PROTOCOL

EarGenie assessment of a minimum viable product (MVP): a first in human trial of an fNIRS measure of sound detection and speech discrimination in normal hearing infants

Protocol Number: 98058
Protocol Version: 3
Date: 15 September 2023
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Principal Investigator: Professor Colette McKay

Sponsor: The Bionics Institute
384-388 Albert St, East Melbourne
Victoria, AUSTRALIA

This Protocol version 3.0, dated 15 September 2023 was approved by
The Royal Children's Hospital Human Research Ethics Committee on
04 October 2023

1. PROTOCOL

CLINICAL TRIAL IDENTIFIER

EarGenie Minimum Viable Product (MVP)

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Document history:

Version Number and Date	Summary of changes
Version 1 7 July 2023	Protocol v1
Version 2 1 August 2023	Change of Project Title Correction of numbering in section 9 Addressing RCH DTS questions from letter dated 28/7/2023
Version 3 15 September 2023	Addressing RCH HREC questions from letter dated 6/9/2023

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.

1 CONTENTS

2 PROTOCOL SYNOPSIS

Title	EarGenie assessment of a minimum viable product (MVP): a first in human trial of an fNIRS measure of sound detection and speech discrimination in normal hearing infants
Trial Description	This is a first-in-human clinical trial of EarGenie minimum viable product (MVP).
Objectives	The primary objective of this trial is to establish the safety and comfort of EarGenie MVP. The secondary objective of this trial is to obtain preliminary evidence that the test results obtained when using EarGenie MVP to test normally-hearing infants are largely consistent with those obtained by a cohort of 36 normally-hearing infants previously tested in our lab with the NIRx NIRScout continuous wave near infrared spectrometer.
Outcomes and Outcome Measures	The primary outcome is that EarGenie MVP is safe and comfortable for use in human infants. The measure is documentation of any adverse events (safety) or discomfort (e.g., crying, not settling to sleep) shown by the baby when wearing the device. The secondary outcome is that the test results obtained with EarGenie MVP are largely consistent with the sensitivity and specificity of the test results formerly obtained with our NIRx NIRScout research device in normal-hearing infants, thus confirming the suitability of EarGenie MVP for further clinical studies. The outcome measure is the proportion of babies who show a significant detection and discrimination response and also produce fNIRS average waveforms with shape consistent with those shown in the previous studies. To be consistent with the NIRx results we would require not more than 1(/10) baby (or 10%) to have an absent detection response at 65 dB SPL and not more than 3 (/10) babies (or 30%) to show an absent discrimination response for “Ba” versus “Ga”.
Trial Population	Ten infants with normal hearing
Description of sites enrolling participants	This trial will be conducted at the Bionics Institute, 384-388 Albert Street, East Melbourne, Victoria, Australia.
Description of Interventions	Each infant will have functional near-infrared spectroscopy (fNIRS) performed using EarGenie MVP, to measure changes in cortical blood oxygenation in response to increased neural activity during sound detection and discrimination. During testing, which is performed during natural sleep, the infant wears the custom-made headgear while sounds are presented either through tubephones or via a loudspeaker. The infant will be presented with different speech sounds at 65 dB SPL. The device runs two automated tests, one to measure whether the baby detected the sound and the other to test whether the

	baby discriminated between two different speech sounds (“Ba” and “Ga”). The sound levels used are not hazardous to the individual. The headgear comprises a soft material headband and a detachable, Bluetooth-enabled, battery-powered montage. The montage is made up of a flexible printed circuit board, flat-surfaced optical LED emitters and detectors and a flexible montage cover. The montage is positioned so that the sensors are located over the regions of the brain that process sound and language. Near infrared light, with 740 nm and 860 nm centre wavelengths, travels from each emitter through the scalp and underlying cortical brain tissues. The detectors measure that portion of the light that is transmitted back to the scalp (the rest being harmlessly absorbed or scattered) and, from these optical measurements, changes in oxygenated and de-oxygenated haemoglobin concentrations are calculated. Changes in these measures that are time locked to the presentation of sound, or a change of sound, provide an index of sound detection and discrimination, respectively. The EarGenie MVP device is controlled using a graphical user interface running on a laptop computer, which allows the user to control sound presentation, visualise optical measurements and obtain the results of our patented, automated response-detection algorithm in real time.
Trial Duration	6 months or until 10 infants have been tested, whichever is shorter
Participant Duration	Infants will have just one test session, which typically takes around 2 hours.

3 GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
ADE	Adverse Device Effect
AE	Adverse Event
AR	Adverse Reaction
ASADE	Anticipated Serious Adverse Device Effect
CAPA	Corrective And Preventative Action plan
COI	Conflict of Interest
CRF / eCRF	Case Report Form / electronic Case Report Form
DMC SMC	Data Monitoring Committee / Safety Monitoring Committee
DSMB	Data Safety Monitoring Board
fNIRS	Functional near infrared spectroscopy
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee

IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identity
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
MVP	Minimum Viable Product
PI / CPI	Principal Investigator / Coordinating or Chief Principal Investigator
PICF	Participant Information and Consent Form
QA	Quality Assurance
QC	Quality Control
RCH	Royal Children's Hospital (Melbourne)
RGO	Research Governance Office
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
USADE	Unanticipated Serious Adverse Device
USM	Urgent Safety Measure

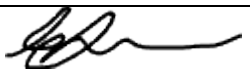
4 INVESTIGATOR AGREEMENT

I have read the protocol entitled "EarGenie assessment of a minimum viable product (MVP): a first in human trial of an fNIRS measure of sound detection and speech discrimination in normal hearing infants."

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki and the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.

I will ensure that trial staff fully understand and follow the protocol and evidence of their training is documented on the trial training log.

Name	Role	Signature and date
Colette McKay	Principal Investigator	5/7/2023
Julia Wunderlich	Investigator	6/7/2023 
Darren Mao	Investigator	6/7/2023 
Gautam Balasubramanian	Investigator	 7/07/2023
Linty McDonald	Investigator	6/7/2023 

5 ADMINISTRATIVE INFORMATION

5.1 Trial registration

5.1.1 Trial registry

This trial has been registered on ClinicalTrials.gov.

Identifier: NCT05962814

5.2 Sponsor

Trial Sponsor	The Bionics Institute
Contact name	Professor Colette McKay
Address	384-388 Albert St, East Melbourne
Sponsor-Investigator (where applicable)	NA

5.3 Expected duration of study

This study will be conducted over 6 months or until 10 infants have been tested, whichever is shorter.

