CONFIDENTIAL

CAVA: Healthy Volunteer Trial
Clinical Investigation Plan

Full title of project:	**Production of a device to obtain continuous ambulatory vestibular assessment (CAVA) – healthy volunteer trial**
Short title of project:	**CAVA – Healthy Volunteer Trial**
MRC reference:	**MR/P026265/1**
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Date:	**20th September 2018**
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PROTOCOL SIGNATURE PAGE

Full title of project:	**Production of a device to obtain continuous ambulatory vestibular assessment (CAVA) – healthy volunteer trial**
Protocol Version:	**2.5 (20th September 2018)**
Sponsor:	**Norfolk & Norwich University Hospitals NHS Foundation Trust**

Principal Investigator's Declaration

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct this trial in compliance with all stipulations of the protocol, regulations and in accordance with Good Clinical Practice (GCP).

Principal Investigator's Name: JOHN PHILLIPS.

Principal Investigator's Signature: J Phillips.

Date: 20th Sept 2018

1 INTRODUCTION

1.1 In 2017, the Medical Research Council awarded a grant as part of their Biomedical Catalyst: Development Pathway Funding Scheme to Mr John Phillips and his team at the University of East Anglia, to develop a medical device to aid diagnosis in individuals experiencing dizziness, vertigo and balance problems. This grant is to develop an early prototype, and then to formally test it in healthy volunteers, and then later, in individuals who experience vertigo.

1.2 This document outlines the clinical investigational plan for the first of two formal clinical trials. This clinical investigation plan is for a healthy volunteer trial.

2 SCIENTIFIC RATIONALE

2.1 In England and Wales, eight out of every 1,000 patients are likely to consult with their General Practitioner complaining of dizziness every year. Symptoms of dizziness or imbalance are experienced by 30% of the population by the age of 65 years (Roydhouse 1974). One in four in the community have 'significant' dizziness at any given time (Nazareth 1999).

2.2 Eye movements are key in assessing the function of the inner ear and the vestibular system (Huh 2013). There is a dipole potential (the corneo-retinal potential) between the front and the back of the eyeball that allows eye movements to be measured electronically. The intimate relationship between eye movements and the inner ear is mediated by a neural reflex called the vestibulo-ocular reflex (VOR). The main purpose of this reflex is to stabilise images on the retina during head movements. This reflex is administered in a manner whereby the eyes move in the opposite direction to the direction of the head movement. The VOR does not require visual input and so is active both in total darkness and when the eyes are closed. As this is a brainstem reflex, it is also active when a subject is asleep or in a coma, and as such is used clinically to diagnose brainstem death.

2.3 The common causes of vestibular dysfunction occur momentarily, and by the time a patient presents to a specialist, they are asymptomatic (Molnar 2014). Two conditions which particularly attract considerable attention in the clinical and research communities are Meniere's disease and Vestibular Migraine. The causes of these conditions are not fully understood and their assessment is challenging (Phillips 2010). Both of these conditions may result in dizziness lasting for many hours, but because patients may be asymptomatic for days, weeks or even months between attacks, it is often the case that there are few findings to be identified when the patient is assessed. Meniere's disease and Vestibular Migraine are provided as examples, but these conditions are not unique in their mode of presentation, as the majority of balance disorders present in this manner.

2.4 There are many traditional and contemporary balance tests available, but they still provide only a snapshot of vestibular function when performed in the absence of an actual 'dizzy attack' (Phillips 2011). By developing a device that can capture the characteristic eye movements (nystagmus) that are produced during a 'dizzy attack', we will be able to identify the aetiology of these episodes of imbalance. Parallels can be drawn between our device and the 24-hour ECG tape that is used to identify cardiac arrhythmias.

2.5 Nystagmus is a clinical sign which is often specific to the inner ear. However, a number of patterns of nystagmus are produced as a consequence of conditions that are not caused solely by a malfunction of the inner ear (Serra 2002). Therefore, the identification of nystagmus will not only allow us to differentiate between the many vestibular causes for a 'dizzy attack', but

would also allow us to understand the role of different types of nystagmus as a consequence of certain other nervous system pathologies.

2.6 The assessment of the dizzy patient can be challenging for all clinicians involved in managing their care. John Phillips has been commissioned by the British Medical Journal to write a learning module to help clinicians understand how to assess these patients (Phillips 2015). This module outlines the processes and pathways to differentiate inner ear dizziness from non inner ear dizziness from the outset. This essential first step would be refined significantly by the introduction of our proposed device.

2.7 A recent Royal College of Physicians working party report confirms our expectation that detailed occulomotor assessment will 'frequently enable an appropriate diagnosis to be made without the use of expensive resources' (RCP 2007, Halmaghi 2005). According to the RCP report, balance services in the UK have been 'particularly neglected due to limited training, resources and manpower', so our proposal will fulfill a significant unmet clinical need. 'Dizzy patients' present via a variety of routes: A&E departments, general practitioners, self-referral to ENT, cardiologists, neurologists or audiovestibular physicians. The Department of Health have proposed a referral pathway to allow treatment within an 18-week target. However, due to the complexity in the manner that these patients present, and the overlap of aetiologies between multiple specialties, patients are often seen by several clinicians from different disciplines before a diagnosis is made. The US National Institutes of Health report that the mean number of physicians a patient with vertigo visits before receiving a correct diagnosis is 4.5, and a similar finding is reported from specialist balance centres in the UK (RCP 2007). Our proposed device could be made available at the point of initial referral to avoid delay in diagnosis and ensure cost-effective use of appropriate resources. This is particularly significant as the cost of falls to the NHS and social services in people over 60 years old in 1999 was £981 million (Scuffham et al, 2003). Another consideration is that in 80% of affected individuals, vertigo results in a medical consultation, interruption of daily activities, or sick leave (Neuhauser et al, 2005).

3 THE DEVICE

3.1 The device is composed of two components: a bespoke single-use sensor array that adheres to the participant's face, and a small reusable module that contains a battery, microcomputer, data storage facility, battery and connection port. A series of preliminary prototype devices have been manufactured and tested as part of a preliminary programme of work aimed at developing the overall project to this stage. This work has been completed by the primary research team in collaboration with a design agency (Wright Design Limited). The device is a lightweight, durable, body-worn monitoring device that can be worn day and night. It will be worn on the face and head but will minimally intrude into the patient's normal lifestyle.

3.2 Preliminary prototype devices have been developed to be able to record the maximal ocular excursions and velocities that are observed in clinical practice. These preliminary prototype devices have consistently, accurately, precisely and reliably identified periods of physiological nystagmus in subjects both stationary and in motion and have produced consistent signals at the beginning and end of each trial period. The sensor array has been reported to be comfortable and there have been no adverse skin reactions. The evolved device that will be used for this trial, will be provided to a participant for a 30 day period at a time and will include an 'event marker' button. Although not relevant to this first trial, actual dizzy patients would depress this button during an episode of dizziness. The absence of any nystagmus during this period would indicate a cause of dizziness that is not related to a malfunction affecting the

VOR. To further clarify subject activity during episodes of either nystagmus and/or dizziness, the final device will contain an accelerometer which will enable retrospective correlation between activities that may be implicated in the cause of dizziness and/or variation in the signal produced.

3.3 Independent market research

We have commissioned some independent market research which has provided further insight into other uses for the device. Currently, clinical trials into the use of new treatments for dizziness rely on the participant completing questionnaires or diaries. The use of the device, would enable an objective measure of the frequency of vertigo in these patients. There is increasing interest in the use of ambulatory telemetry for individuals with other primary neurological conditions; as such, our device might be of interest in the field of stroke medicine.

3.4 Patient and public involvement

Early on in the design process, a focus group was formed to allow the design company to interact with potential users of this device. This was a very useful exercise, and allowed all participants to provide input to the device design, and the format of the device trials.

4 AIMS AND OBJECTIVES

4.1 The overall aim of this trial is to further develop and test a fully evolved device for the continuous recording of eye movements over a prolonged period of time. For the purpose of this study, the monitoring period is 23 hours a day, for 30 days.

4.2 The overall trial objectives and how we will present the data relating to them, are as follows:

i. **The device produces data that allows recognition of nystagmus with a diagnostic sensitivity of 95% or greater.**
We will report the sensitivity and specificity of the computer algorithm's classification results. This will be calculated from the number of true positives, false positives, true negatives, and false negatives. These values are produced by applying the trial data to computer algorithms developed by the project's Research Associate. For clarity, we will also present these values.

ii. **The device produces data that allows recognition of nystagmus with a diagnostic specificity of 95% or greater.**
As in point i.

iii. **The device provides less than 5% non-useful data and less than 5 drop-outs for each single day of the trial for each participant.**
In a tabular format, we will present the proportion of non-useful data for each participant, for each day, and the number of drop-outs for each person, for each day. Non-useful data will be determined from missing data which is not reported as a compliance issue. Drop outs will be defined as any periods of missing data which are at least an hour apart.

iv. **The device provides less than 5% non-useful data and less than 60 drop-outs for the entirety of the 30-day trial for each participant.**

In a tabular format, we will present the proportion of non-useful data for each participant, across the entire period that they were supposed to be wearing the device during the trial. Non-useful data and drop outs will be defined as in iii.

v. **There is a minimum of 80% compliance with wearing the device for each single day of the trial for a minimum of 80% of participants.**
In a tabular format, we will present the proportion of compliance for each participant, for each day of their involvement in the trial. This data will be determined from the trial diaries. From this table, we will calculate the proportion of participants who demonstrated a minimum of 80% compliance for each single day.

vi. **There is a minimum of 80% compliance with wearing the device for the entirety of the 30-day trial for a minimum of 80% of participants.**
In a tabular format, we will present the proportion of compliance for each participant, across the entire period that they were supposed to wear the device during the trial. This data will be determined from the trial diaries. Additionally, we will present the proportion of these participants who demonstrated a minimum of 80% compliance.

vii. **The device's event-marker, timestamping hardware and accelerometer function correctly.**
We will present a report detailing the results of tests performed to evaluate this objective. The results of the event marker function test will consist of the approximate time that the button was pressed, the time that the device reported that the button was pressed, and a pass or fail indication, based on whether the button press was registered. The timestamping hardware test result will consist of the time difference (in dd:hh:mm:ss) between the time logged on the device following the activation of the event marker, and that of a real-time clock on a desktop computer. The accelerometer test will consist of a table listing the head movements performed and whether they could be identified manually from the accelerometer data. We will present all data for each device, as well as averaging and calculating the proportion of tests passed from the total pool of devices.

viii. **To derive further user reported data regarding the day to day experience of using the device and to acquire further safety data regarding the device.**
We will write a report which details the results of the post-trial questionnaires filled in by each participant, summarising the conclusions of the report. This report will cover topics such as the safety, usability, tolerability of wear etc.

ix. **To derive further experimental data using the device whilst being used in a clinical testing environment, to enable the correlation between device data, and clinical testing data.**
We intend to compare data produced by the CAVA device to data captured using conventional Videonystagmography (VNG), gathered during a standard balance assessment procedure. From the eye movement data captured, we will make estimates of the onset, end, beat direction, beat frequency and Short Phase Velocity (SPV), and then compare the two systems.

5 METHODOLOGY

5.1 Overview

Healthy individuals will be recruited from the local area to participate in this trial. It is intended that this trial will be advertised at the University of East Anglia. Participants will be required to wear the device for thirty days. During this period, they will induce physiological nystagmus by viewing optokinetic video footage. This replicates the typical eye-movements observed when watching a passenger on a moving train looking out of a window.

