on a large scale. A few case report/series studies suggested a potential effectiveness of IVR on visual perception in teenagers, adults and elderly[12,14,16] but more information as to the potential of use and effectiveness of this technology in children and young teenagers is necessary.

2.2 BACKGROUND

Evidence in the literature[11-16] support the hypothesis that an IVR audiovisual stimulation approach using the binocular 3D multiple object tracking (3D-MOT) in the head-mounted display (HMD) Oculus Go/Quest could provide a suitable visual rehabilitation approach for children with visual field defects. The central features of the 3D-MOT closely match attentionally demanding real-life situations[17,18]. The setup of the task is highly dynamic as the objects change their location over time, requiring a continuous deployment of visual attention to avoid confusions between the objects[18]. 3D-MOT can be combined with fixation (still or tracking) while allocating the attention in the visual space to track other moving objects (covert attention) with the peripheral retina, a situation found in complex dynamic scene recognition[18,19]. 3D-MOT stimulation programs displayed on monitors or TV screens have been shown to increase brain capacity for complex processes such as anticipation, eye-tracking, field of view and even decision-making in healthy and pathological participants[20–22]. Recent work in low-vision patients with homonymous hemianopsia indicated a beneficial effect of audiovisual 3D-MOT IVR stimulation program using the Oculus Go on contrast sensitivity, fixation stability, reading speed and field of vision[23].
There are currently no visual rehabilitation strategies for children presenting visual field defects consecutive to a brain tumor or its treatment. The use of IVR in children aged 4-10 years old has not raised any safety concerns[24]. Moreover, by using the remotely controlled and stand-alone Oculus Go, our strategy favors a home-based stimulation program which will increase compliance and adherence to the program.

2.3 RISK/BENEFIT ASSESSMENT

Potential Risks:

There are no risks for patients enrolled in the study. The use of IVR may cause moderate dizziness, nausea or disorientation for continuous stimulation above 10 minutes[25]. If nausea, dizziness or disorientation is experienced during IVR stimulation, stopping the VR stimulation immediately restores normal condition[25]. A recent study on the effects of IVR in 4-10 years old children indicate great tolerability with a prevalence of discomfort and induced effect of IVR lower than reported in adults[24].

Patients will be assessed for IVR sensitivity using the Virtual-Reality Induced Symptoms and Effects (VRISE) questionnaire score at inclusion[26] (exclusion criteria: three (3) consecutive VRISE score < 25).

At-home VR stimulation will be 5 minutes of continuous stimulation as specified in the "Study Intervention" section, below the critical 10 minutes threshold inducing effects and symptoms[25,26].

There are no risks for the community/public nor for the institution.

Potential Benefits:

We anticipate the HH patients will be able to adhere and comply to the home-based audiovisual stimulation program without any symptoms or effects.
We expect the potential benefits IVR stimulation will correspond to:
- an improved fixation stability,
- an enhanced reading speed.
- an improved field of vision

All together increasing self-dependency and quality of life which ultimately impact health care cost by:
- reducing the burden of disease,
- decrease of the global cost of vision impairment.

3 OBJECTIVES AND ENDPOINTS

No visual rehabilitation procedures are currently existing for children with visual field loss consecutive to brain tumor. The visual and auditory modalities of the 3D-MOT IVR stimulation program could potentially improve visual perception in the peripheral fields and saccades/volitional eye movements towards pre-designated targets. Improved oculomotor control will also result in better fixation stability which in turn ameliorates visual perception (reading, visual field).

PRIMARY OBJECTIVE:
Feasibility:

- Adherence to the home-based stimulation protocol. Each time the patients performed an audiovisual IVR session, data about the session (device ID#, subject #, date/time, time to complete the task/block, number of tasks/blocks performed, total stimulation time, total duration of the session) are recorded by the NeurofyResearch application in the Oculus Go and sent through Wi-Fi to a dedicated and secured laboratory computer.
- VRISE questionnaire scores recorded before and after each session and sent though Wi-Fi to a dedicated and secured laboratory computer in real-time.
- Retention rate.

SECONDARY OBJECTIVE:
Secondary endpoint measures will be performed at Toronto Western hospital during baseline and final visit (visit 1 and 6) and at 1 month (visit 7) and 6 months (visit 8) follow-up.

<u>Visual acuity:</u>
- Best Corrected Visual Acuity (BCVA) scores for distance and near vision – ETDRS/Colenbrander charts.
- Fixation stability - MAIA microperimeter, CentreVue

- Contrast sensitivity – FACT test.