5.4 Contributorship

Name	Summary of contribution
Professor Colette McKay	Overview of protocol

Name	Summary of contribution
Dr Julia Wunderlich	Drafting of protocol

6 INTRODUCTION AND BACKGROUND

6.1 Trial rationale and aim

As part of our ongoing research program (RCH Ethics 71941), and using a research fNIRS device (NIRx NIRscout), we have developed test protocols and signal processing algorithms that can reliably inform whether an infant has detected sounds and whether their brain can distinguish between two different speech sounds (McKay, Wunderlich et al. 2023). We have now developed a clinical investigation device prototype (EarGenie MVP) using the same principles but with hardware and software that is specific for use in audiology clinics. This proposed clinical trial will evaluate the safety and basic functionality of our EarGenie MVP, which has been developed in collaboration with the commercial industrial design house Design + Industry (D+I).

The primary aim of this trial is to establish the safety and comfort of EarGenie MVP.

The secondary aim is to obtain preliminary evidence that the test results obtained when using EarGenie MVP to test normally-hearing infants are largely consistent with those obtained in a cohort of 36 normally-hearing infants previously tested in our lab with the NIRx NIRScout continuous wave near infrared spectrometer, thus confirming the basic functionality of EarGenie MVP.

6.2 Background

Paediatric audiologists rely on a battery of audiological tests to characterise the degree (mild through to profound) and nature (e.g., sensorineural vs auditory neuropathy) of hearing loss in infants (AAA 2020). Key amongst these tests are the electrophysiological measures, auditory brainstem response (ABR) and auditory steady state response (ASSR), which can be used to estimate hearing acuity at different frequencies of sound and to determine the nature of any hearing loss (Sininger, Hunter et al. 2020). However, audiologists have long recognised the absence of a key element vital for clinical decision making, namely an objective measure of speech discrimination for infants, and support the development of a clinically viable objective measure for inclusion in the existing test battery (JCIH, 2019).

Speech discrimination information is critical to a detailed understanding of hearing dis/abilities. In older children and adults, it is gained through behavioural testing and is a critical element when deciding rehabilitation strategies. For example, the decision to recommend a cochlear implant for an adult is based in great part on their measured ability to understand speech (Leigh, Dettman et al. 2016, van der Straaten, Briaire et al. 2020). Despite decades of research, and two candidate techniques (mismatch response and acoustic change complex, (Wable, van den Abbeele et al. 2000, Uhler, Hunter et al. 2018), there is still no test of speech discrimination that can be used in the infant diagnostic audiology clinic. Consequently, paediatric audiologists are compelled to make recommendations based primarily on hearing acuity (AAA 2013), or to wait until behavioural results become available. The latter option has the obvious disadvantage of delaying effective habilitation by many months and undermines the rationale of early diagnosis though newborn hearing screening (Ching, Dillon et al. 2018).

Our completed research with the NIRx system is summarised in our paper (McKay, Wunderlich et al. 2023)). Essentially, our novel test procedures and analysis algorithms were shown to provide test accuracies as follows:

- Detection of speech sounds at 65 dB SPL: sensitivity 97%, specificity 100%
- Discrimination of "Ba" from "Ga" at 65 dB SPL: sensitivity 78% specificity 100%

The average haemodynamic response waveform shapes generated by the detection and discrimination testing are shown in Fig. 1 and 2, respectively.

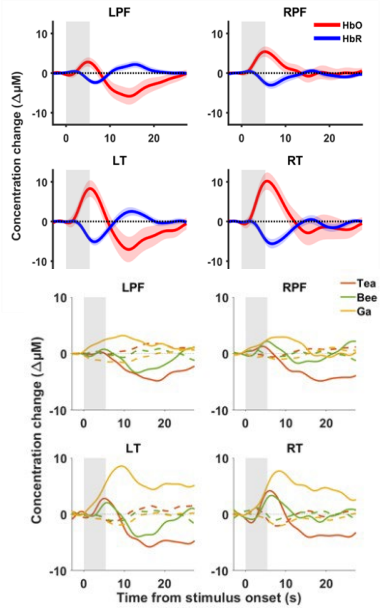


Figure 1 Average response waveforms in left and right temporal areas (LT, LR) and left and right prefrontal areas (LPF, RPR) in response to detection of "Ba" at 65 dB SPL. The grey shaded region is the duration of the stimulus in the silence baseline.

Figure 2 Average waveforms of responses (changes in HbO (solid) and HbR (dotted)) to discrimination of "Ba" from "Tea", "Bee", and "Ga". Grey shaded region is the duration of the novel stimulus in the non-silence baseline.

Given the success of our development of this fNIRS test, we have built a prototype system (EarGenie MVP) that can automatically run the tests and generate results so that clinicians can easily perform the tests. In this clinical trial, we aim to confirm its safety and basic functionality before performing further clinical studies and trials with EarGenie MVP. The Investigator Brochure outlines how EarGenie MVP functions, is designed, and its safety features.

7 RISK/BENEFIT ASSESSMENT

7.1 Known potential risks

- We do not anticipate any adverse events directly related to the protocol procedures. fNIRS measurements have been safely used in research studies in paediatric populations across the world for many years, and in our laboratory for the past five years, without adverse events. It is a safe technology suitable for use in infants. Other test procedures, such as otoscopy and tympanometry or head circumference measurements, are standard clinical procedures which do not cause discomfort and are not expected to cause distress.
- The EarGenie MVP has been designed by a medical device prototyping company to be safe. It has no mains power attached to any part that is in contact with the infant. The montage contains a 3.7V lithium polymer (LiPo) battery (see Investigator's Brochure for details), which is not in contact with the infant, and can only be recharged using a dedicated charging cradle (i.e., it is impossible to attempt to charge the battery while on the infant's head). The headgear communicates to the dedicated computer via Bluetooth. Only the headband and montage cover are in contact with the infant. The headband is made from soft medical grade material (see IB) and the optode montage is covered with a thin flexible single-use cover made from TPU (Thermoplastic Polyurethane), a material commonly used in healthcare applications, with no known aggravation effects. To mitigate cross-infection risk, the montage

covers are designed to be single use, and the headband is wipeable with alcohol wipes or similar after each use.