5.2 We intend to confirm that the device will be able to capture any occurrence, of a minimum period of thirty seconds, of artificially induced nystagmus, within a 24-hour period of time. Each participant will be provided with the device and enough single-use electrode arrays to allow the array to be changed every 24 hours, for thirty days. Participants will be allowed to remove the sensor array for up to 60 minutes each day to allow them to wash and/or shower. On eight of the thirty days for which they wear the array, each participant will be required to induce physiological nystagmus by viewing optokinetic video footage. The footage will be viewed on a portable screen (of a deactivated mobile phone) inside a VR headset. These will be issued to the participants at the beginning of the trial. Participants will undertake the procedure whilst stationary for the first four days, and whilst walking gently on the spot for the remaining four days. The identity of these days will not be revealed to the blinded investigator who will later analyse the data. At the end of the thirty-day trial, the sensitivity and specificity of the device will be determined by assessing whether the data can be used to correctly identify the dates that participants induced nystagmus.

5.3 At the end of the thirty-day device trial, the participant will complete a questionnaire regarding their experiences using the device. The participant will then undergo caloric vestibular testing, whilst wearing the device.

5.4 Inclusion criteria

Adults aged 18 and over
Able to commit to 30 days of continuous wear of the trial device as per the study plan
Own a telephone

5.5 Exclusion criteria

Potential participants who have a history of dermatological disease or damage around the forehead
Potential participants who have an allergy to plasters and/or medical adhesives (similarly to materials used in the device)
History of dizziness, vertigo, balance disorders, or syncope
History of hypertension or cardiac problems (uncontrolled, acute or de-compensated phase)
History of ear disease, or previous ear surgery
History of psychotic/neurotic disorders or epilepsy
History of eye disease, or previous eye surgery
Pregnant or nursing mothers
Unable to follow the testing protocol

5.6 Clinical trial process

i. Posters advertising the trial will be placed around the University of East Anglia (UEA). The poster will also be distributed internally to staff and students at UEA by email (See appendix A for the email template, which includes a copy of the poster). Potential participants may request more information about the study by contacting the research team through the contact details given on the poster.

ii. Potential participants will be provided with a participant information sheet – see appendix B.

iii. At the consenting visit, the participant information sheet and consent form (see appendix C) will be fully discussed, and the potential participant will be invited to ask questions.

iv. If the participant agrees to be involved with this trial and signs a consent form, inclusion and exclusion criteria will be confirmed, and data collection forms will be filled in – see appendix D. In addition, if the participant agrees, a letter will be sent to the participant's GP detailing their involvement in the trial – see appendix E.

v. The participant will be provided with verbal and written instructions regarding a number of processes they are required to follow during the trial. There will be instructions provided and training given on how to activate, apply and take care of the device – see appendix F. There will be instructions and training on how to power, charge and activate the mobile phone - see appendix G. In addition, they will receive instructions on how to view the optokinetic video footage – see appendix H. A practical demonstration of the necessary processes required will also be provided.

vi. The participant will be provided with a trial diary – see appendix I. The diary lists the eight individual days when he/she will activate the device event marker and run the optokinetic video footage, as well as the dates of their face-to-face hospital visits. The diary also provides space for participants to record the precise date and time of each viewing of the optokinetic video, a space for recording deviations from the trial protocol, and for recording any other events that the participant feels could be relevant to the trial.

vii. A demonstration of all the necessary trial processes will be provided. The training process will follow a strict protocol - see appendix J. The participant will be asked to demonstrate that they can follow the protocol correctly. If they are unable to do this, they will be excluded. See appendix J. Before the participant is released with the device, it will be plugged into a computer and a battery will be installed into it. Once connected to a computer, it will appear as a portable drive. A blank text file will be transferred to the device to synchronise the device's internal clock. The device will start logging once it is detached from the computer. Whilst wearing the device, participants will be asked to stand a fixed distance from a wall chart and to look between certain positions on the chart. This will provide data which may be useful for device calibration, post-trial.

viii. On day four or five of the trial, the participant will be invited to return to confirm that they are getting on well with the device, there are no issues, the sensor array has been applied correctly, and that there have been no skin reactions. The participant will

undertake their second viewing of the optokinetic video during this visit, allowing the team to check that the protocol is being followed correctly.

ix. On day thirteen, the participant will be invited to return to confirm that they are getting on well with the device, there are no issues, the sensor array has been applied correctly, and that there have been no skin reactions. A member of the research team will employ the event marker and record the exact date and time that this activity is performed. After the device has been removed from the participant, the device will be plugged into a computer to re-synchronise the device's internal clock, which is performed by replacing the provisioning file (blank text file) on the device. Whilst plugged into the computer, the device's battery will be changed. An interim download of the data will be performed and submitted to the un-blinded investigator (SC), to confirm that the study protocol has be followed as instructed. If there is evidence that the participant has not been complying with the study protocol as instructed, future participant involvement in the trial will be terminated.

x. On day thirty-two (thirty-two to thirty-six), the participant will be invited to return the device, mobile phone and all accessories. At this point, the participant will:

a. Complete a questionnaire regarding their experiences using the device – see appendix K. We will use a predefined questionnaire that assesses a broad range of parameters related to user acceptability; both quantitative data as well as qualitative data will be acquired.

b. Perform three specific head movements; one in each plane of axis with the device in place – see appendix L.

c. Undergo caloric vestibular testing whilst wearing the device. Caloric testing will be completed according to British Society of Audiology recommended procedures (BSA 2010).

d. Whilst wearing the device, participants will be asked to stand a fixed distance from a wall chart and to look between certain positions on the chart. This will provide data which may be useful for device calibration, post-trial.

5.7 <u>Dry run participant</u>

A dry run of all trial processes will be conducted using the first participant recruited for the trial. This participant will undergo the same trial processes as the remaining participants, for example: recruitment, device and VR headset training, wearing the device for 30 days and return hospital visits. The device data recorded during the dry run will also be subject to the same processing steps as the data captured by the remaining 15 participants, such as: data download, re-segmentation, randomisation and nystagmus identification.

The purpose of the dry run is to test all trial procedures in a manner which is representative of how they will be performed by the remaining 15 participants. This test is important as the duration of the trial and the amount of data captured cannot be realistically simulated in advance. The dry run will provide an opportunity for the research team to refine their technique for executing the study protocol and to simultaneously confirm the functionality of the computer software used in a number of trial processes. In the event that any easily overcome, yet trial threatening issues are identified during the dry run (e.g. device bugs), the device's firmware may be updated prior to the remaining participants starting the trial. The

dry run participant will be subject to the same safety and ethical considerations as the remaining participants. For example, the same safety stopping criteria will apply and they will have the right to withdraw from the trial without providing a reason.

None of the research team will be blinded from the true identity of the randomised data derived from the dry run participant's data. Therefore, the identity of the data files containing nystagmus will be known to all members of the research team. This will allow the team to extensively examine the data to confirm that the software-dependent procedures and the device itself are functioning as intended. As a main objective of the trial requires the blinded investigator to process randomised trial data through a nystagmus detection algorithm, the eye movement data captured by the first participant will be excluded from the data used to measure the sensitivity and specificity of that algorithm. However, the participant's remaining data (e.g. safety data and caloric testing data) will be included in our final analysis.

5.8 Optokinetic Video Footage

An optokinetic video stimulus will be viewed by trial participants in order to induce physiological nystagmus. The footage consists of a black dot rolling across the screen. To ensure that the CAVA device is capable of recording a variety of eye movement characteristics, the speed and direction of the rolling dot will vary by participant. During enrolment, each participant will be assigned a specific video for use throughout the trial. 8 out of the 15 participants will be assigned rightward rolling dots (inducing left-beating nystagmus), and 7 will be given leftward rolling dots (inducing right-beating nystagmus). Three separate speeds will also be used (slow, medium and fast), with 5 participants assigned to each speed. In summary, the videos will be distributed as follows:

i. 3 participants assigned rightward rolling dots at a slow speed.

ii. 2 participants assigned leftward rolling dots at a slow speed.

iii. 3 participants assigned rightward rolling dots at a medium speed.

iv. 2 participants assigned leftward rolling dots at a medium speed.

v. 2 participants assigned rightward rolling dots at a fast speed.

vi. 3 participants assigned leftward rolling dots at a fast speed.

5.9 Data handling protocol

Once the device has been returned, the device data will be downloaded by the blinded investigator (JN). JN will use software to parse and re-segment the data into 30 full calendar days' worth of data and will upload the data to the University of East Anglia's research storage. The unblinded investigator (SC) will then download a copy of the data. SC will manually review the data to confirm that the device was capturing meaningful data during the trial. The success of the trial is determined in part by the sensitivity and specificity of the nystagmus detection algorithm used by JN, for which a *ground-truth* labelling of the data is required (i.e. whether nystagmus is present or not). In the event that a participant does not wear their device or does not view the optokinetic video, their diary may indicate the presence of nystagmus, when in fact it is absent from the data. The detection algorithm may then be incorrectly judged as having failed to identify a period of nystagmus. For this reason, it would be inappropriate to include non-meaningful data in the pool of randomised data passed to JN.

SC will judge whether data is meaningful by manually reviewing it for evidence that the device has been recording an informative signal (i.e. not simply a flat line), and in so doing determine if the device has been worn by the participant. SC will also examine the recorded signals for any evidence of the characteristic nystagmus waveform on the dates and times logged in the participant's trial diary. An absence of any nystagmus, irrespective of its quality, would suggest that the participant had not viewed the optokinetic video, despite having claimed to have done so. A false claim would be grounds for all of the participant's data to be deemed non-meaningful. All non-meaningful data will be excluded from further analysis.

After SC has confirmed that the device data is meaningful, he will assign each of the individual 'days of data' a unique identifier, and then reorder the files into a random order. Using a coding sheet only the un-blinded investigator (SC) will be able to determine the origin (participant and date) for each 'day of data'. The data will then be analysed off-line by the blinded investigator (JN). JN will apply a computer algorithm to the data files, which has been developed as part of the scientific research element of this MRC funded project. This algorithm will produce a list of the files which it has identified as containing nystagmus. The accuracy of this algorithm will be determined by SC, who will compare the predicted dates generated by JN to the *ground-truth* dates from the trial diaries. A document detailing the data download processes can be found in appendix M.

Trial participants will wear the device for 30 days in total. However, the first and last days of the trial (days 1 and 31, respectively) will be half days, as the device will be applied in the morning of day 1 and removed for the last time on the morning of day 31. During the re-segmentation process, the blinded investigator (JN) will append the data from day 31 to the end of the file from day 1, making 1 full day. Additionally, when the device is disconnected from a computer (e.g. during day 13's face to face visit), the device will start logging to a new data file. Therefore, where days comprise multiple data files, such files will also be joined together. Finally, the device's internal clock does not account for British Daylight Saving Time (DST), and so the re-segmenting procedure will also include adjustments for DST. Any periods of time where the device was not worn for a legitimate reason (e.g. during the face-to-face visits) will be excluded from calculations of user compliance and device functioning.

5.10 For each participant, the un-blinded investigator (SC) will submit the following anonymized data for statistical analysis by the project statistician:

i. Number of true positive days.

ii. Number of false positive days.

iii. Number of true negative days.

iv. Number of false negative days.

v. Duration of use for each day of the trial for each participant

5.11 <u>Verification of correct time-stamping, and correct event-marking</u>
Confirmation of correct time-stamping and event-marker function will be achieved by comparing the written record of when the event marker was employed with the downloaded record of when the event-marker was employed.

5.12 Verification of correct accelerometer functioning

This will be confirmed by reviewing data from day thirty-two of the trial.

5.13 Study activities and evaluations

Each participant's involvement in the trial will follow a predetermined schedule, as defined below. A detailed description of each activity can be found in the Clinical Investigation Flowchart (See appendix N).