Field of Vision:
- Humphrey full field 120 – Humphrey Field Analyzer 3, Zeiss
- Esterman binocular field - Humphrey Field Analyzer 3, Zeiss

Reading Speed:
- Minnesota Low Vision Reading - MNREAD test.

Quality of life:
- Children's Vision Function Questionnaire (39 questions)

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that the home-based audiovisual 3D-MOT IVR stimulation program can be performed by HH pediatric patients and that this program will improve visual perception, reading speed and quality of life. For our trial design, we used the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) instrument, initiated and supported by the NIH Pragmatic Trials Collaborative Project to generalize knowledge about the conduct of pragmatic research. PRECIS-2 takes the innovative approach of translating ratings on nine domains related to trial design to a readily understood wheel format that communicates where the trial design falls on the explanatory (scored 1) - pragmatic (scored 5) continuum[30,31] (Figure 1). All eligible patients in our study will be patients from care center at Sickkids, Toronto recruited through regular appointments made at the clinic (eligibility – recruitment). The setting of the trial corresponds to clinical visual care centers (setting). Information sheets will be given out to participants. Provider expertise corresponds to low-vision care center (organization). The group of patient will follow the study protocol from home, which can be usual practice in visual rehabilitation procedures. The delivery of the intervention is flexible with IVR stimulation every 2 days (± 1 day) at any time during the day (delivery). Adherence will be evaluated every 2 days; patients are free to "not-comply" and there will be no measures to improve adherence (adherence). Follow up of the primary outcome (adherence to the protocol) will be sent automatically through Wi-Fi to a dedicated and secured laboratory computer in real-time after each session. Secondary outcome will be assessed at the final visit after 4 weeks (follow-up secondary outcome at 1 month and 6 months). An Intention-to-treat will be performed for the analysis of the primary outcome (primary analysis). According to the PRECIS-2-wheel results (Figure 1), we propose an ***interventional, pragmatic, single center pilot study*** to assess ***the feasibility and potential effectiveness of IVR stimulation in pediatric population of homonymous hemianopia patients***.

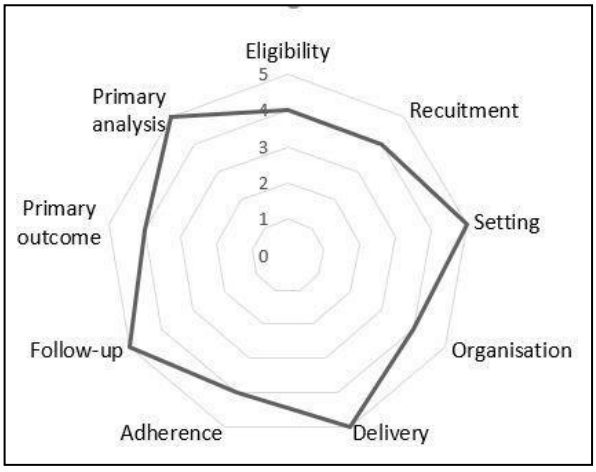


Figure 1: PRECIS-2 wheel indicating that our study is a pragmatic trial (scores >3).

Primary outcome corresponds to the feasibility of the study in terms of adherence, retention rates and recruitment. We specified, a priori, 4 feasibility objectives for our pilot study to be considered successful:

1. ≥ 8/10 patient (80%) completed the protocol.
2. IVR stimulation protocol is considered complete if the patient performed ≥12 sessions out of 15.
3. ≤ 3 consecutive VRISE score < 25 per patient during the treatment period.
4. ≤ 2 dropouts (20%) for cybersickness (discomfort symptoms experienced in VR)

Completion of the sessions will be monitored in real-time. After each block, a data sheet (.csv, 2 kb) containing device ID#, subject #, date/time, time to complete the task/block, number of tasks/blocks performed, total stimulation time, total duration of the session will be sent though Wi-Fi to a dedicated and secured laboratory computer in real-time (if no Wi-Fi access is available at the end of each block, data are stored in the device and sent as soon as Wi-Fi is again available – data storage capacity 500 Mo. No extra costs are incurred to the patients' Wi-Fi plan for sending data). Each session contains 3 data sheets. A session is considered complete when 3 blocks of 5 min stimulation are performed. If no data sheets are received on the lab's computer for a period of 3 consecutive days or missed/incomplete sessions are observed, the participant's parent will be contacted by phone and email to identify the cause (no Wi-Fi, Oculus Go malfunction, dropout) and appropriate action will be taken. Before and after each session, the participant will answer to the VRISE questionnaire (5 questions scored 1 to 7 using the Oculus Go). After the completion of the questionnaire, the detailed score will be sent though Wi-Fi to a dedicated and secured laboratory computer in real-time.