- Our clinical team is led by an expert paediatric audiologist with over 35 years' experience in infant diagnostics; all testers are either qualified audiologists or trained and directly supervised during testing (at elbow) by qualified audiologists.
- The fNIRS test can only be carried out if the infant is either asleep or quietly being entertained. Testing will be discontinued if the baby becomes distressed and cannot be resettled at any time.

Discomfort or skin damage from headgear

We expect that babies will not experience discomfort from wearing the headgear, which holds the optical emitters and detectors and electronics. It is made up of a headband made from a soft material which is easily fitted on the infant's head using low profile velcro hooks that are easy to adjust and undo. The montage containing the optodes is a flexible, moulded assembly which clips into the headband. The only parts of the headgear that contact the baby's scalp are the head band and the flexible montage cover. There are no cables to hinder movement or cause entanglement.

The headgear can be positioned before the baby is settled to sleep or once they are asleep. Our experience, gained by testing over 100 babies with our research device (NIRx NIRScout) and a cap covering the whole head, is that placement causes only minor disturbance, and that the great majority of babies continue to sleep once it is placed. We reasonably expect that babies will experience less disturbance with this more comfortable headgear than from the NIRx research device.

The case report form for each infant will capture any discomfort or observable effects on the baby's skin as this study's primary outcome measures (along with any unexpected adverse events).

Time and travel

We schedule a 2-hour appointment for the test session and recognise that this is a substantial time commitment for a family with a young baby. As experienced audiologists we are sensitive to this and make every effort to schedule appointments that are convenient for the family. Families are reimbursed their travel expenses and provided with free onsite parking.

Sound levels

Our test protocols use soft to comfortably loud level sounds and do not involve high-level sounds, however it is recognised that there is potential for their accidental presentation due to operator or technical error. To avoid this potential risk, all sounds, which are stored digitally as .wav files, are measured using a calibrated sound level meter at the time that the protocol is developed. On the day of testing the pre-test protocol involves both listening to the sounds and measuring them with a sound level meter to ensure that there are no sound artifacts and that presentation levels are correct.

7.2 Known potential benefits

There is no benefit of participation to the normal hearing infants. The benefit of this clinical trial is in the development of a clinical hearing device to improve the management of babies with hearing loss and thereby facilitate their language development.

7.3 Assessment of potential risks and benefits

Overall, the risks of participation are limited, and mainly relate to time and potential discomfort. The benefits of the study, in terms of development of a clinical fNIRS device to inform management of hearing-impaired infants and prevent or reduce language delay, outweighs the possible risks.

8 TRIAL OBJECTIVES AND OUTCOMES

8.1 Objectives

8.1.1 Primary objective

The primary objective of this trial is to establish the safety and comfort of EarGenie MVP.

8.1.2 Secondary objective

The secondary objective of this trial is to obtain preliminary evidence that the test results obtained when using EarGenie MVP to test normally-hearing infants are largely consistent with those obtained by a cohort of 36 normally-hearing infants previously tested in our lab with the NIRx NIRScout continuous wave near infrared spectrometer.

8.2 Outcomes

Table listing objectives and outcomes.

OBJECTIVE	OUTCOME & OUTCOME MEASURE
Primary	
The primary objective of this trial is to establish the safety and comfort of EarGenie MVP.	The intended outcome is that EarGenie MVP is safe and comfortable for use in human infants. The measure is the incidence of any adverse events recorded (safety) and incidence of discomfort. The measures of discomfort will include observations of crying, attempts to remove headgear, verbal indications of distress (in an infant with developed speech), and observations of any marks left by the headgear on the skin, along with the duration (in minutes) of such incidents. The summary report will be presented as incidence of such events along with their duration, and a full description of each incident.
Secondary	
The secondary objective of this trial is to obtain preliminary evidence of device feasibility by showing that the test results obtained when using EarGenie MVP to test normally-hearing infants are largely consistent with those obtained by a cohort of 36 normally-hearing infants previously tested in our lab with the NIRx NIRScout continuous wave near infrared spectrometer.	The secondary outcome is that the test results obtained with EarGenie MVP are largely consistent with the sensitivity and specificity of the test results formerly obtained with our NIRx NIRScout research device in normal-hearing infants, thus confirming the suitability of EarGenie MVP for further clinical studies. The outcome measure is the proportion of babies who show a significant detection and discrimination response and also produce fNIRS average waveforms with shape consistent with those shown in the previous studies. Specifically, we expect that at least 9/10 infants (90%) will show a significant detection response for “Ba” at 65 dB SPL, and that their average waveforms for

OBJECTIVE	OUTCOME & OUTCOME MEASURE
	this test should consist of a positive HbO peak around 5-8 s latency, or a negative HbO response with latency 12-16 s, or a shape consistent with a combination of these shapes (refer to Figure 1). For the test of discrimination of "Ba" from "Ga", we expect that at least 7/10 infants (70%) will show a significant discrimination response, and that their average response waveforms should consist of a positive HbO response with latency 6-12 s or a negative HbO response with latency 12-20 s, or a combination of both these shapes (Figure 2).

9 TRIAL DESIGN

9.1 Overall design

This is a first-in-human trial of a new medical device prototype (EarGenie MVP). Ten infants with normal hearing will be tested with EarGenie MVP, to confirm the safety and comfort of EarGenie MVP for infants. The results of the fNIRS tests of speech sound detection and discrimination in these infants will be used to confirm the functionality of EarGenie MVP and to obtain preliminary evidence that the test results that it outputs are consistent with the results obtained previously for 36 normal hearing infants (aged 2-20 months) using our research device NIRx. The NIRx device (NIRx NIRScout) a research device with CE marking. Those infants produced fNIRS responses of shapes with predictable characteristics that did not vary with age or between infants. Because of this consistency across age and individuals, we are confident that comparison of the new data with the previous data will enable us to determine preliminary device feasibility.

9.2 Justification for dose

Not applicable

9.3 Trial population

The infants participating in this trial will have no known hearing loss, having either passed newborn hearing screening or diagnostic audiological assessment.

9.4 Eligibility criteria

9.4.1 Inclusion **criteria**

Each infant must meet all of the following criteria to be enrolled in this trial:

- Is between the ages of 1 and 24 months at the time of fNIRS testing.
- Has no known hearing loss, having either passed newborn hearing screening or diagnostic audiological assessment.
- Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf.