Day	Activity	Location	Staff Member
- >7	PIS sent to potential participant	Home	R. Nurse / RA
0	Consent, enrolment and introduction	NNUH	JP
0	Device & headset training	NNUH	RA
0	Wall chart exercises	NNUH	RA
4-5	Face to face review	NNUH	R. Nurse / RA
13	Face to face review, battery change, timestamp and event marker test	NNUH	R. Nurse / RA
32-36	Trial hardware returned	NNUH	R. Nurse / RA
32-36	Questionnaire completed	NNUH	R. Nurse / RA
32-36	Accelerometer tests	NNUH	RA
32-36	Wall chart exercises	NNUH	RA
32-36	Caloric testing	NNUH	R. Nurse / RA / JFG
32-36	End of study	NNUH	R. Nurse / RA
0-36	Optional interim review	NNUH	R. Nurse / RA / JP

RA = Research Associate
JFG = Dr John Fitzgerald (Consultant Clinical Scientist)

5.14 Adverse event reporting

Timely, accurate, and complete reporting and analysis of safety information from this trial will be conducted in accordance with Good Clinical Practice. We will assess skin reactions according to the International Contact Dermatitis Research Group scoring system.

5.15 Policy for reimbursement of participant costs and expenses

Participants will be reimbursed for the inconvenience endured as a result of participating in this trial. This reimbursement will be staged according to the length of their involvement as detailed below. All payments will be provided at the end of the trial. Travelling expenses

and parking charges will be fully reimbursed. Payment may be withheld if the study materials are damaged or lost.

Drop out after one week	£100
Drop out or termination after two weeks	£200
Drop out after three weeks	£300
Drop out after four weeks (caloric testing not completed)	£400
Completion of the whole trial (4 weeks with caloric testing completed)	£500

5.16.1 Early participant termination procedure and policy

The purpose of early termination is to:

1. Allow early identification of poor participant compliance.
2. Allow early identification of device failure.
3. Allow early identification of safety issues.

Early termination would allow mitigation of valuable wasted time and resources.

5.16.2 *Process*

- At 13 days, device data will be downloaded, but not erased from the device.
- Data would be assessed by SJC.
- A decision for termination will be provided within 24 hours.
- A decision for early participant termination would be determined to be the - consequence of poor participant compliance in circumstances where data is being recorded, but there is a persistent period of eye or head inactivity during the day.
- A decision for early participant termination would be determined to be the consequence of poor participant compliance in circumstances where the device data shows that the device's electrodes have not been applied correctly to the face.
- A decision for early participant termination would be determined to be the consequence of poor participant compliance in circumstances where the trial diary has not been completed.
- A decision for early participant termination would be determined to be the consequence of poor participant compliance in circumstances where the trial diary or data captured indicates that the participant has repeatedly worn the device for periods exceeding 24 hours.
- A decision for early participant termination would be determined to be the consequence of device failure in circumstances where no data is recorded.

5.16.3 *Policy*

In cases of poor participant compliance, participant data would be omitted from final analysis. In cases of device failure, participant data would be submitted for final analysis.

5.16.4 *Safety stopping criteria*

If any evidence of skin irritation is visible during any of the return visits of a participant, including during any additional visits, then that participant's involvement in the investigation will cease. Additionally, if a participant reports an adverse event which has affected their safety and which could conceivably be linked to the use of the CAVA device, that participant's involvement in the investigation will cease. Data captured up until the point of

exclusion will be submitted for final analysis unless the safety issue in question is deemed to have affected the quality of the signal recorded.

5.16.5 *Other circumstances*

In cases of device misuse causing damage to the device, e.g. accidental exposure to water, trauma to the device, etc; participants will be terminated early from the trial, and data would be submitted for final analysis.

5.17.1 Early study termination procedure and policy

The purpose of early study termination is to:

1. Allow early identification of a consistent pattern of device failure.
2. Allow early identification of safety issues.

5.17.2 *Process*

- Participants will be encouraged to report any unusual device operations or safety concerns throughout their involvement in the trial, both in their trial diary and by contacting the research team.
- Adverse event reporting will be used to track and assess the risks identified.
- The safety stopping criteria (5.17.4) will determine whether the trial will be terminated on the basis of safety.
- Early study termination would be determined to be the consequence of a consistent pattern of device failure if 2 or more devices are found to have recorded no data, during any of the return visits.

5.17.3 *Policy*

In cases of device failure, participant data would be submitted for final analysis. For termination due to safety issues, data captured up until the point of exclusion will be submitted for final analysis unless the safety issue in question is deemed to have affected the quality of the signal recorded.

5.17.4 *Safety stopping criteria*

The study will be terminated if we identify any unforeseen safety issues which apply to the use of the CAVA device, and which constitute a likely and significant hazard to participant safety.

6 OUTCOMES & DATA ANALYSIS

6.1 Nystagmus identification

This will be derived for each participant by comparing the actual nystagmus data and the device-derived nystagmus data. Data will be collated to calculate an overall value for sensitivity and specificity for all participants – see appendix O.

6.2 Signal production

This will be calculated for each participant by appraising the percentage of non-useful data and number of drop-outs for each day of device usage, as well as for the entire thirty-day trial. Data will be collated to calculate an overall value for device reliability for all participants.

6.3 Device compliance

This will be calculated for each participant by appraising the percentage of time the device was worn for each day of the trial usage, as well as for the entire thirty-day trial. Data will be collated to calculate an overall value for device compliance for all participants.

6.3 Event-marker, timestamping hardware and accelerometer

For each participant, data derived during return visits will be assessed to confirm that the event-marker functions, that the timestamping hardware is accurate, and that the accelerometer provides appropriate data.

6.4 Appraisal of satisfaction questionnaires and safety information

A questionnaire will be completed by each participant at the end of trial to assess the comfort and acceptability of the device. Safety information will also be acquired throughout each participant trial. All data collected will be analysed using qualitative methods.

6.5 Appraisal of data from caloric vestibular testing

Data recorded using traditional caloric testing techniques will be compared visually to the data recorded by the device.

7 REFERENCES

Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease. American Academy of Otolaryngology-Head and Neck Foundation, Inc. Otolaryngol Head Neck Surg. 1995;113(3):181-5.

British Society of Audiology. Recommended procedures: The Caloric test. April 2010

Halmagyi GM. Diagnosis and management of vertigo. Clin Med 2005;5(2):159–65. Huh YE, Kim JS. Bedside evaluation of dizzy patients. J Clin Neurol. 2013;9(4):203-13

Molnar A, McGee S. Diagnosing and Treating Dizziness. Med Clin North Am. 2014;98(3):583-596

Phillips JS, Mallinson AI. Vertigo: diagnosis and management. BMJ Learning. http://learning.bmj.com/learning/module-intro/.html?moduleId=10016740. Accessed 1st March 2015.

Phillips JS, Mallinson AI, Hamid MA. Cost-effective evaluation of the vestibular patient. Curr Opin Otolaryngol Head Neck Surg. 2011.

Phillips J, Longridge N, Mallinson A, Robinson G. Migraine and vertigo: a marriage of convenience? Headache. 2010;50(8):1362-5.

Rauch S. Ambulatory Vestibular Monitoring. New Dimensions in Designing Medical Devices. 2008

Royal College of Physicians. Hearing and balance disorders: achieving excellence in diagnosis and management. Report of a Working Party. London: RCP, 2007.

McCaslin D. Electronystamography/Videonystagmography. Plural Publishing, 2012

Nazareth I, Yardley L, Owens N, Luxon LM. Outcome of symptoms of dizziness in a general practice community sample. Family Practice 1999;16(6):616–19.

Neuhauser NK, von Brevern M, Radtke A, Lezius et al. Epidemiology of vestibular vertigo. A neurotologic survey of the general population. Neurology 2005;65:898–904.
Roydhouse N. Vertigo and its treatment. Drugs 1974;7:297–309.

Serra A, Leigh RJ. Diagnostic value of nystagmus: spontaneous and induced ocular oscillations. Neurol Neurosurg Psychiatry. 2002;73(6):615-8.

Scuffham P, Chaplin S, Legood R. The incidence and cost of unintentional falls in older people in the United Kingdom. J Epidemiol Community Health 2003;57:740

Zimetbaum P, Goldman A. Ambulatory arrhythmia monitoring: choosing the right device. Circulation. 2010;122(16):1629-36.

7 APPENDICES

7.1 APPENDIX A: EMAIL TEMPLATE AND POSTER

Dear Department Manager,

My name is Jacob Newman and I am a research associate in the School of Computing Sciences. I am working on a project to develop a wearable medical device, which is hoped will aid the treatment of patients suffering from dizziness.

We are currently seeking healthy volunteers to take part in a clinical trial to evaluate our device. More information about the study, including details of how to get involved, can be found in the attached poster.

I would be most grateful if you could forward this email (including the poster) to the staff and students in your department. If you have any questions about this project, please get in touch.

Yours sincerely,

Jacob Newman

HEALTHY VOLUNTEERS NEEDED for a clinical trial

NHS
Norfolk and Norwich University Hospitals
NHS Foundation Trust

The Norfolk and Norwich University Hospital is seeking volunteers to participate in a clinical trial to evaluate a wearable medical device. It is hoped that the device will aid the treatment of patients suffering from dizziness.

Participation in the study requires you to wear a medical device on your face for up to thirty days. At the end of the trial, you would be asked to undergo a routine balance assessment test, known as a caloric test.

You may be eligible to take part if:

- You are aged 18 or over.
- You can to commit to wearing a medical device for 30 days.
- You are in good health.

You will receive up to £500 for taking part, and your travel expenses will be paid.

For more information, call (01603) 593054 or visit www.cava-project.org

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7.2 APPENDIX B: PARTICIPANT INFORMATION SHEET

This document has been produced as an independent standalone document.

7.3 APPENDIX C: CONSENT FORM

This document has been produced as an independent standalone document.

7.4 APPENDIX D: DATA COLLECTION FORMS

This document has been produced as an independent standalone document.

7.5 APPENDIX E: GP LETTER

This document has been produced as an independent standalone document.

7.6 APPENDIX F: INFORMATION REGARDING THE USE OF THE DEVICE

Please note: *The following instructions are extracts from the full "Trial Instructions for Participants" document supplied to each trial participant.*

Introduction

These instructions explain every aspect of using the device and its accessories during the 30-day trial. Dr Jacob Newman (Research Scientist) will go through this information with you and instruct you on everything you will be expected to do during the trial. If you have any questions, please ask him.

Please remember:

- You are required to wear the device for 23 hours a day, for a period of 30 days.
- We hope that you will take part in the entire trial, however you are free to withdraw from the trial at any time. The longer you participate in the trial, the more money you will receive at the end. You can receive up to a maximum of £500 if you complete the entire trial, including the balance assessment at the hospital.
- We request that if you already know of any reason why you will have to withdraw from the trial prematurely, please inform the research team as soon as possible.

Please familiarise yourself with the **CONTACT INFORMATION** presented in the *Important Information* section at the end of this document. It explains what you should do in the event of an emergency and how to contact the research team.