Secondary outcome corresponds to potential effectiveness of IVR stimulation measured by visual perception and quality of life assessed following standard procedures used in low-vision rehabilitation[27] and collected at the low-vision clinic by ophthalmologists. Endpoints will measure change from baseline at 2 and 4 weeks in:

- Best Corrected Visual Acuity, distance and near vision (ETDRS chart, Colenbrander chart).
- Mean fixation stability (MAIA micro-perimeter).
- Contrast sensitivity (FACT test).
- Points not seen – Humphrey full field 120 (HFA3, Zeiss)
- Points not seen – Esterman binocular field (HFA3, Zeiss)
- Mean Reading speed (wpm – Minnesota Low Vision Reading test, MNREAD test[28]).
- Quality of life scores (Children's Vision Function Questionnaire[29]).

There will be no measure to minimize bias as this study is a feasibility study testing the adherence and compliance to the visual rehabilitation procedure.

INTERVENTION:

Immersive virtual-reality stimulation (IVR): 1 session of 3 blocks of 15 trials of 20 seconds each. Rest time is 1-2 minute(s) between blocks. 1 session lasts 19 minutes.1 session every 2 days for 4 weeks (15 sessions total).

EXPECTED DURATION OF SUBJECT PARTICIPATION:

The duration of subject's participation is 7 months, including follow-up.
Treatment period: 4 weeks
Follow-up period: 6 months

EXPECTED FREQUENCY AND DURATION OF STUDY VISITS FOR STUDY PARTICIPANTS

Screening/inclusion visit: 1-1.5 hours
Baseline assessment visit: 1.5 hours (visit 1)

Intermediate assessment: 1.5 hours (visit 2)
Final assessment visit: 1.5 hours (visit 3)
Follow-up visit 1 month: 1.5 hours (visit 4)
Follow-up visit 6 months: 1.5 hours (visit 5)

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Evidence in the literature[11-16] support the hypothesis that an IVR audiovisual stimulation approach using the binocular 3D multiple object tracking (3D-MOT) in the head-mounted display (HMD) Oculus Go/Quest could provide a suitable visual rehabilitation approach for children with visual field defects. The central features of the 3D-MOT closely match attentionally demanding real-life situations[17,18]. The setup of the task is highly dynamic as the objects change their location over time, requiring a continuous deployment of visual attention to avoid confusions between the objects[18]. 3D-MOT can be combined with fixation (still or tracking) while allocating the attention in the visual space to track other moving objects (covert attention) with the peripheral retina, a situation found in complex dynamic scene recognition[18,19]. 3D-MOT stimulation programs displayed on monitors or TV screens have been shown to increase brain capacity for complex processes such as anticipation, eye-tracking, field of view and even decision-making in healthy and pathological participants[20–22]. Recent work in low-vision patients with homonymous hemianopsia indicated a beneficial effect of audiovisual 3D-MOT IVR stimulation program using the Oculus Go on contrast sensitivity, fixation stability, reading speed and field of vision[23].
There are currently no visual rehabilitation strategies for children presenting visual field defects consecutive to a brain tumor or its treatment. The use of IVR in children aged 4-10 years old has not raised any safety concerns[24]. Moreover, by using the remotely controlled and stand-alone Oculus Go, our strategy favors a home-based stimulation program which will increase compliance and adherence to the program.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in **Section 1.3, Schedule of Activities (SoA)**. The duration of participation for each individual participant who completes all study visits will be 7 months.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally. It is estimated that it will take 24 months from when the study opens to enrollment until the end of the study.

5 STUDY POPULATION

Male and female patients > 8 years-old with diagnosed homonymous hemianopsia with no prior visual rehabilitation interventions.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Homonymous hemianopsia
2. Male and female.
3. > 8 years old
4. Interpupillary distance >=56 mm

5. 5. BCVA > 20/20
6. Ability to follow the visual and auditory stimuli and training instructions.
7. Home Wi-Fi access.

5.2 EXCLUSION CRITERIA

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

1. Ocular diseases
2. Both eyes with media opacity that impairs microperimetry testing.
3. Inability to perform during testing and training.
4. Consumption of psychoactive drugs.
5. 3 consecutive VRISE scores < 25 at inclusion.
6. History of vertigo or dizziness
7. Prior vision rehabilitation interventions.