9.4.2 Exclusion criteria

Infants with skin conditions such as cradle cap, eczema, or other skin conditions will be excluded.

There are no additional exclusion criteria other than not meeting the inclusion criteria.

9.5 Lifestyle considerations

Not applicable

9.6 Screen failures

Screen failures are defined as participants who consent to participate in the trial but who are found, during the screening procedures, to be ineligible to continue in the trial. Since the screening process only consists of establishing from the parent the age and normal hearing status of the infant, the screening and consenting process is usually rolled into one event.

9.7 Recruitment and identification of potential participants

Recruitment of infants and their parents/guardians

Infants and their parents/guardians will be recruited through any of the following means:

- Social media and the Bionics Institute website
- Word of mouth

For recruitment via social media etc, advertisement will take place through Bionics Institute website, social media platforms Facebook and Instagram, online platforms such as the University of Melbourne staff noticeboard, and relevant notice boards etc e.g., maternal and child health centres, early learning centres, and other relevant community centres. We do not expect any difficulty recruiting 10 infants based on our current recruitment rate for other studies.

9.8 Consent

Written consent will be obtained using a face-to-face process and a paper consent form. Since all the infant participants will be under 2 years of age, consent will be sought from their parent/guardian.

The investigator or delegated member of the trial team will discuss the trial with the parent/guardian and will provide them with the Participant Information and Consent Form (PICF), which will describe the purpose of the trial, eligibility for inclusion, the procedures to be followed, and the risks and benefits of participation.

The investigator will conduct the informed consent discussion following confirmation of eligibility and will check that the parent/guardian comprehends the information provided. The investigator will answer any questions about the trial.

The parent/guardian will be invited to provide written consent. Consent will be voluntary and free from coercion.

The investigator who conducted the consent discussion will also sign the informed consent form. A copy of the consent form will be given to the parent/guardian.

At any point, parents/guardians can withdraw from the project with no consequences. Testing can be stopped at any stage should the parent/guardian not wish to proceed further.

10 INTERVENTION

10.1 Treatment arms

All infants undergo fNIRS testing using the EarGenie MVP

10.2 Trial Intervention(s)

10.2.1 Description of trial investigational products

10.2.1.1 EarGenie MVP

Product name	EarGenie MVP
Device Type	Continuous wave near-infrared spectroscopy (NIRS) imaging system

Please see Investigator's Brochure for further engineering design details and safety features.

The device runs two automated tests to measure sound detection and discrimination in sleeping infants. The device plays speech sounds, either through a loudspeaker, or via tubephones, at user-defined intensities, durations and timing. It has a user interface on a dedicated computer that enables a clinician to check the sound calibration and optode function before a test starts. Sound calibration involves using a sound level meter to measure the sound being output by the device. These sound measurements are routinely made by the research audiologist when setting up for the test, when the infant is not present. Optode function checking is initiated by the user in the graphical user interface (GUI) and involves automatic adjustment, within safe limits, of the intensity of light being emitted by the light emitting diodes (LEDs) so that the detectors are operating within an optimal range. The user interface also presents information about the test being run, such as a raw data stream and progress of the on-line analysis. After the test is complete it outputs a test report indicating whether the infant heard the sounds and/or discriminated between the sounds presented, along with a confidence estimate and data quality statement. See Section 12.3 for details of the test protocol in this project. Section 12.3 describes the specific sounds to be used in this project for device feasibility testing ("ba" and "ga") and their durations (repeated 5.4 s).

11 RANDOMISATION AND BLINDING

11.1 Concealment mechanism

All infants undergo fNIRS testing so there is no randomisation or blinding for them or their parents/guardians.

11.2 Breaking of the trial blind

NA.

12 TRIAL VISITS AND PROCEDURES

12.1 Trial timeline

Each infant will have a single fNIRS test.

12.2 Schedule of assessments

The schedule of interventions for infants (Time is relative to enrolment)

	Enrolment	fNIRS test session 1
TIME POINT	Day 1	within 4 weeks
ENROLMENT:		
Eligibility screen	X	
Informed consent		X
INTERVENTIONS:		
Otoscopy and tympanometry		X
fNIRS tests		X

12.3 Description of procedures

Screening for eligibility

Determination of infant eligibility will be undertaken by confirming that the infant has passed hearing screening or diagnostic audiological assessment and is under the age of 2 years. The infant will be assigned an anonymising code.

The fNIRS test session

Before completing the fNIRS tests, the infant will undergo otoscopy and tympanometry to exclude possible temporary conductive hearing loss associated with abnormal tympanometric results. These are standard audiological procedures. If the infant has abnormal tympanometric results in both ears on the day, the test session will terminated. The parent/guardian will be advised of the finding and its possible consequences (possible conductive hearing loss, possible progression to acute otitis media) and advised to seek medical advice should the infant show signs of illness or if hearing loss is suspected.

All assessments in the fNIRS test session will be undertaken by qualified paediatric audiologists who are trained in the fNIRS procedures.

For the fNIRS tests, the infant will be asleep. The appointment will be scheduled to just before their usual daytime nap time to make it easier to get the infant to sleep. The parent will guide the getting-to sleep process.

After the infant is asleep, the headgear will be placed on the infant's head and optode calibration procedure is undertaken to ensure the equipment is ready. During the actual test, blocks of speech sounds lasting 5.4 seconds will be played to the infant either via tubephone or via speakers at a comfortable level (65 dB SPL). Tubephones are sound transducers that are inserted in the ear and are used in standard audiological testing of infants. Testing will usually proceed for the duration of the infant's sleep period (usually around 40 minutes). If the infant remains asleep after the main fNIRS tests are completed (detection of "Ba" at 65 dB SPL, and discrimination of "Ba" from "Ga"), further speech sounds will continue to be played at levels within the comfortable loudness range until the baby wakes. The responses to those additional sounds will not be used in the main study outcome analysis of preliminary functionality (Section 16) but will provide additional support for this. Leaving the headgear on and functioning for the duration of the infant's sleep cycle (around 40 minutes) is important for obtaining the safety and comfort information.

Our outcome measures for device feasibility are the incidence of detection and discrimination responses obtained. Specifically, we expect that at least 9/10 infants (90%) will show a significant detection response for "Ba" at 65 dB SPL, and that their average waveforms for this test should consist of a positive HbO peak around 5-8 s latency, or a negative HbO response with latency 12-16 s, or a shape consistent with a combination of these shapes (refer to Figure 1). For the test of discrimination of "Ba" from "Ga", we expect that at least 7/10 infants (70%) will show a significant discrimination response, and that their average response waveforms should consist of a positive HbO response with latency 6-12 s or a negative HbO response with latency 12-20 s, or a combination of both these shapes (Figure 2).