You have been given a trial pack which contains the following items:

1 x trial instructions for participants (this document)
1 x instructions for use
1 x device logging module
35 x sealed electrode arrays (35 each of left and right mounts)
1 x medical adhesive remover
1 x mobile phone
1 x mobile phone charging cable
1 x mobile phone charging adapter
10 x mobile phone screen cleaning wipes
1 x pack of antibacterial wipes for the VR headset
1 x virtual reality (VR) headset
1 x trial diary
1 x ballpoint pen

General Trial Instructions

DURING the trial, you **should** follow these rules and procedures:

- You **should** go about your normal daily activities whilst wearing the device.
- You **should avoid** looking out of the side window of a moving vehicle (car or train) as a passenger for a prolonged period of time. If you do, please record this activity in your trial diary.
- You **should not** use a swivel chair or spin yourself excessively. If you do, please record this activity in your trial diary.
- You may drink alcohol during the trial, however we request that you do not drink to the extent that you might experience a hangover and feel dizzy as a result. If you do experience dizziness as a result of alcohol consumption, please record this activity in your trial diary.
- You **should not** immerse the device in water (i.e. no swimming or showering whilst wearing the device. Avoid exposing the device to rain). If the device is accidentally or unavoidably exposed to water, you should make a note in your trial diary and contact a member of the research team for further assistance.
- You **should** remove the device once a day, for an hour, to allow you to clean and shower (see guide, *Removing the Device*).
- After washing, you **should** make sure that your skin is completely dry before reapplying the device and a new sensor array (see guide, *Putting on the Device*).
- You **should** only view the optokinetic stimulus on the 8 separate days listed in your trial diary (see guide, *Optokinetic Video Stimulus*). On the first 4 of these days you **should** watch the video while sitting or standing still. On the last four you **should** watch the video while walking gently on the spot. When you watch the video, you **should** make sure that you are in an open space, free from physical obstacles and psychological distractions. You **should not** view the optokinetic stimulus at any other time during the trial.
- You **should** make notes in your trial diary indicating the date and time of when you viewed the optokinetic stimulus. Also make note of any times you accidentally looked out of the window of a moving vehicle as a passenger, or of any unexpected events that occur during the trial
- If you have to charge the mobile phone, you **should** make a note in your trial diary, listing the date and time.
- You **should** also take note in your diary of any unusual device or sensor operation, or any other unexpected events that occurred during the trial.

At the **END** of the trial, the following activities will take place:

- On day 35 you will return to the clinic with the device, its accessories and all used and unused sensor arrays.
- We will ask you to complete a questionnaire on your experiences of using the device.
- We will ask you to perform some simple head movements whilst wearing the device.
- A medical scientist will perform a balance assessment on you (caloric testing) whilst wearing the device.
- You will be debriefed from the trial.

Device Instructions

The CAVA device is comprised of three main components: Two single-use electrode mounts that adhere to either side of your face, and an electronic, reusable logging module which stores the signal from the electrodes, and which rests behind the ear (Diagrams 1 and 2).

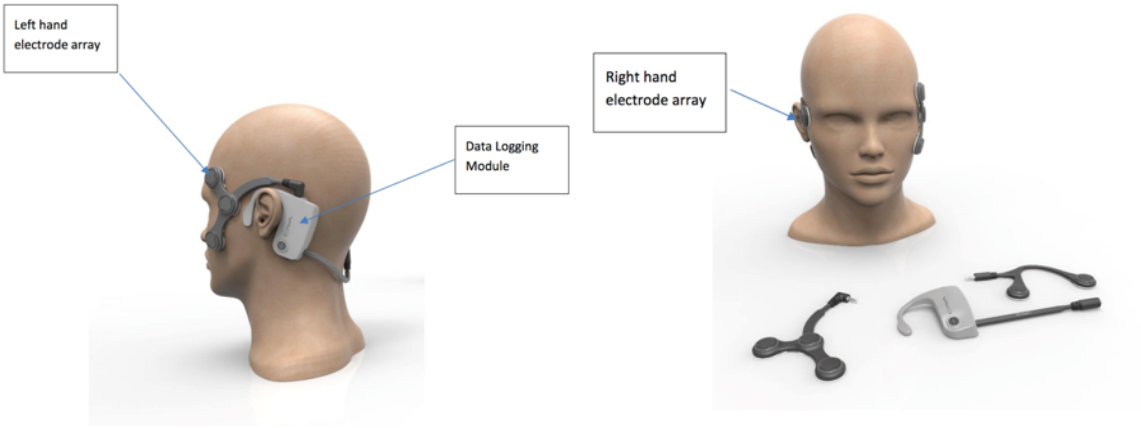


Diagram 1 - CAVA device components: Electrode mounts and logging unit.

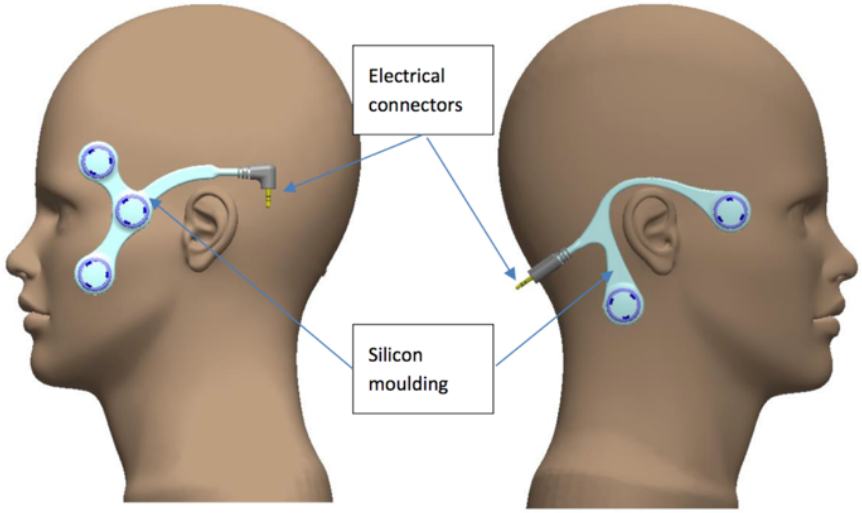


Diagram 2 - CAVA device positioning on the head.

Putting on the Device

- You do not need to switch the device on or off. It will remain powered throughout the trial.
- You **should not** reapply the same electrode mount more than once. Always use a new mount.
- The electrodes **should** be applied to clean skin, free from oils or lotions. Use soap and water to clean the areas where they will be applied. Make sure your skin is completely dry in the areas where the electrode's adhesive pads will attach to your face.
- You **should** use a mirror to help you apply the device to your face.
- If you wear spectacles, you **should** remove them until you have put the device on successfully.
- If you make a mistake which means that the electrodes won't be applied to the right place or will not stay in place, you should remove them and then start again with a new electrode array.
- Diagram 3 shows what to do before you apply the device and Diagram 4 shows how to apply the device to your face
- Once you have applied the device to your face, you **should** check the status of the device to ensure that it is functioning correctly. See the guide, *Checking the Status of the Device*, for instructions on this process.

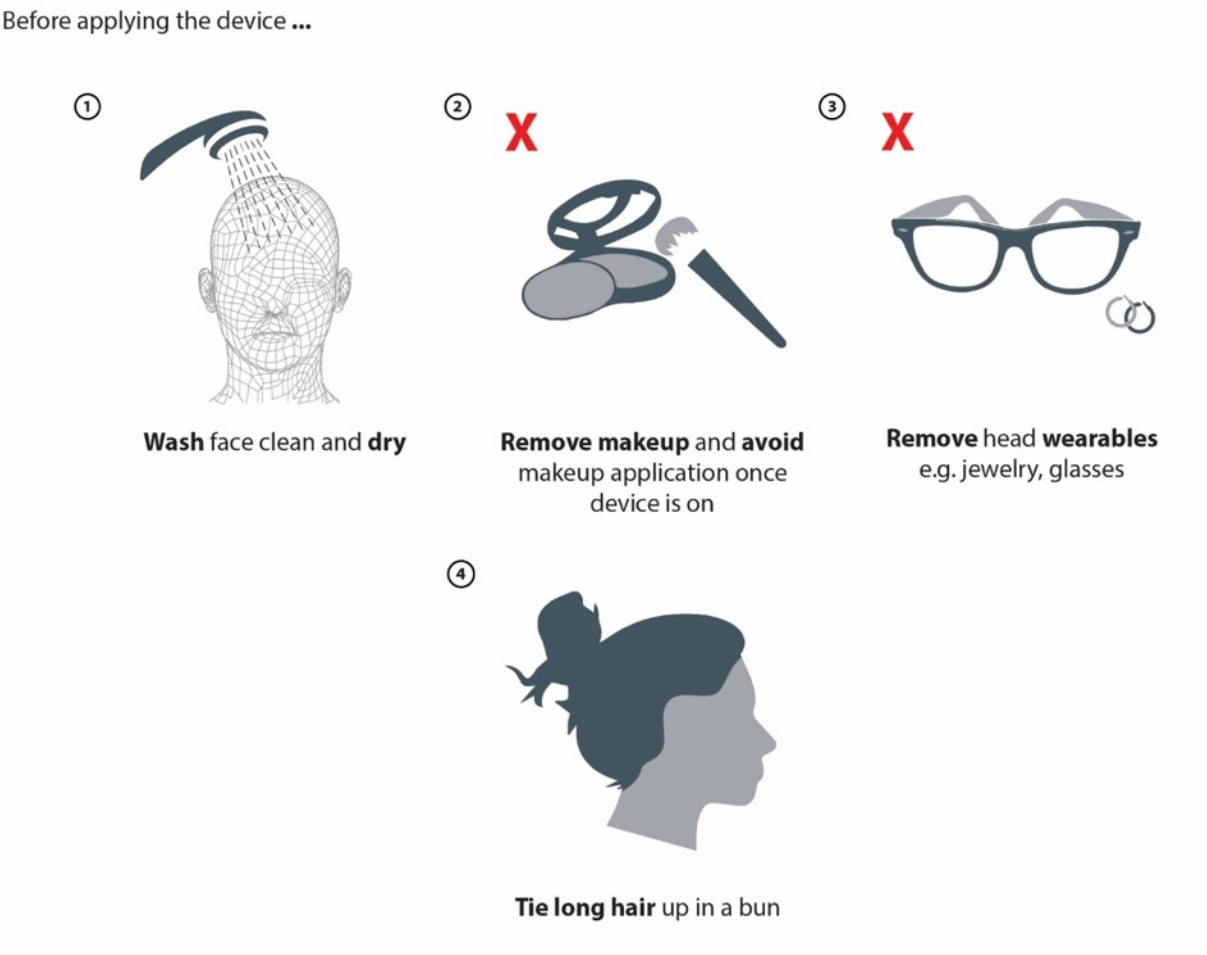


Diagram 3 – Before applying the device.