5.3 LIFESTYLE

Psychoactive drugs consumption is not permitted (including medicinal cannabis).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly 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. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a inability to follow the visual and auditory stimuli and training instructions may be rescreened after 4 weeks to a maximum of 3 times. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Dr. Bouffet and Dr. Reginald will identify potential participants among their patients at the Hospital for Sick Children. Drs. Bouffet and Reginald will make initial contact with potential participants. We will identify patients with homonymous hemianopia for a total of 10 participants. We will ensure 5 patients had lesions involving the optic chiasm and 5 not involving the optic chiasm

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The device used is the commercially available virtual-reality, standalone, head mounted display Oculus Quest 2 (Facebook Technologies, Qualcom, Xiaomi). There are currently 34 clinical trials registered on Clinicaltrials.gov using the Oculus Go or Quest: 12 in the US and 4 in Canada. Dr Reber's lab (co-

investigator) is currently running a clinical study using the Oculus Quest 2 in elderly patient with macular degeneration (NCT04685824, UHN REB approval 20-6143). The application uploaded in this device is the NeurofyResearch application, developed and owned jointly by UHN and Neuropowertrain (Research and Collaboration Agreement). It is a modified version of the Neurofy application, owned by Neuropowertrain, used for perceptual/cognitive training in professional athletes.

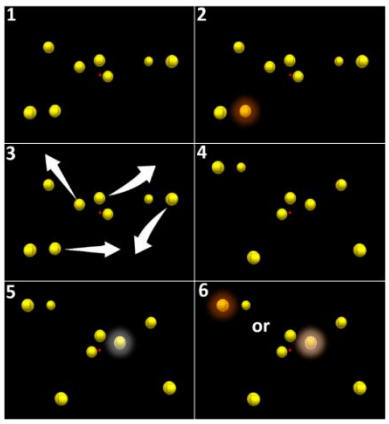


Figure 2: representation of the 3D-MOT stimulation procedure:
1. 8 spheres appear in the headset **2**. One sphere is cued (red) and returns to yellow after 5 seconds. **3.** All spheres start moving randomly for 20 seconds. **4.** After 20 seconds, the spheres stop moving. **5.** The patient must select using laser pointer (white) the ball corresponding to the cued one. **6**. The result is displayed corresponding to either a hit (correct selection) or a miss (wrong selection). Sequence returns to 1. for the next trial.

Audiovisual IVR stimulation procedure
This procedure corresponds to:
- 1 session every 2 days (± 1 day) for 4 weeks.
- 1 session = 3 blocks of 15 audiovisual stimulation tasks (2 min break between each block).
- 1 task = 20 seconds audiovisual IVR stimulation (3D-MOT + correlated sound).

The audiovisual stimulation task (the *NeurofyResearch* application) involves the 3D multiple-object-tracking (3D-MOT) paradigm composed of 8 high-contrast spheres which features are adapted to the visual ability of low-vision patients (luminosity = 100cd/m^2, size = 1.57° of visual angle). The spheres move for 20 seconds following random linear paths, bouncing on one another and on the walls of a virtual 3D cube when collisions occur. The overall span of the movement of the spheres covers 80° and 60° of horizontal and vertical visual angle respectively. The initial speed of the spheres is adjustable, from 3°/s. to 240°/s. and determined during the inclusion visit (figure 2).

6.1.2 DOSING AND ADMINISTRATION

The patient, comfortably seated, is asked to track the moving cued target (1 sphere) among moving distractors (7 spheres) for 20 seconds. A spatial sound (50Hz, 25-65dBHL) is correlated to the movement of the cued target. After 20 seconds, the movement stops and the patient is asked to select, using a laser pointer, the cued sphere among the distractors (mark-all procedure). If the selection is correct (i.e. corresponding to the cued target) a positive feedback sound is provided and the speed of the spheres in the next trial is increased by 0.05log. If the selection is incorrect (i.e. corresponding to a distractor) a negative feedback sound is provided and the speed of the spheres in the next trial is decreased by 0.05log (adaptative simple up-down staircase). After each block of 5 minutes, the system sends data relative to the time spent performing the tasks (primary outcome) to our dedicated and secured laboratory computer through Wi-Fi and resets. This procedure takes approximately 1 minute and can be stopped by the patient for a longer break in between blocks if necessary (time of the break is recorded). After 3 blocks, the system

stops and goes on stand-by mode until the next session. The next session (to be performed 48 hours later) will be automatically uploaded in the device and will be initiated by the patient.

Audiovisual IVR stimulation, 1 session every 2 days for 4 weeks (15 sessions). 1 session = 3 x 5 minutes audiovisual stimulation.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study team will provide each participant a Virtual reality headset (Oculus Quest 2) to take home and perform the visual training intervention. At study completion, the participants will return the headsetto the study team for cleaning and storage procedures as developed by IPAC.