During the test session, the infant will be monitored for any signs of discomfort or distress, and after the session. The measures of discomfort will include observations of crying, attempts to remove headgear, verbal indications of distress (in an infant with developed speech), and, after the test, observations of any marks left by the headgear on the skin, along with the duration (in minutes) of such incidents. The infant's skin will be examined to detect any signs of skin reaction or areas affected by too much pressure of the head gear. If any distress or skin reactions occur in the test session, the parents will be contacted in the following 48 hours to document whether the problem resolved and how long it took. Any comments provided by the parents within 48 hours of the test re any potential side effects noticed will be recorded. All of this information will be documented on the Case Report Form. All Case Report Forms will be collated and summarised in a final report re safety, along with any recorded adverse events.

Adverse events: Since fNIRS tests are considered to be non-invasive and safe, we do not anticipate any serious adverse events. However, if an adverse event occurs, the ethics committee will be informed if required by their procedures, and the standard procedures of the Bionics Institute will be followed (see Section 13).

12.4 Notes on specific trial visits

12.4.1 Screening

Initial screening for eligibility of infants will be conducted usually via phone or email after a parent expresses interest. Screening questions are a) has your child passed newborn hearing screening or been confirmed as having normal hearing in a diagnostic assessment? and b) Is your child under 2 years of age? There are no additional screening test procedures.

12.4.2 Unscheduled visit

Unscheduled visits are not anticipated.

12.5 Treatment discontinuation, participant withdrawals and losses to follow up

12.5.1 Discontinuation of treatment - participant remains in trial for follow up

Not applicable.

12.5.2 Withdrawal of consent - participant withdraws from all trial participation

Participants are free to withdraw from the trial at any time upon their request or the request of their legally acceptable representative.

The data from infant participants who have completed all of the fNIRS testing when their parent/guardian withdrew consent will be included in the trial unless the parent/guardian asks us not to use the data.

A dedicated Case Report Form will be used to capture the date of participant withdrawal of consent.

12.5.3 Losses to follow-up
Not applicable.

12.5.4 Replacements
Infant participants who withdraw from the trial at any time before or during fNIRS testing can be replaced.

12.5.5 Trial Closure
An infant participant is considered to have completed the trial when partial or complete fNIRS test results have been obtained in one test session.

The end of the trial is defined as completion of fNIRS tests on 10 infants. At this stage, the Sponsor-Investigator will ensure that all HRECs and RGOs as well as all regulatory and funding bodies have been notified.

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the trial is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform trial participants, HREC and RGO, the funding (where applicable) and regulatory bodies, providing the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of an unexpected, significant, or unacceptable risk to participants that meets the definition of a Significant Safety Issue (SSI) (for the definition refer to Section 8.1).
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

In the case of concerns about safety, protocol compliance or data quality, the trial may resume once the concerns have been addressed to the satisfaction of the sponsor, HREC, RGO, funding and/or regulatory bodies.

12.5.6 Continuation of therapy
Not applicable

13 SAFETY MONITORING AND REPORTING
As this is a first-in-human use of the EarGenie MVP there are no known Adverse Device Effects for this particular device. However, there are many fNIRS devices that have been used in research for more than 20 years and recently in clinical settings, and there have been no reports of serious adverse device events due to use of fNIRS that we can find. The technology is non-invasive, and the devices are designed to ensure electrical, optical, electromagnetic and other safety. The Investigator Brochure lists five areas where potential hazards may occur, being electrical safety, electromagnetic compatibility, battery failure, biocompatibility, and mechanical pressure points on the baby's head, and ways these have been mitigated in the design of EarGenie MVP. The potential adverse effects related to these hazards are captured in the case report document and would all be exhibited as marks or irritation on the baby's skin or untoward signs of distress, apart from electrocution, which is not possible with EarGenie MVP as there is no power attached to the headgear.

Adverse events will be classified and graded in accordance with the "Common Terminology Criteria for Adverse Events (CTCAE) v5.0" (2017).

13.1 Definitions

13.1.1 Definitions for use in trials involving investigational medical devices

Participant-specific adverse events

Adverse Device Effect (ADE): Adverse event related to the use of an investigational medical device.

Note: This definition includes adverse events resulting from insufficient or inadequate instruction for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device and includes 'comparator' if the comparator is a medical device.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the investigational medical device.

Note: This definition includes events related to the investigational medical device or the comparator. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

For the purposes of this trial, examples of an AE do not include:

- Anticipated fluctuations of pre-existing disease(s) or condition(s) present or detected at screening.
- Expected signs and symptoms or progression of the disease being studied, unless there is substantial increase in severity or frequency of the condition, which has not been attributed to natural history.
- Planned hospital visits and or hospital stays (e.g., rehabilitation or respite care, elective surgery)

Exacerbation of an existing condition should be reported as an AE if the event meets the protocol definition of an AE.

For the purposes of this trial, examples of an AE do include:

- Evidence of skin irritation or injury left after headgear is removed
- Evidence of untoward, developmentally relevant, signs of significant distress in the infant such as crying, attempts to remove headgear, verbal indications of distress (in an infant with developed speech),

Device Deficiencies: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Note: Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator.

Serious Adverse Device Effect (SADE): An adverse device effect that has resulted in any of the consequences of a Serious Adverse Event (SAE).

Serious Adverse Event (SAE): An adverse event that:

a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalisation, or

- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c. Led to foetal distress, foetal death or a congenital anomaly or birth defect including physical or mental impairment.

Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the clinical protocol, without serious deterioration in health, is not considered a serious adverse event.

For the purposed of this trial, SADEs are not anticipated, as the procedure is non-invasive and the device designed to be electrically safe.

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the current version of the risk analysis report. USADEs require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA.

Safety issues (require expedited reporting)

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Comment: An SSI is a new safety issue or validated signal considered by the Sponsor in relation to the IMD that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the IMD which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the IMD.

Urgent Safety Measure (USM)

A measure required to be taken to eliminate an immediate hazard to a participant's health or safety.

Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

13.2 Capturing and eliciting adverse event/reaction information

Adverse events will be captured through observation or spontaneous parental report during the infant's session at the Bionics Institute, or if spontaneously reported by their parents up to 48 hours following. Events will be followed until resolution or stabilisation. They will be recorded for each infant on their Case Report Form (CRF).

13.3 Documentation of AEs

For the purposes of this trial the investigator is responsible for recording all Adverse Events, as according to the definition in the preceding definition section.

The AE will be described in the source documents and/or captured directly on the CRF and will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity (mild, moderate, or severe – what is the impact on the participant's daily life?)
- Seriousness (i.e., is it an SAE?)
- Any action taken, (e.g., treatment, follow-up tests)

- The outcome (recovery, death, continuing, worsening)
- The likelihood of the relationship of the AE to the trial investigational medical device (Unrelated, Possible, Probable, Definite)

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

13.4 Assessing the seriousness of a participant's AE

The seriousness of an AE will be assessed by an investigator according to the definition in in the preceding section on definitions with the following exception(s):

- Hospitalisation due to progression of disease will not be considered an SAE for the purposes of this trial.
- Elective surgery planned at the time of enrolment.

13.5 Assessing the relatedness (causality) of a participant's AE

All adverse events must have their relationship to trial intervention assessed by the investigator who evaluates the adverse event 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 trial investigational product should always be suspected.

The relationship of the event to the trial intervention will be assessed as follows:

- Unrelated: There is no association between the investigational device and the reported event. AEs in this category do not have a reasonable temporal relationship to exposure to the test product or can be explained by a commonly occurring alternative aetiology.
- Possible: The event could have cause or contributed to the AE. AEs in this category follow a reasonable temporal sequence from the time of exposure to the investigational device and/or follow a known response pattern to the test article but could also have been produced by other factors.
- Probable: The association of the event with the trial investigational device seems likely. AEs in this category follow a reasonable temporal sequence from the time of exposure to the investigational device and are consistent with the known mechanisms of the device, or judgement based on the investigators clinical experience.
- Definite: The AE is a consequence of application of the trial investigational device. AEs in the category cannot be explained by concurrent illness, progression of disease state or concurrent medication reaction. Such events may be widely documented as having an association with the investigational device or that they occur after rechallenge.

13.6 Assessing the expectedness of a participant's AE

The Principal Investigator 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 trial.
The severity of an Adverse Event will be assessed as follows:

- Mild: Events that require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate: Events that cause sufficient discomfort to interfere with daily activity and/or require a simple dose of medication.
- Severe: Events that prevent usual daily activity or require complex treatment.

13.7 Reporting of safety events

The Principal Investigator or delegate is responsible for recording all safety events in the source document.

The Principal Investigator is responsible for expedited reporting (as soon as possible but within 24 hours of becoming aware of the event) all SAEs, USADEs and USMs to the Sponsor and the approving HREC in accordance with the NHMRC's '*Safety monitoring and reporting in clinical trials involving therapeutic goods'* (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation. These reports should be submitted using the trial Expedited Safety Report Form (see Appendix).

The Principal Investigator is also responsible for reporting SSIs, USMs and USADES to the local research governance office within 72 hours of becoming aware of the event and in accordance with their local governance authorisation.

The Sponsor is responsible for the following reporting to the HREC(s) and TGA in accordance with the NHMRC's *'Safety monitoring and reporting in clinical trials involving therapeutic goods'* (November 2016) and any additional requirements of the approving HREC:

1. All USADEs: fatal or life threatening, no later than 7 calendar days of becoming aware of the issue, all others, within 15 calendar days.
2. All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.
3. All other SSIs within 15 calendar days of instigating or becoming aware of the issue.
4. For SSIs leading to an amendment of trial documentation:
    a. Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.
    b. Submit amendment to the HREC without undue delay.
5. For SSIs leading to temporary halt or early termination of a trial for safety reasons:
    a. Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.
    b. For a temporary halt, notify the PI, HREC and TGA when the trial restarts, including evidence that it is safe to do so.

The Sponsor or delegate is responsible for providing the additional safety information to the approving HREC:

1. Provide an annual safety report, including a summary of the trial's evolving safety profile.
2. Provide any updated Product Information/Investigator's Brochure for the investigational products (if applicable).

14 DATA AND INFORMATION MANAGEMENT

14.1 Overview

The Principal Investigator is responsible for storing essential trial documents relevant to data management and maintaining a site-specific record of the location of the site's data management-related Essential Documents.

The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring, and available. Changes to source data (hardcopy and electronic) must be

traceable, must not obscure the original entry, and must be explained where this is necessary. A site-specific Source Document Plan will be maintained to indicate the location(s) of source documents.

The Principal Investigator will also maintain accurate CRFs (i.e., the data collection forms) and be responsible for ensuring that the collected and reported data is accurate, legible, complete, entered in a timely manner and enduring. To maintain the integrity of the data, any changes to data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these trial-related duties and functions.

14.2 Data management

All data will be stored at the Bionics Institute. Paper documents will be kept in a locked filing cabinet in a key card secured location. Digital records will be stored securely on the Bionics Institute's servers in a way consistent with the Bionics Institute's data management quality control system. Access to data (including keys to the filing cabinet) will only be available to delegated team members. All data will be de-identified with participant codes and the key to the codes kept in a different location on the secure server. All information (including consent forms) will be retained according to the Bionics Institute data retention policies for a period of 25 years after completion of the trial after which the paper records will be shredded, and electronic de-identified data archived in the Bionics Institute's secure data archive system.

Secondary use of data: The de-identified data may be used for any follow-on studies at the Bionics Institute and may be shared with other researchers on request via a secure web site, as required by many refereed journals and funding agencies. In the latter case, no key to the ID codes will be made available.

14.2.1 Data generation (source data)

In this trial, the following types of data will be collected:

- Personal identifying information (names, dates of birth, contact details)
- Sensitive information including health data (medical, perinatal, and developmental history, languages spoken at home)
- Clinical findings, measurements, and observations (otoscopic findings, tympanometric measurements, head circumference measurements, observations made during fNIRS testing)
- Photographs taken during testing to document test conditions
- fNIRS data recordings

Source Document Plan

The source documents for this trial include:

- The signed parent/guardian information and e-consent forms.
- Personal identifying information collected electronically via REDCap or in person in written form.
- Sensitive information collected either prior to or on the day of fNIRS testing (whichever is more practical).
- Case Report Forms
- Clinical findings, measurements and observations recorded in the laboratory logbook.
- fNIRS data recorded on the EarGenie MVP device and stored on Bionics Institute servers.