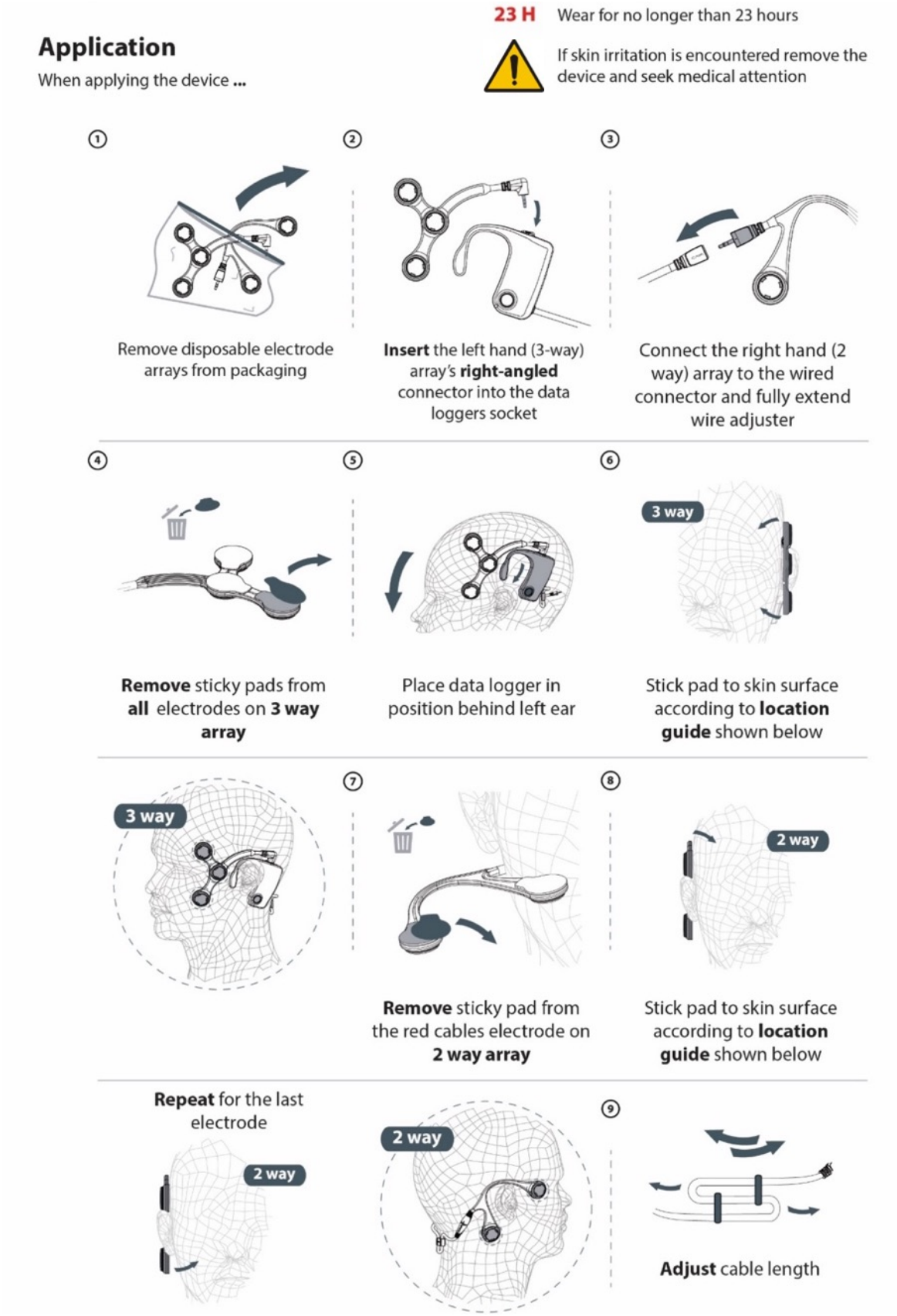


Diagram 4 – Putting on the device.

Checking the Status of the Device

- You can check the status of the CAVA device by pressing and holding the event marker button for 2 seconds. You will need to use a mirror to see the status LED on the device. See Diagram 5 below for a guide to this process.
- The device has four possible LED patterns: steady green (device/battery OK), flashing green (low battery), steady red (battery/device problem), flashing red (electrode disconnection).
- When you have attached the device to your face, you should check the status of the device. You will need to use a mirror see the status LED. If the device is connected and functioning correctly, a steady green LED will illuminate for 10 seconds. If any other pattern of LED is displayed please refer to the *Troubleshooting* guide in the *Maintenance* section of this document.

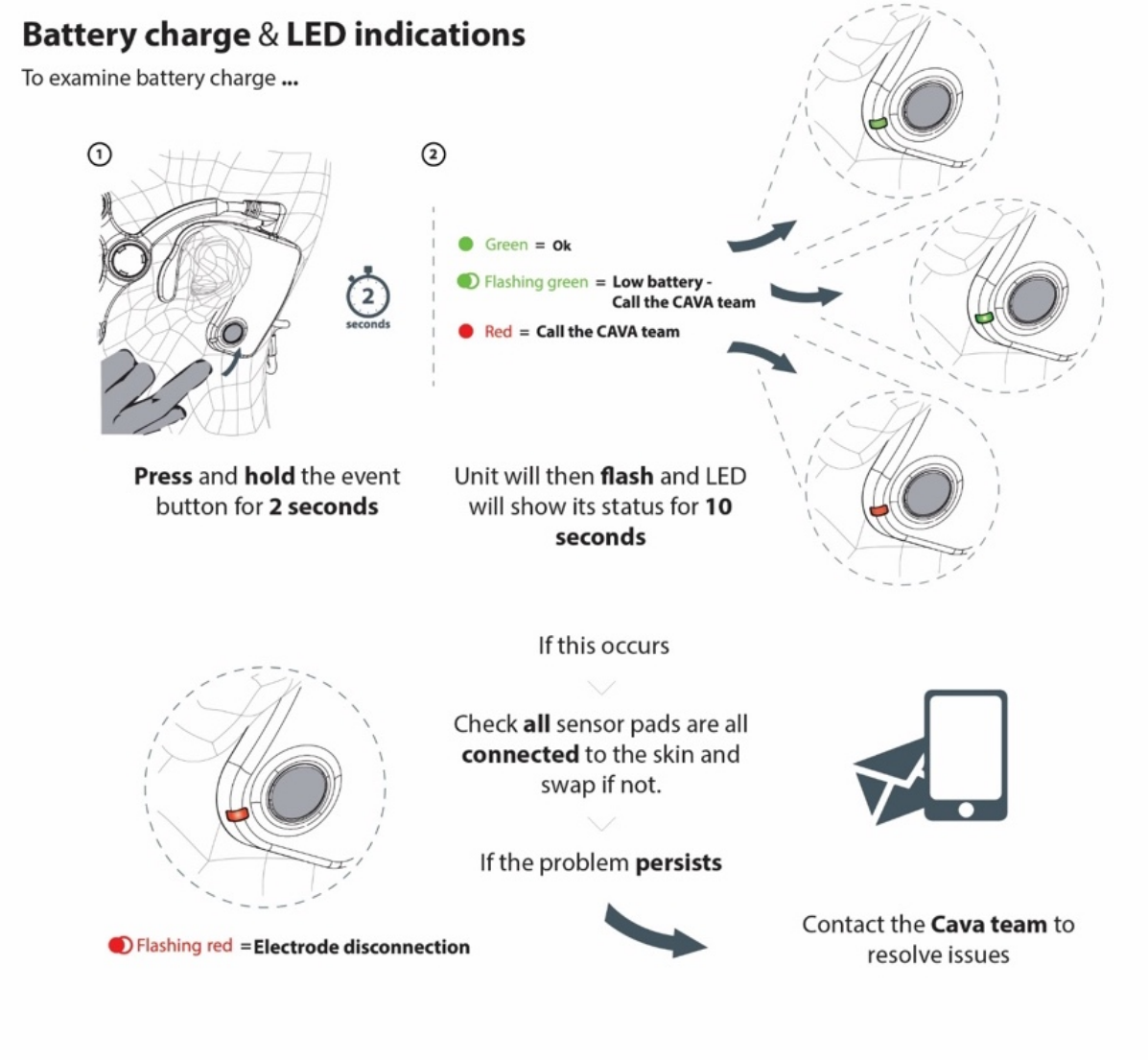


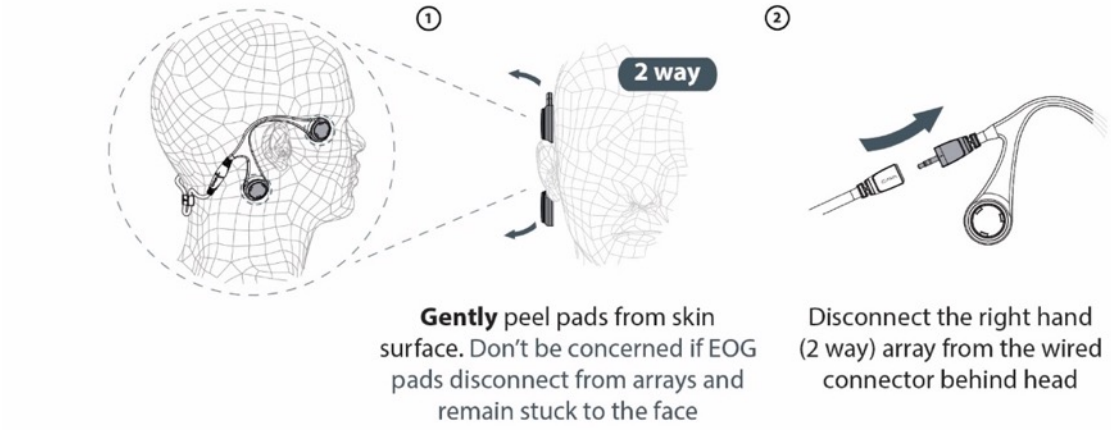
Diagram 5 – Checking the status of the device.

Removing the Device

- Once a day you **should** remove the logging unit and the electrode array for up to an hour to clean or shower yourself, being sure to clean your face.
- This hour may be in the morning or in the evening, but once you have selected a time you should try to stick to it, as you **should not** wear the device for more than 23 hours at a time.
- Once you have unplugged the electrode mounts from the logging unit, you **should** use the medical adhesive remover to help remove the electrodes.
- When removing each electrode from your face, you **should** support the skin next to the electrode so that it is under tension, before slowly rolling each electrode back onto itself.
- To remove the device, you **should** follow the instructions in Diagram 6, below.
- Once removed, you **should** detach the electrode mounts from the logging unit and store them in the bag provided. You will need to return them to the clinic at the end of the trial.

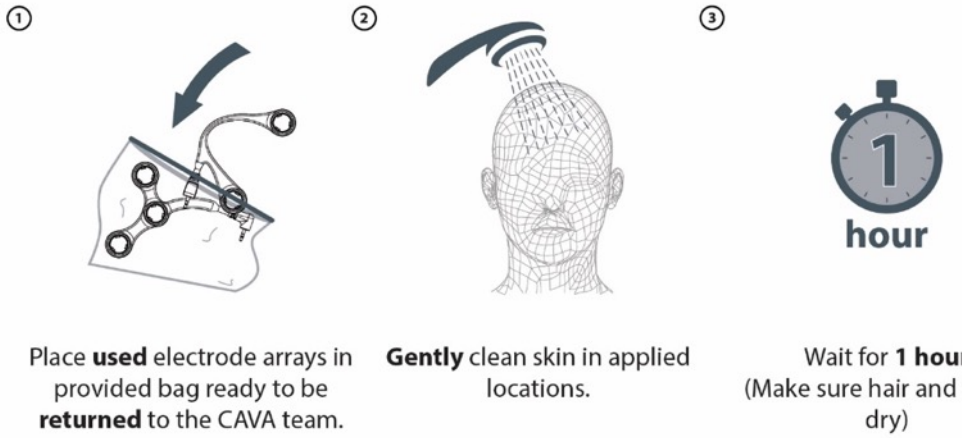
Removal

When Removing the device ...



Subsequent actions

After removing the device ...



Re-apply the device following **application** instructions > **Check** the sensors following **LED indication** instructions

Diagram 6 – Removing the device.

Cleaning Information

- Only clean the main sensor unit using a lightly damp cloth or non-alcohol containing cleaning wipe.
- Allow to dry before re-applying.
- On no account use a bleach or alcohol-based detergent on the unit.
- Before viewing the optokinetic footage, ensure that the phone screen and VR headset lenses are clean by using one of the Zeiss lens cleaning wipes you have been supplied with.
- After use, the cushioning on the VR headset should be cleaned using one of the antibacterial wipes supplied to you, and then wiped dry with a paper towel.