6.2.2 PRODUCT STORAGE AND STABILITY

Standalone, virtual-reality, head-mounted display Oculus Go/Quest 2.

To keep your Oculus Quest 2 safe, follow these tips:

- To avoid damaging your lenses and display, keep your Quest 2 away from direct sunlight. Your headset can be permanently damaged from less than a minute of exposure to direct sunlight.
- To avoid scratching your lenses, keep your Quest 2 away from sharp objects (example: cable tips,keys).
- To avoid damaging your headset or straps, be gentle when adjusting your headset and tightening the straps.
- Do not use or wear your headset while connected to the power adapter or charging.

To avoid general damage:

- Don’t leave your Quest 2 in extremely hot locations (example: inside of a car).
- Don’t leave your Quest 2 near heat sources (example: furnace).
- Don’t leave your Quest 2 near pets or small children.
- Don’t eat, drink or smoke near your Quest 2.
- Secure your Quest 2 in a safe place when you’re not using it.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There will be no measure to minimize bias as this study is a feasibility study testing the adherence and compliance to the visual rehabilitation procedure.

6.4 STUDY INTERVENTION COMPLIANCE

This corresponds to the primary objective and will be monitored in real-time after each blocks of tasks.

6.5 CONCOMITANT THERAPY

Supportive care will be administered as needed in accordance with SickKids standard clinical practices. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.
Use of psychoactive drugs is prohibited while participants are on the study intervention.

7.1 DISCONTINUATION OF STUDY INTERVENTION

The participant, or the participant's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject.

7 DISCONTINUATION AND WITHDRAWAL

Discontinuation from visual training 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 PI 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).

Withdrawn patient will go for a final visit at the clinic with primary and secondary outcome assessment. Primary outcomes (adherence, VRISE scores, retention) collected until the withdrawal date will be analyzed. Secondary outcomes (BCVA, fixation stability, contrast sensitivity, reading speed, visual fields and quality of life) will be assessed during final visit and analyzed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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:

- Withdrawal of informed consent (participant or parent/guardian withdraw for any reason)
- 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
- Significant study intervention non-compliance
- Disease progression which requires discontinuation of the study intervention
- Requirement of prohibited concomitant medication(s) that requires discontinuation of the study intervention
- Three consecutive VRISE scores < 25 during the 4-week home-based audiovisual IVR stimulation procedure will terminate the investigational intervention.

The reason for participant discontinuation or withdrawal from the study will be recorded in the study “Study termination” CRF. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced. The data from participants who are withdrawn or discontinued from the study will be used in the analysis unless the participant requests otherwise.

The Oculus Quest 2 device will be turned off remotely preventing its use by the participant. The participant will return the Oculus Go/Quest including all the equipment (storage box, batteries, remote control, straps) at the final visit.

Withdrawn patients will be replaced to reach a total number of 10 evaluable patients.
Patients will be contacted after 24 hours by phone or email and evaluated for residual virtual-reality symptoms and effects (VRISE questionnaire).

8 STUDY ASSESSMENTS AND PROCEDURES

A participant will be considered lost to follow-up if they fail to return for two scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 24 hours and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Principal 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, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.3 LOST TO FOLLOW-UP

We will assess feasibility of the study (primary outcome) and potential effectiveness (secondary outcome - visual acuity, reading speed, visual fields and quality of life) of IVR stimulation. A feasibility assessment is required as such home-based visual rehabilitation approach using IVR HMD for children has never been tested.

8.1 ASSESSMENTS

Feasibility will be assessed in real-time every 2 days during and after home-based IVR stimulation. The device, the Oculus Quest 2 will record feasibility outcome measures, sent the data to a dedicated and secured laboratory computer through Wi-Fi. The number of completed trials, blocks and sessions will be compared to the protocol.

Visual assessments performed at every study visit will include:

- Best Corrected Visual Acuity, distance and near vision (ETDRS chart, Colenbrander chart).
- Mean fixation stability (MAIA micro-perimeter).
- Contrast sensitivity (FACT test).
- Points not seen – Humphrey full field 120 (HFA3, Zeiss)
- Points not seen – Esterman binocular field (HFA3, Zeiss)
- Mean Reading speed (wpm – Minnesota Low Vision Reading test, MNREAD test[28]).
- Quality of life scores (Children's Vision Function Questionnaire[29]).

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Safety will be assessed by adverse events (AEs), premature withdrawals for AEs, rates of AEs.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An Adverse Event (AE) is any untoward medical occurrence associated with the use of an intervention in a study participant, which does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the intervention, whether or not considered related to the investigational intervention.