A Source Document Plan will be maintained that documents the source, i.e., original recording, for each data discrete item or category of items collected for the trial. This Source Document Plan, signed

and dated by the Principal Investigator, will be prepared prior to recruitment of the first participant and will be filed in the site's Investigator Site File.

14.2.2 Data capture methods and data use, storage, access, and disclosure during the trial

Data collection methods

Data for this trial consists of electronic data output by the EarGenie MVP and paper and electronic forms.

Data will be collected and entered into REDCap from hardcopy or electronic data collection forms which will be completed by the researchers.

The following licensed research data collection tools will be used:

- REDCap

Use of the data

The data will be used for the analyses specified in the protocol.

Following the completion and analysis of the trial, the data will be retained long-term following the BI's mandatory archive period for use in future research projects.

Storage and access

Hard copy data will be stored at the Bionics Institute in a locked cabinet in a secure location, accessible to the research team only.

Electronic data will be securely stored in REDCap database system and in files stored in Bionics Institute's file servers, which are backed up nightly. Files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team.

REDCap is hosted on Bionics Institute infrastructure and is subject to the same security and backup regimen as Institute other systems (e.g., the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via a Bionics Institute user account or (for external collaborators) via a REDCap user account created by the Bionics Institute system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the trial team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this trial. The trial site will permit access to such records.

Disclosure

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the HREC, Research Governance Office or regulatory agencies. In this case, consent to provide the results

to the infant's managing audiologist will be requested. However, refusal of this consent (however unlikely) will not exclude the infant from participation in the study.

14.2.3 Data confidentiality

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

1. The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.
2. Participant identifiers will be stored separately to the data collected; documents with identifiers will be stored with restricted access.
3. Participant data will be identified through use of a unique participant trial number/code assigned to the trial participant ("re-identifiable"). The Principal Investigator is responsible for the storage of a master-file of names and other identifiable data with the participant ID; access to this document will be restricted to the trial team and authorised persons as listed previously. The master file will be stored securely, and separately, from trial data in locked/ password-protected databases with passwords kept separately.
4. Separation of the roles responsible for management of identifiers and those responsible for analysing content. The data will be analysed by researchers who will be provided with anonymised data identified only by the unique participant trial ID.

14.2.4 Quality assurance

Outcome data are input directly and stored in the REDCap database.

14.2.5 Archiving - Data and document retention

The data will be archived and retained until the oldest infant reaches 25 years, as per guidance for clinical trials.

At the end of the trial period, data will be archived via two means:

Electronic data (e.g., fNIRS raw data, and REDCap data) will be stored on a secure server at the Bionics Institute, which is backed up nightly.

Hard copy laboratory notebooks will be stored in a locked filing cabinet in the dedicated archive space at the Institute, clearly labelled with clinical trial dates and titles for easy retrieval if necessary. After the time period when the data may want to be reused for research has elapsed, the hard copy lab notebooks will be scanned and included in the digital archive until the 25 years is complete.

The consent forms will also be scanned and included in the trial archive. The trial re-identification document matching trial IDs to personal IDs will be stored in the archive along with the other documents but will be password protected. The long-term custodian of the archive (the person in the role of Chief Technology Officer/Head of Research Operations) will retain the password to re-identify the data in the 25-year period.

Records will not be destroyed without the written consent of the Sponsor Investigator / Site Principal Investigator. It is not intended that the electronic data be destroyed at the end of the archive period. However, the re-identification document will be deleted using secure deletion software.

14.2.6 Data sharing

Beginning 1 month following the end of the trial, the following will be made available long-term for use by future researchers from a recognised research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept Bionics Institute's conditions for access:

- Individual participant raw fNIRS data (prior to processing) after de-identification
- Trial stimulus presentation protocol

15 TRIAL OVERSIGHT

15.1 Governance structure

The Principal Investigator is responsible for supervising any individual or party to whom they have delegated tasks. They will provide continuous supervision and documentation of their oversight. As part of meeting this GCP requirement, the project's clinical team, made up of the PI and research audiologists, one of whom is the trial coordinator, will act as the trial management group (TMG). The TMG will provide close oversight over all aspects of the trial, ensuring that there is a forum for identifying and addressing issues. The TMG will formally and regularly review and evaluate the accumulated trial data for participant safety, device deficiencies, trial conduct and progress, and make determinations under the PI concerning the continuation, modification, or termination of the trial.

15.2 Site Monitoring

Trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial complies with the currently approved protocol and amendment(s), good clinical practice, and applicable regulatory requirements.

Monitoring for this trial is the responsibility of the sponsor and will be performed onsite by the Bionics Institute's Research Governance Office. The monitor will compare the trial processes and documentation with the trial protocol and the requirements of ICH-Good Clinical Practice (GCP) and ISO 14155 (ISO) guidelines, with an emphasis on critical data and processes for the specific trial. This will include review of signed consent forms and the consent process, safety events and data related to the primary outcome.

The extent and frequency of monitoring will be detailed in the trial Monitoring Plan. The monitoring schedule may be revised if recruitment is slower or faster than expected, requested by the sponsor in response to any issues arising, or if there is an elevation or reduction in the risk profile of the trial.

The research team will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

15.3 Quality Control and Quality Assurance

The Principal Investigator has responsibilities in relation to quality management, including the development of SOPs that identify, evaluate and control risk for all aspects of the trial, e.g., trial design, source data management, training, eligibility, informed consent, and adverse event reporting. The Principal Investigator will also implement quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the relevant trial personnel for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, good clinical practice, and applicable regulatory requirements.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Sponsor will perform a root cause analysis and corrective and preventative action plan

(CAPA) in collaboration with the Principal Investigator. This will be entered into the Bionics Institute's Quality Management System.

16 STATISTICAL METHODS

16.1 Sample Size Estimation

NA. We propose that 10 infants are sufficient to establish safety and preliminary evidence for functionality as detailed in Section 16.3. As this is primarily a safety study and only preliminary confirmation of functionality is evaluated, statistical analysis is not appropriate.

16.2 Population to be analysed

All infants in the study.

16.2.1 Handling of missing data

NA. There is only one test session and if a parent withdraws before or during the session, we will replace that infant with another.