Charging the Mobile Phone

- The mobile phone should only be turned on for the purpose of viewing the optokinetic video stimulus. It should be switched off after you have finished viewing the video. The battery in the mobile phone should stay charged sufficiently to use it on 8 occasions during the trial. However, if the battery charge falls below 20%, you should recharge the phone as follows.
- You **should** insert one end of the phone charging cable into the bottom of the phone and the other end into the phone's wall adapter.
- You **should** plug the wall adapter into a plug socket and turn the socket on.
- Ensure that the charging icon is visible next to the battery indicator. If it is not, ensure that the previous steps have been followed correctly.
- The phone **should** charge to about 90% in less than 2 hours.
- Once the charge reaches over 90%, you **should** switch off the plug socket, unplug the cables, and resume the *Optokinetic Video Stimulus* steps where necessary.
- If the phone will not turn on at all or will not charge, you **should** contact the research team at the hospital (See **CONTACT INFORMATION** in the *Important Information* section at the end of this document).

Troubleshooting

- If, when checking the status of the device, the steady green LED does not illuminate, check that all the cable connectors are inserted correctly and that the electrodes are applied correctly to your face. When you recheck the status, if the green LED still fails to show, remove the device and repeat the procedure for putting on the device.
- If the green LED flashes or shows a red light, you should contact the research team (See **CONTACT INFORMATION** in the *Important Information* section at the end of this document).
- If the steady green LED does not show after following these instructions, you should contact the research team at the hospital for advice (See **CONTACT INFORMATION**).

Important Information

During the trial, please follow these rules:

- Please **AVOID** looking out of a side-facing window in a moving car or train as a passenger for a prolonged period of time. However, if this situation is unavoidable, please make precise notes in your diary of the dates and times that these events occurred.
- You may drink alcohol during the trial, however we request that you do not drink to the extent that you might experience a hangover and feel dizzy as a result. If you do experience dizziness as a result of alcohol consumption, please make precise notes in your diary of the dates and times that the dizziness occurred.
- Please **DO NOT** use a swivel chair during the trial or otherwise spin yourself excessively. As above, if this situation is unavoidable, please make notes in your diary.
- Please **DO NOT** view the optokinetic stimulus on days other than the 8 days listed in your trial diary.

The followings warnings apply to using the CAVA device. Failure to follow these practices may lead to injury or harm.

WARNINGS

- Only to be used by trial participant under the guidance of medical personnel.

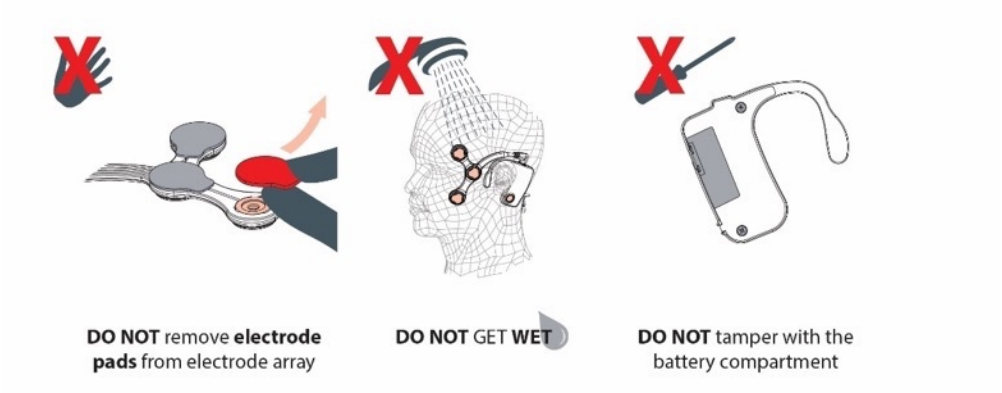
The device should not be used by:

- Users with a history of skin sensitivities / allergic reactions to materials used in the device or similar items such as plasters or medical adhesives.
- Users with inflamed or broken skin where the sensor is worn.
- Users who experience rashing or irritation should discontinue use and seek medical advice.
- Children and young adults less than 18 years old.
- Only connect the provided sensors to the main unit. On no account should the unit be connected to other devices such as USB chargers, laptops etc.
- Only clean the device using the instruction provided in this manual.
- Users engaged in activities which require the user of a safety personal protective equipment (e.g.: cycle helmet) must remove this device if it interferes with the safe operation of the protective equipment.
- Remove this device if you are passing through equipment which uses electromagnetic energy to screen or monitor people. This includes MRI, X RAY or CT scanners and devices like airport security scanners.
- Always make your healthcare carers aware of the fact you are wearing the trial equipment when attending clinics etc. A description card is provided at the end of the manual which can be used for this purpose.

The following cautions apply to using the CAVA device. Failure to follow these practices may affect the performance of the device.

CAUTIONS

- Avoid exposure to moisture and water. The device should be removed before bathing or washing.
- No user serviceable parts – The device should not be opened or disassembled



CONTACT INFORMATION

If you have a medical issue or medical question concerning the trial, please contact:

Ms Catherine Wright (Research Nurse) or Mr John Phillips (Surgeon)
Norfolk & Norwich University Hospitals NHS Trust
Colney Lane
Norwich
NR4 7UY
Tel: (01603) 286286

If you need to speak to the research team for any non-medical reason during the trial, please contact:

Dr Jacob Newman (Research Scientist)
University of East Anglia
Norwich Research Park
NR4 7TJ
Tel: (01603) 593054

Following is a list of example scenarios in which you **should** contact the research team:

- In the event of any unexpected issues or complications arising from wearing the device, immediately contact Catherine Wright (Research Nurse) or another member of the Research team.
- If you experience skin irritation or any other unexpected side effects whilst wearing the device, remove the device and immediately contact Catherine Wright (Research Nurse) or another member of the Research team.
- If the device will not turn on or will not display a steady green LED when applied to your face, contact Dr Jacob Newman (Research Scientist).
- If you have issues related to the mobile phone, including using or charging the phone, please contact Dr Jacob Newman (Research Scientist).
- If you have any other questions or concerns during or after the trial, do not hesitate to contact any member of the research team.

7.7 APPENDIX G: INFORMATION REGARDING THE USE OF THE MOBILE PHONE

Please note: *The following instructions are extracts from the full "Trial Instructions for Participants" document supplied to each trial participant.*

Notes on the Mobile Phone and VR Headset

The mobile phone supplied to you does not contain a sim card and is set to "airplane mode", which means that it cannot access Wi-Fi or Bluetooth. The phone is not intended to be used for any purpose other than viewing the optokinetic stimulus on the 8 days listed in your trial diary. The phone is fixed to the removable tray in the VR headset (Diagram 7). As described in the guide, *Optokinetic Video Stimulus,* the phone should only be turned on for the purpose of viewing the stimulus and should be turned off at all other times. The battery in the phone should remain charged for the duration of the trial, however, if its charge falls below 20% you should follow the steps in the guide, *Charging the Mobile Phone,* in the *Maintenance* section of this document.

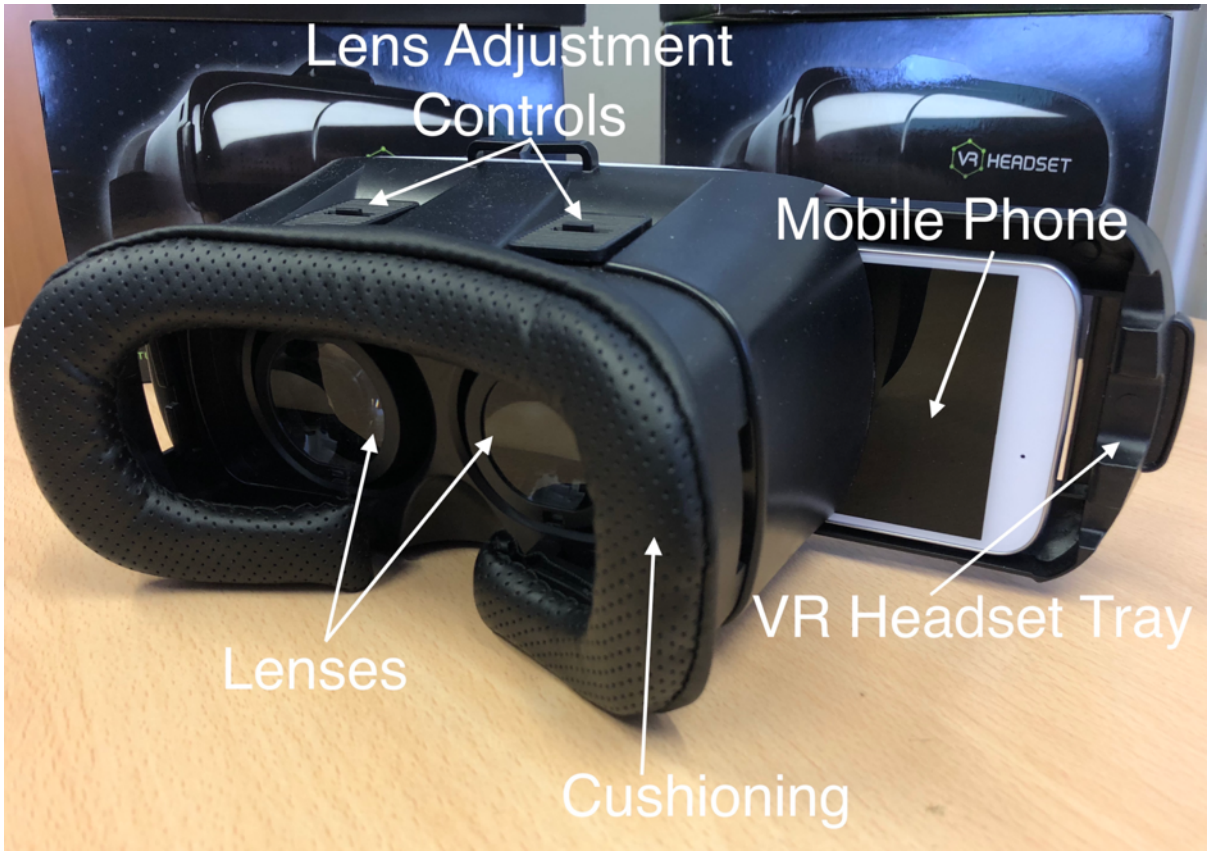


Diagram 7 - VR headset with headset tray partially inserted.

Before using the phone and headset, you should ensure that the phone screen and VR headset lenses are clean, using the lens wipes supplied to you. Instructions on how to view the optokinetic stimulus using the phone and headset can be found in the guide, *Optokinetic Video Stimulus.* These instructions also state that you should use the lens adjustment controls (Diagram 7) if the calibration image appears to be blurry or if you can see a double image. Sliding the controls forwards and backwards adjusts the focus, while left and right adjusts the distance between the lenses. Once you have viewed the video stimulus, you should wipe the cushioning on the VR headset using one of the antibacterial wipes supplied to you, and then wipe it dry with a paper towel. Remember to turn the phone off and store the tray inside the VR headset when it is not in use.

7.8 APPENDIX H: FOLLOWING THE NYSTAGMUS TESTING PROTOCOL USE OF THE DEVICE

Please note: *The following instructions are extracts from the full "Trial Instructions for Participants" document supplied to each trial participant.*

Please thoroughly familiarise yourself with these instructions before you attempt to watch the video stimulus.

- The optokinetic video stimulus is a 55-second video containing three segments. The video starts with a 20-second on-screen countdown, followed by the optokinetic stimulus, which is a 30-second video showing black dots rolling across the screen. Finally, the video ends by displaying a green background for 5 seconds.
- You **should** view the optokinetic video stimulus on 8 separate days of the 30-day trial. These dates are listed in your trial diary, provided to you by the research team.
- You **should** make a note in your trial diary of the dates and times that you viewed the optokinetic stimulus. You must also press and hold the event marker button on the device (for 1 second) at the start and the end of viewing the stimulus (Diagram 8).
- On each of the 8 days, you **should** use the VR headset and mobile phone to watch one play of the entire optokinetic video. On the first 4 of these days you will watch the video while remaining still, and on the last 4 you will walk gently on the spot.
- When you watch the video, you **should** make sure that you are in an open space, free from physical obstacles and psychological distractions.
- You **should** watch the video at some time between 10am and 12pm (midday).
- You **should** only watch the video if you have been wearing the device for at least 10 minutes.
- If you attempt to view the stimulus but you are unable to or something goes wrong, please contact Dr Jacob Newman (see **CONTACT INFORMATION** in the *Important Information* section), who will advise you on how to fix the issues you are having. If the delay stops you from viewing the stimulus between 10am and midday, you will be instructed you to view the stimulus in the afternoon or during the following day.