Stable chronic conditions which are present prior to entry in the study and do not worsen are not considered AE. These pre-existing conditions will be documented in the participant's medical history.

AEs will be the primary safety endpoints. Known AEs induced by IVR stimulation are nausea, dizziness and disorientation. The severity of these AEs will be scored using the validated VRISE questionnaire. A VRISE score < 25 is considered as an AE. Three (3) consecutive VRISE scores < 25 will lead to the withdrawal of the study.

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

AE are classified as serious or non-serious. A Serious Adverse Event is any AE that is:

- fatal
- life-threatening
- requires or prolongs inpatient hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

The term "life-threatening" in the definition of "serious" refers to an AE in which the participant was at risk of death at the time of the event. It does not refer to an AE that hypothetically might have caused death if it were more severe.

Serious Adverse Events will be documented for any incident that:

(a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its directions for use; and

(b) has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur. "Serious deterioration in the state of health" means: a life-threatening disease, disorder or abnormal physical state; the permanent impairment of a body function or permanent damage to a body structure; or a condition that necessitates an unexpected medical or surgical intervention to prevent such a disease, disorder or abnormal physical state or permanent impairment or damage.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

VRISE questionnaire for assessing AEs related to audiovisual IVR stimulation will be recorded electronically (.csv file) after each home-based session (every 2 days) and sent though Wi-Fi to a dedicated and secured laboratory computer in real-time.

8.2.3.1 SEVERITY OF EVENT

The severity of an AE is assessed by VRISE questionnaire:

- Three (3) consecutive VRISE scores < 25 will lead to the withdrawal of the study.

8.2.3.3 EXPECTEDNESS

All Adverse Events (AEs) must have their relationship to the study intervention assessed by a qualified physician who is part of the study team based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **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 should be clinically plausible.
- **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.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **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).
- **Unrelated** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

A qualified physician who is part of the study team 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.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All Adverse Events (AEs) or Serious Adverse Events (SAEs) due to IVR stimulation resolve as soon as the stimulation stops[25]. Investigators will follow-up the participant at 24 hours by phone or email assessing the severity of the AEs using the VRISE questionnaire

AE reporting will begin at the time of signing of the informed consent (screening) and will continue until discharge from the study. AEs will be elicited by:

- spontaneous report by participants and/or parents,
- by 3 consecutive VRISE scores < 25,
- by observation (by the investigators and/or healthcare staff).

AEs will be documented in the source documents and the eCRF within 24 hrs.

All AEs and SAEs occurring while on study must be documented regardless of relationship. Information to be collected includes event description, date and time (if possible) of onset, date and time (if possible) of resolution/stabilization of the event, outcome, and the assessment of seriousness, expectedness, relationship to study intervention and severity by a delegated qualified physician.

Any baseline condition recorded in the medical history that deteriorates at any time during the study, will be recorded as an AE or SAE.

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.

Events will be followed for outcome information until resolution or in the opinion of the PI or qualified physician delegate, the participant is stable and does not require further follow-up, or the participant is deemed lost to follow-up.

8.2.5 ADVERSE EVENT REPORTING

AE will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

Adverse events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

Participants and/or their parent/legal guardian will be informed in a timely manner of any new information, including safety information, that is relevant to that participant's willingness to continue participation. The communication of this information will be documented through a revised REB approved Informed Consent Form, where possible, based on the timeliness of the information.

In the event that a study procedure detects a new clinically important secondary finding/incidental finding, the qualified physician will notify the Most Responsible Physician (MRP) physician at SickKids (if the participant is being treated at SickKids) or request the participant's family doctor's name and contact information in order to arrange medical follow-up to interpret the significance of the findings.

8.2.8 REPORTING OF PREGNANCY

If a participant becomes pregnant, the study drug will be permanently discontinued, and the participant will complete the evaluations/procedures for the early termination visit.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

Feasibility is considered when the following primary endpoints criteria are met:

1. ≥ 8/10 patient (80%) completed the protocol.
2. IVR stimulation protocol is considered complete if the patient performed ≥12 sessions out of 15.
3. ≤ 3 consecutive VRISE score < 25 per patient during the treatment period.
4. ≤ 2 dropouts (20%) for cybersickness (discomfort symptoms experienced in VR)

- Secondary Endpoint(s):

Secondary endpoint measures will be performed at Toronto Western hospital during baseline (visit 1), after 2 weeks (visit 2), after treatment at 4 weeks (visit 3) and at 1-month (visit 4) and 6 months (visit 5) follow-up. Results will be compared to basline.