16.3 Methods of analysis

Safety analysis: A careful recording during all of the 10 test sessions of any signs of discomfort from the infant, along with any parent reports of such discomfort within 48 hours of the test, will be noted on Case Report Forms and collated and summarised at the end of the study. Any adverse events will be recorded and managed as per Section 13. The data will be presented as incidence of such events along with their duration, and a full description of each incident.

To obtain preliminary evidence of the functionality of the EarGenie MVP, the automatic reports generated by EarGenie MVP, which includes the test result and the average haemodynamic response waveforms related to that test, will be examined. We expect infants with normal hearing to be able to both hear the speech sounds and to be able to discriminate them. Therefore, we expect a majority of infants to return a positive test result (as in our previous research with the NIRx system), and that the waveforms generated should have characteristics in common with what we expect from our previous research. These data will be summarised as proportions of infants for whom the EarGenie MVP test showed a) a significant detection, and b) a significant discrimination as detailed below.

Specifically, we expect that at least 9/10 infants will show a significant detection response for "Ba" at 65 dB SPL, and that their average waveforms for this test should consist of a positive HbO peak around 5-8 s latency, or a negative HbO response with latency 12-16 s, or a shape consistent with a combination of these shapes (refer to Figure 1).

For the test of discrimination of "Ba" from "Ga", we expect that at least 7/10 infants will show a significant discrimination response, and that their average response waveforms should consist of a positive HbO response with latency 6-12 s or a negative HbO response with latency 12-20 s, or a combination of both these shapes (Figure 2).

16.4 Interim Analyses

No interim analysis planned.

17 ETHICS AND DISSEMINATION

17.1 Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the HREC prior to commencing the research. A letter of protocol approval by HREC will be obtained prior to the commencement of the trial, as well as approval for other trial documents requiring HREC review.

17.2 Amendments to the protocol

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participant's willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented.

17.3 Protocol Deviations and Serious Breaches

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Principal Investigator, who will assess for seriousness. Those deviations deemed to affect to a significant degree rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done in a timely manner (Principal Investigator to report to the Sponsor-Investigator within 72 hours and to the Bionics Institute RGO within 7 days; Sponsor-Investigator to review and submit to the approving HREC within 7 days).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken, and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

18 CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover clinical information relating to participating participants.

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (clinic or hospital) for the participants in this trial. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

19 PARTICIPANT REIMBURSEMENT

There are no costs associated with participating in this research project, nor will participants nor their caregivers be paid. The parents/guardians of infant participants and any other research participants will be reimbursed for any reasonable travel expenses associated with attending fNIRS testing sessions at the Bionics Institute. The amount of reimbursement will be in the range of $30 to $100 and will be commensurate with the travel expenses incurred.

20 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

Investigators will declare any conflict of interest or financial interest related to this trial. These will be recorded on the Bionics Institute Conflict of Interest (COI) register and managed by the Bionics Institute consistent with their COI policy. Notifications of relevant conflicts of interest will be submitted to journals when requesting publication. Bionics Institute/Researchers Colette McKay, Julia Wunderlich, Darren Mao, and Gautam Balasubramanian hold patents in relation to the methods used to measure sound discrimination and detection from fNIRS data.

21 DISSEMINATION AND TRANSLATION PLAN

The findings of this project will not be published in journals. Will be provide our results on clinicaltrials.gov when the trial is completed.

The results of this clinical trial will be used to support the use of the EarGenie MVP in further clinical trials to determine its clinical value and obtain feedback on its useability. These future clinical trials will aim to support the commercialisation pathway of the fNIRS test as part of the EarGenie® hearing system by enabling prototype updates to be generated that could proceed to regulatory approval.

22 REFERENCES

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23 APPENDIX

Expedited Safety Report Form

EXPEDITED SAFETY REPORT FORM	
Reporting requirement: Principal Investigator to report to Sponsor all *SAEs, SUSARs and USMs within 24 hours of **trial** staff becoming aware of the event. *Except those identified in the protocol as not needing immediate reporting	
HREC Reference #	
Project title	

Section A: To be completed by the Principal Investigator		
Site:		
Local Site Principal Investigator:		
Participant Enrolment OR Randomisation No.:		
Date the safety event occurred:		
Date Local Site Principal Investigator became aware of the safety event:		
Participant's date of birth, age, and weight:		
Event description and management:		
Event outcome (synopsis):		
Trial phase (amend to reflect protocol)	☐ Screening ☐ Active participation ☐ Follow Up	
Relationship to the trial device		☐ Unrelated ☐ Unlikely to be related ☐ Possibly related ☐ Probably related
Expectedness (only complete for SAEs that are probably/possibly related):		☐ Not applicable ☐ Expected ☐ *Unexpected *Report SUSAR to local RGO within 72 hours of becoming aware of event
Was an Urgent Safety Measure (USM) instigated? A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.		* ☐ Yes ☐ No *Report to local RGO within 72 hours of becoming aware of event
Name and Signature (of local PI or delegate)		Date

Section B: To be completed by the Sponsor	
Is this event a Significant Safety Issue (SSI)? A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability of the trial. Often SSIs do not fall within the definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR), thus are not reported as SUSARs but require other action such as the reporting of an urgent safety measure (USM), an amendment, a temporary halt or early termination of a trial.	*☐ Yes ☒ No * Report to TGA, HREC and all site PIs within 15 days of becoming aware of event
Is this event an Urgent Safety Measure (USM)? A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.	* ☐ Yes ☐ No *Report to TGA, HREC and all site PIs within 72 hours of becoming aware of event
Is this event a USADE?	* ☐ Yes ☐ No *Report to TGA within 7 days of becoming aware of the event if fatal/life threatening, otherwise report within 15 calendar days
Does the protocol require amending as a result of this safety event? (If Yes, submit an amended protocol to approving HREC)	☐ Yes ☐ No
Do the participant information statements require amending as a result of this safety event? (If Yes, submit an amendment request to approving HREC and RGOs with the amended forms)	☐ Yes ☐ No
Is a temporary halt or early termination of the trial required as a result of this safety event? (If Yes, ensure actions are taken within 15 days of decision to halt)	☐ Yes ☐ No
Name and Signature (of Sponsor)	Date

Please email one signed copy to the Sponsor Bionics Institute *(rgo@bionicsinstitute.org)* and retain the signed original in the Site Investigator File