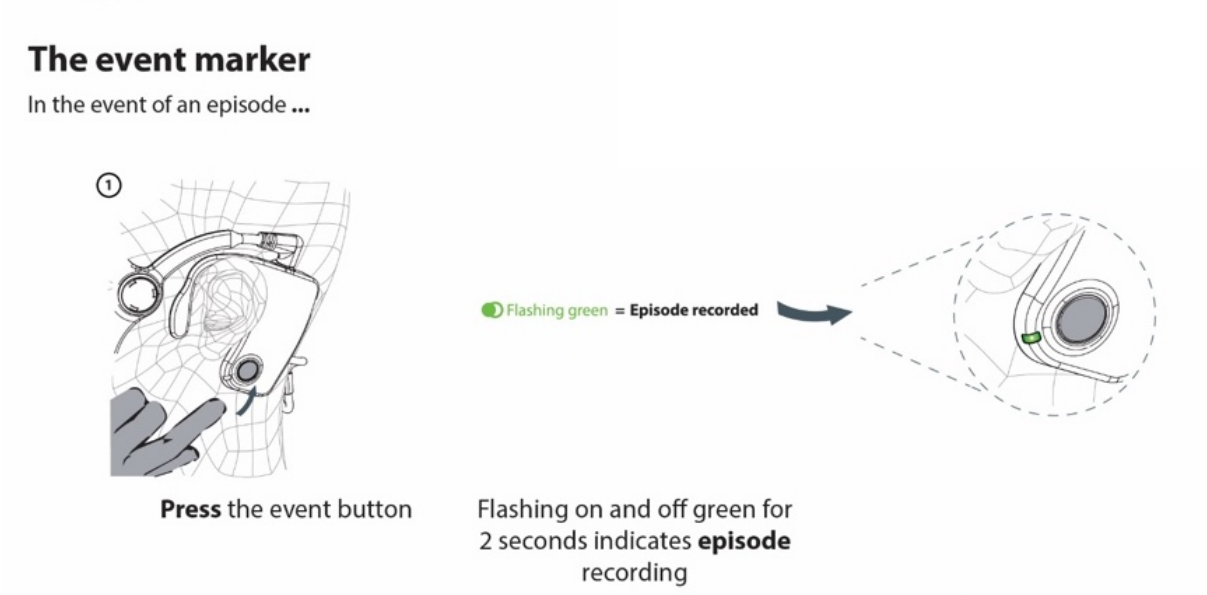


Diagram 8 – Activating the event marker.

To view the optokinetic video, you should follow these 13 steps:

1. Check the status of the device (*See the guide, Checking the Status of the Device*). If the status LED is red or flashing, you **should** contact the research team (See **CONTACT INFORMATION**).
2. Take the tray out of the VR headset.
3. Ensure that the phone screen and VR headset lenses are clean by using one of the Zeiss lens cleaning wipes you have been supplied with.
4. Turn the mobile phone on by holding the power button on the right-hand side until the screen turns on. Wait until the lock screen is displayed. Swipe upwards from the middle of the screen to unlock the phone, revealing the home screen.
5. If the phone has less than 20% battery power remaining, follow the steps in the *Charging the Mobile Phone* guide, in the *Maintenance* section of this document.
6. Open the **Kodi** app on the phone, then tap **Favourites.**
7. If you wear glasses, you **should** remove them now.
8. Tap on **calibration.png** and slide the tray back into the VR headset. Look at the image through the headset. If it is blurred, adjust the controls on the headset until it is clear. You may only have to follow this step once as the headset should remain calibrated. When complete, remove the tray from the headset and exit the image by pressing the screen for two seconds.
9. You are almost ready to view the optokinetic video, but before you do, you **should** read the following information and instructions:
    - The video will start with a 20-second countdown, giving you time to slide the tray back into the headset and to look through the eyepieces.
    - If the countdown starts but you are not ready to view the optokinetic footage, do not look at the phone until at least 1 minute has passed, then replay the video if necessary.
    - After the countdown, the stimulus will be shown. It is a 30-second clip of dots rolling across the screen.
    - On the first 4 days that you watch the video, you **should** stay still (sitting or standing) while watching the video.
    - On the last 4 days that you watch the video, you **should** walk gently on the spot while watching the video.
    - You **should** make sure that you are in an open space, free from physical obstacles and psychological distractions.
    - The video will end by displaying a green screen for 5 seconds.
    - You **should** try to follow every dot across the screen with your eyes.
    - You **should not** shut your eyes or look at the edge of the video.
10. When you are ready to watch the video, you **should** make a note of the date and time in your trial diary and press the event marker on the CAVA device (Diagram 5).
11. To watch the optokinetic video, tap on **opto_video.mp4,** slide the tray back into the headset, look through the eyepieces and wait for the rolling dots clip to begin. When the green screen is displayed, you may stop watching the video and move the headset away from your face.
12. When you have finished watching the video, remove the tray from the headset and turn the phone off by holding the power button until a button appears on the screen saying “Power off”. Press this button and then the “Touch to power off” button which follows it. You should slide the tray back into the VR headset.
13. The cushioning on the VR headset should be cleaned using one of the antibacterial wipes supplied to you, and then wiped dry with a paper towel.

7.9 APPENDIX I: TRIAL DIARY

Trial Diary

Please fill in this diary daily. Please use this diary to record the times you carried out each trial activity and to list any unexpected events that occurred.

Day	Date (*dd/mm*)	Trial Event	Time device taken off *hh:mm am/pm*	Time device put on *hh:mm am/pm*	Optokinetic video day	Time video viewed *hh:mm am/pm*	Accidental activities (looking out of train window, spinning on chair etc)	All other events (Discomfort, device won't turn on, electrodes won't stick etc)
1		First day wearing device	-		YES (STANDING OR SITTING STILL)			
2		-			NO			
3		-			NO			
4		Face to face review at hospital			NO			
5		Face to face review at hospital			YES (STANDING OR SITTING STILL)			
6		-			NO			
7		-			NO			

PARTICIPANT ID:_____

Day	Date (*dd/mm*)	Trial Event	Time device taken off *hh:mm am/pm*	Time device put on *hh:mm am/pm*	Optokinetic video day	Time video viewed *hh:mm am/pm*	Accidental activities (looking out of train window, spinning on chair etc)	All other events (Discomfort, device won't turn on, electrodes won't stick etc)
8		-			YES (STANDING OR SITTING STILL)			
9		-			NO			
10		-			NO			
11		-			NO			
12		-			YES (STANDING OR SITTING STILL)			
13		Face to face review at hospital			NO			
14		-			NO			
15		-			YES (WALKING GENTLY ON THE SPOT)			

PARTICIPANT ID:_____

Day	Date (*dd/mm*)	Trial Event	Time device taken off *hh:mm am/pm*	Time device put on *hh:mm am/pm*	Optokinetic video day	Time video viewed *hh:mm am/pm*	Accidental activities (looking out of train window, spinning on chair etc)	All other events (Discomfort, device won't turn on, electrodes won't stick etc)
16		-			NO			
17		-			NO			
18		-			NO			
19		-			YES (WALKING GENTLY ON THE SPOT)			
20		-			NO			
21		-			NO			
22		-			YES (WALKING GENTLY ON THE SPOT)			
23		-			NO			

PARTICIPANT ID:_____

Day	Date (*dd/mm*)	Trial Event	Time device taken off *hh:mm am/pm*	Time device put on *hh:mm am/pm*	Optokinetic video day	Time video viewed *hh:mm am/pm*	Accidental activities (looking out of train window, spinning on chair etc)	All other events (Discomfort, device won't turn on, electrodes won't stick etc)
24		-			NO			
25		-			NO			
26		-			YES (WALKING GENTLY ON THE SPOT)			
27		-			NO			
28		-			NO			
29		-			NO			
30		Last full day wearing device			NO			
31		Last day wearing device		-	NO			

PARTICIPANT ID:_____

If an entry will not fit in the diary table, please use this box instead. Please date your comments.

PARTICIPANT ID:_____

7.10 APPENDIX J: CLINICAL TRIAL TESTING PROTOCOL TRAINING

Device training
- Applying the device
- Removing the device

Mobile phone training
- Optokinetic video preparation
- Viewing of the optokinetic stimulus
- Maintenance of the mobile phone

Trial training
- Looking after the device
- When to view the nystagmus
- Using the trial diary
- When to visit the hospital

Dr Jacob Newman (JN) will demonstrate all aspects of the mobile phone training and device training to the participant. Following an initial attempt, during which they may ask questions and ask for assistance, they must demonstrate the procedures unaided in 2 consecutive attempts. Participants will be provided with written instructions describing the trial training, which they must read and explain to JN. They must show a clear understanding of the tasks that have to be performed during the trial.

Early termination criteria
All training procedures, except viewing of the optokinetic stimulus, will be judged visually. For example, it is clear visually whether the device training procedures (applying and removing the device) are being demonstrated correctly. Viewing of the optokinetic stimulus will be judged according to the quality of the nystagmus signal captured by the CAVA device, and by watching the participant's eyes while they observe the optokinetic stimulus on a screen. The instructions provided to the participants aim to elicit a "look" nystagmus response, which should produce a regular and visually identifiable nystagmus signal. Participants will be judged to have not followed the viewing instructions if nystagmus is either not present, or if it changes in a way which suggests a "stare" response is being produced. Failure to understand the trial training will be judged on the participant's ability to consistently read and explain the activities that they must perform during the trial.

Criteria:
- Failure to demonstrate the device and mobile phone training procedures correctly on 2 consecutive attempts.
- 3 consecutive failed attempts to demonstrate the device and mobile phone training procedures.
- Failure to accurately recite the trial training procedures on 3 consecutive attempts.
- A clear and repeated misunderstanding of the trial procedures.

7.11 APPENDIX K: PARTICIPANT EXPERIENCE QUESTIONNAIRE

Thank you for taking part in our study. Please fill in this short questionnaire to share your experiences of using the device. It should take about 10 minutes to complete. There is a space below each question where you can provide additional information if you'd like to. We may use your answers anonymously for research or promotional purposes – please let the team know if you are not happy for us to use the data in this way.

1 - How easy did you find putting on the device and sensors?

Very Hard 1	2	3	4	Very Easy 5

Comments:

2 - How easy did you find taking off the device and sensors?

Very Hard 1	2	3	4	Very Easy 5

Comments:

3 - How easy did you find sleeping whilst wearing the device and sensors?

Very Hard 1	2	3	4	Very Easy 5

Comments:

4 - How comfortable did you find the sensors on your face?

Very Uncomfortable 1	2	3	4	Very Comfortable 5

Comments:

5 - How comfortable did you find the device on your ear?

Very Uncomfortable 1	2	3	4	Very Comfortable 5

Comments:

6 - How much did the device interfere with your normal daily activities?

A lot 1	2	3	4	Not at all 5

Comments:

7 – During an average day, how aware were you of the device and sensors on your face?

Very Aware 1	2	3	4	Not at all aware 5

Comments:

8 - By the end of the trial, how self-conscious did you feel wearing the device?