Visual acuity:
- Best Corrected Visual Acuity (BCVA) scores for distance and near vision – ETDRS/Colenbrander charts.
- Fixation stability - MAIA microperimeter, CentreVue
- Contrast sensitivity – FACT test.

Field of Vision:
- Humphrey full field 120 – Humphrey Field Analyzer 3, Zeiss
- Esterman binocular field - Humphrey Field Analyzer 3, Zeiss

Reading Speed:
- Minnesota Low Vision Reading - MNREAD test.

Quality of life:
- Children's Vision Function Questionnaire (39 questions)

- Exploratory Endpoint(s):

None

9.2 SAMPLE SIZE DETERMINATION

The CONSORT guidelines state that sample size calculations may not be required for feasibility studies, however it is important that the sample be representative of the target study population[33]. For this pilot study, we will recruit 10 patients.

9.3 POPULATIONS FOR ANALYSES

The following study populations are defined and will be analyzed as specified below. The population evaluable for safety will be the safety population.

The Intent to Treat (ITT) population: the total population of patients registered in the study.

Safety population: all registered participants who received at least one visual training session.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Results will be reported using descriptive statistics (mean, 95%CI).
Normality of the distribution will be assessed (skewness and kurtosis). If not normally distributed, data will be transformed (Log_{10}) or non-parametric Kruskal-Wallis test will be used.

Bayesian repeated measures ANOVA will be used to analyze and compare baseline, 2 weeks, 4 weeks, 1 month and 6 months outcome measures.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

As recommended by CONSORT guidelines, analysis will be performed following an Intention-To-Treat (ITT) approach[32].

Primary outcome corresponds to the feasibility of the study in terms of adherence, retention rates and recruitment. We specified, a priori, 4 feasibility objectives for our pilot study to be considered successful:

1. ≥ 8/10 patient (80%) completed the protocol.
2. IVR stimulation protocol is considered complete if the patient performed ≥12 sessions out of 15.
3. ≤ 3 consecutive VRISE score < 25 per patient during the treatment period.
4. ≤ 2 dropouts (20%) for cybersickness (discomfort symptoms experienced in VR)

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

We will visualize and report results using descriptive statistics (including frequency distributions, a measure of central tendency and a measure of dispersion) of secondary outcomes. Statistical comparison between the 2 conditions (baseline and after treatment) for the secondary outcomes will be made using two-way ANOVA with repeated measures. Statistical analyses will be performed by our colleague biostatistician and epidemiologist Dr. Jin.

9.4.4 SAFETY ANALYSES

We will report results using descriptive statistics (including frequency distributions, a measure of central tendency and a measure of dispersion) average VRISE scores.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Summary statistics will be used to describe baseline characteristics and other outcomes of interest. Categorical endpoints will be summarized using proportions and frequencies. Continuous endpoints will be summarized using the mean, median, range or standard deviations.

9.4.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Raw data corresponding to primary outcome measures related to IVR stimulation (device ID#, subject #, date/time, time to complete the task/block, number of tasks/blocks performed, total stimulation time, total duration of the session) will be recorded in a digital table (file .csv size = 2 Ko) corresponding to source data. This .csv file, not containing any personal health information nor identification information, will be sent to a dedicated and secured laboratory computer through Wi-Fi and a copy will be stored on the Oculus. Once received on the laboratory computer, these data will be transferred electronically to eCRFs (the original .csv file will be kept on the UHN network and in a separate encrypted and password-secured hard drive in the investigators' office).
Raw data corresponding to secondary outcome measures related to fixation stability will be stored in the device (MAIA microperimeter) and a copy will be transferred electronically to eCRFs through encrypted uhn.ca/uhnresearch.ca emails.
Raw data corresponding to secondary outcome measures related to BCVA, contrast sensitivity, reading speed, visual fields and quality of life will be recorded on dedicated sheet (source document) and transferred manually to eCRFs.

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1.1 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, funding agency, Sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the REB and Sponsor 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 discontinuing the trial
- 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 Sponsor, REB, DSMB, and/or regulatory agency.

10.1.2 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.

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

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name, only by unique study ID number. The patient's name or any identifying information will not appear in any reports published as a result of this study. All identifying information will be kept behind 2 security measures or as per equivalent institutional policy, under the supervision of the study/site PI and will not be transferred outside of the hospital.

The study monitor, auditor and other authorized representatives of the Sponsor, representatives of the Research Ethics Board (REB) or regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the UHN network. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by UHN research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at UHN

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Data collected for this study will be analyzed and stored at UHN. After the study is completed, the de-identified, archived data will be transmitted to and stored at UHN for use by other researchers including those outside of the study. Permission to transmit data to UHN will be included in the informed consent.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Principal Investigator	
Name, degree, title	Eric Bouffet MD
Institution Name	The Hospital for Sick Children
Address	555 University Avenue
Phone Number	4168137500
Email	Eric.bouffet@sickkids.ca

10.1.5 STUDY MONITORING

Monitoring of the trial will be performed to verify that:

- The rights and well-being of participants are protected;
- The reported trial data are accurate, complete, and verifiable from source documents; and
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and local regulations and requirements.

The Sponsor will be responsible for all monitoring activities. Any trial-related duty or function transferred to and assumed by a third party, including monitoring and auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The monitoring plan for the trial will be documented prior to the activation of the study and include the following;

- Follow risk-based practices,
- Document the rationale for the chosen monitoring strategy,
- Reference the Sponsor's process that will be followed to address situations of non-compliance,
- Describe the monitoring responsibilities of all the parties involved, and
- Outline the data and processes to be monitored.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of monitoring by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during monitoring visits and inspections, and that sufficient time is devoted to the process.

Monitoring procedures will be implemented beginning with the data entry system and data checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Monitoring reports will be issued after each monitoring visit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.

10.1.7 DATA HANDLING AND RECORD KEEPING

Auditing of the trial will be performed independently from monitoring to evaluate trial conduct and compliance with the protocol/amendment(s), SOP, ICH GCP and local regulations and requirements.

The Sponsor will be responsible for all auditing activities. Any trial-related duty or function transferred to and assumed by a third party, including auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of auditing by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during audits and inspections, and that sufficient time is devoted to the process.

Auditing reports will be issued after each audit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

We will comply with FDA's ALCOA guidelines to ensure high quality data recording. The delegation of duties log will specify which tasks are delegated to which personnel. Data entered on dedicated source documents will be recorded legibly in black ballpoint pen and signed. Correction fluid or covering labels will not be used.

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

All paper sheets recording BCVA, contrast sensitivity, reading speed, quality of life, and adherence log sheet will be considered source documents.
All digital tables (.csv files) generated by and recorded from the IVR stimulation program in the Oculus Go will be considered source data.
All digital data recorded by MAIA microperimeter will be considered source data.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Where the source data is not collected as part of the participant's medical record, 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 case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

Study data will be entered into REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap is developed and maintained by a team at Vanderbilt University and licensed free of charge by the Research Institute at UHN. The application and data are housed on servers provided by UHN. These servers are located within UHN secure data center. Local support for REDcap is provided UHN Research IT.

10.1.8 PROTOCOL DEVIATIONS

To enable evaluations and/or audits from Health Canada and/or the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition in a secure location for a minimum of 10 years.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.1.7.2 STUDY RECORDS RETENTION

A protocol deviation is any noncompliance with the clinical trial protocol or Manual of Procedures (MOP) requirements, if applicable. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. All protocol deviations will be documented; the Principal Investigator will assess each protocol deviation to determine the impact to the patient's rights, safety or welfare, study efficacy and data integrity. If there is any uncertainty regarding the impact of the protocol deviation, the Principal Investigator will consult with the Medical Monitor.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 2 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the Sponsor. Protocol deviations must be sent to the reviewing REB in accordance with their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing REB requirements.

10.1.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, 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 Hospital for Sick Children has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 REFERENCES

AE	Adverse Event
ADR	Adverse Drug Reaction
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
IB	Investigator's Brochure
ICH	International Council on Harmonization
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MOP	Manual of Procedures
MRP	Most Responsible Physician
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
PHIPA	Personal Health Information Protection Act
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SUADR	Serious unexpected adverse drug reaction
3D-MOT	3D Multiple-Object Tracking
BCVA	Best Corrected Visual Accuity
CVFQ	Children Visual Function Questionnaire
dBHL	Decibels hearing level
ETDRS	Early treatment Diabetic Retinopathy
FACT	Functional Acuity Contrast Test
HH	Homonymous Hemianopia
ITT	Intention to treat
IVR	Immersive Virtual Reality
LVR	Low Vision Rehabilitation
MAIA	Macular Integrity Assessment
MNREAD	Minnesota Low Vision Reading

PRECIS	Pragmatic-Explanatory Continuum Indicator Summary
QoL	Quality of Life
VR	Virtual Reality
VRISE	Virtual-reality Induced Symptoms and Effects

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10.2 ABBREVIATIONS

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