Very self-conscious 1	2	3	4	Not at all self-conscious 5

Comments:

9 - Can you think of any ways that we could improve the device and sensors?
Comments:

10 - Please detail any other experiences or opinions you have relating to the device.
Comments:

Thank you for answering the questionnaire. Please hand it back to a member of the research team.

7.12 APPENDIX L TESTING PROTOCOL FOR THE ACCELEROMETER

Introduction

After each participant has completed the 30-day trial, they will visit the clinic to return the device and its accessories, and to formally debrief from the clinical trial. During their visit, they will perform a number of simple head movements in order to provide data that will be used to evaluate the performance of the accelerometer on the CAVA device. The participants will receive instruction and supervision from the research team (The Research Nurse and Research Associate) during this exercise. This document outlines the testing procedure for evaluating the accelerometer.

Testing Procedure

During their visit to the clinic, participants will be asked to perform three types of head movement activities (Figure 1): A head shaking motion (A), a head nodding motion (B) and a head tilting motion (C). These actions will be used to assess the accelerometer's capability to track motion in the yaw, pitch and roll axes. Each participant will perform these activities first at a "slow" speed and then at a "fast" speed. "Slow" means completing one instruction (e.g. look left) within approximately 4 seconds. "Fast" means completing one instruction within approximately 1 second.

(A) Head shaking:

i) Look forwards | ii) Look left | iii) Look forwards | iv) Look right | v) Look forwards

(B) Head nodding:

i) Look forwards | ii) Look down | iii) Look forwards | iv) Look up | v) Look forwards

(C) Head tilting:

i) Look forwards | ii) Tilt left | iii) Look forwards | iv) Tilt right | v) Look forwards

Figure 1: *The instructions for the three head movement activities.*

The three activities (A, B & C) comprise 5 separate instructions (i to v), and each activity will be repeated three times. Participants will be given time to practice each head movement and a member of the research team will be on hand to demonstrate the required movements. During data collection,

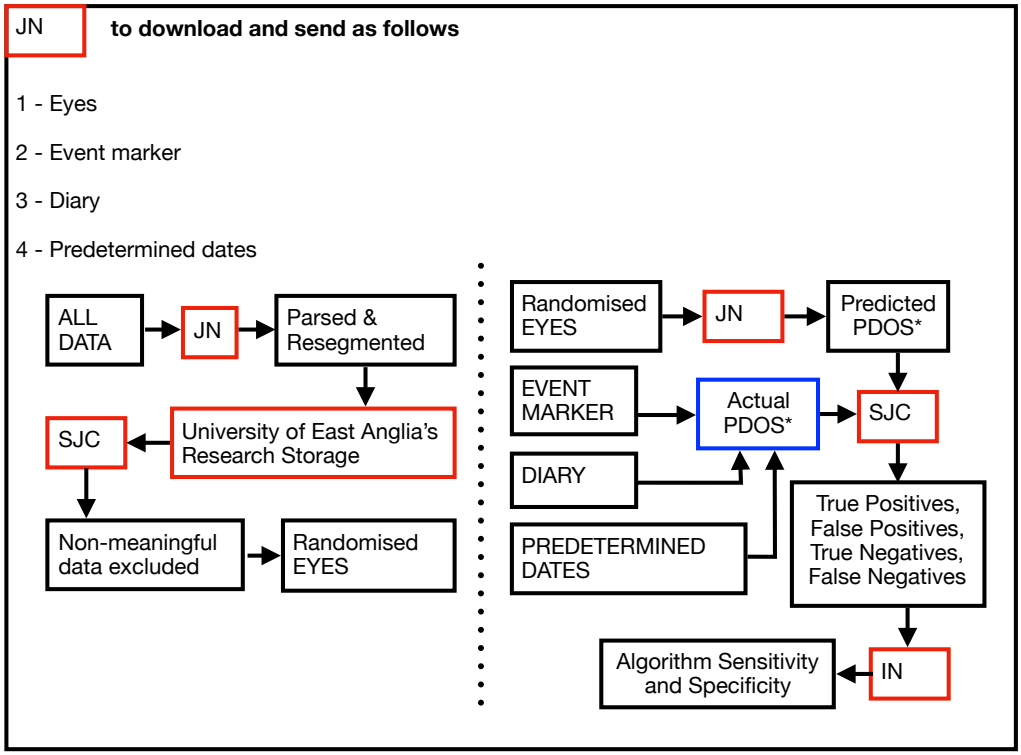
these instructions will be recited to the participant by a member of the research team, after which they must perform the associated action. Between instructions, each participant will confirm when they are ready to proceed. Prior to performing each instruction, the participant will press the event marker on the device, to allow each head movement to be correlated with the data captured by the device. A member of the research team will also record notes on the order of activities performed and any other details relevant to the procedure. The 3 activities and their 5 instructions are as shown in Figure 1.

The accelerometer will be evaluated based on whether a broad correlation is observed between the data captured and the head movements performed. The research associate will visually compare the data for this task. For example, if the participant moved their head to look left, then the research associate will look for evidence of a turn to the left in the accelerometer data. The performance characteristics of the accelerometer have been extensively tested and documented by its manufacturer, therefore we only seek to verify correct functioning of the device rather than its reported degree of accuracy.

7.13 APPENDIX M: DATA DOWNLOAD PROCESSES

Data Download

Once a participant has finished their involvement in the trial, the data from their device will be downloaded, transferred and processed as detailed by the following flowcharts.

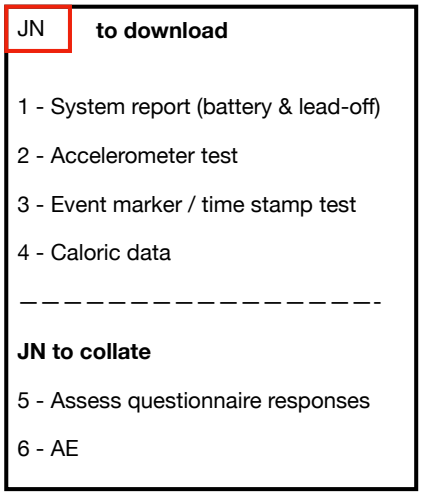


*** PDOS = Participant Dates of Nystagmus.**

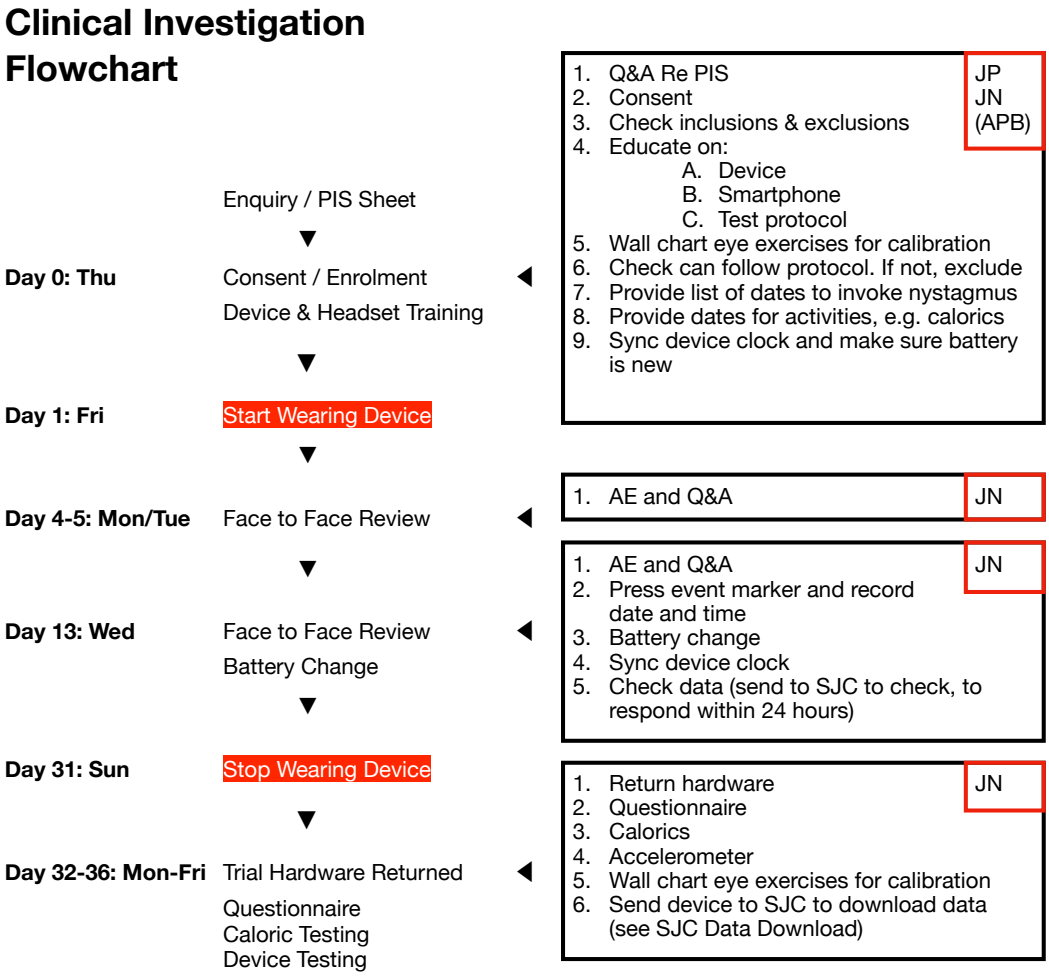
JN is blinded from the Actual PDOS. These dates are known to SJC, who produced the Randomised EYES data.

Data files summary

- System report: Contact time/uptime/battery status
- Eye measurements
- Event marker
- Accelerometer



7.14 APPENDIX N: CLINICAL INVESTIGATION FLOWCHART



7.15 APPENDIX O: STATISTICAL METHODS TO DERIVE SENSITIVITY AND SPECIFICITY VALUES

The success of a diagnostic device to diagnose disease can be appraised by calculating values for sensitivity and specificity. This trial has been designed to exceed the minimum number of nystagmus days and minimum number of total days required to demonstrate with statistical significance a sensitivity and specificity of over 95%. This standard was determined from data in the field of ambulatory cardiac monitoring (Zimetbaum 2010). The calculations below were performed by a medical statistician to determine the minimum number of independent tests required for each milestone.

		Device		
		Positive	Negative	Total
Participant	TRUE	83(97.7)	2(2.3%)	85
	FALSE	2 (2.3%)	83 (97.7%)	85
	Total	85	85	170

N for specificity =1.96^2 * specificity * (1- specificity)/ Margin error^2

N for sensitivity =1.96^2 * sensitivity * (1-sensitivity)/ Margin error^2

The minimum sample size was calculated using the formulae above. All that is required to calculate the minimum sample size is the sensitivity or specificity, and the margin of error. For a sensitivity and specificity of 98% with a maximum marginal error of 3%, for constructing the 95% confidence interval (0.9442 to 1.000), a sample size producing a minimum of 83.6 positive events is required. This is rounded up to 85 events. Therefore, a total sample size of 170 events will be required to test both a specificity and sensitivity of 98% with a marginal error of 3% for both. We define each separate day as an independent test. Each participant will artificially induce nystagmus on eight occasions. Twelve participants will provide 96 artificially induced participant positive events (12x8=96). Twelve participants will provide a total of 360 testing events (12x30=360). We will need to see the following outcome (table below), which will provide a 95% CI for sensitivity of 0.9506 to 1.000 and for specificity a 95% CI of 0.9646 to 0.9975. We have decided to recruit fifteen participants to allow for drop-outs.

		Device		
		Positive	Negative	Total
Participant	TRUE	94(97.92)	2(2.08%)	96
	FALSE	5 (1.89%)	259 (98.11%)	264
	Total	99	261	360