AVERT:
Acute Video-oculography for Vertigo in Emergency Rooms for Rapid Triage

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Trial ID: **AVERT**
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The Principal Investigator (hereafter referred to as Investigator) agrees to conduct the trial as outlined in this protocol with reference to national/local/international regulations and in accordance with current *Good Clinical Practice* (GCP) and *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH).

Any modification to the protocol must be agreed upon by both the Investigator and JHMI and documented in writing. By written agreement to this protocol, the Investigator agrees to allow direct access to all documentation, including source data, to authorized individuals representing JHMI (including monitoring staff and auditors), to Institutional Review Boards (IRB) and/or to regulatory authorities.

Signature: _____ Date: _____

Name Printed: _____

TABLE OF CONTENTS

APPENDIX

1. INTRODUCTION

1.1 ABSTRACT

This study seeks to improve clinical care for peripheral and central vestibular disorders by translating recent advances in vestibular physiology to clinical practice. Vertigo and dizziness lead to ~4.4 million US emergency department (ED) visits annually at a cost of roughly $10 billion. Most of the estimated 1 million patients with peripheral (inner ear) vestibular causes for their symptoms are over-tested, misdiagnosed, and undertreated. Each year in the United States (US), hundreds of millions of dollars are spent on neuroimaging (~$500M CT, ~$100M MRI) trying to detect the 3-5% of patients who have life-threatening posterior fossa strokes causing their vertigo—yet one-third of these vestibular strokes are missed. Accurate, early, and efficient diagnosis will save lives and reduce costs through prompt and appropriate treatments applied in the ED in real time.

Our team has studied dizziness in the ED for more than a decade. We have developed a new approach to differentiate benign peripheral causes from dangerous central ones by careful assessment of three vestibular eye movements (**HINTS**: **H**ead **I**mpulse, **N**ystagmus, **T**est of **S**kew) and hearing. Our approach enables rapid physiologic diagnosis at the bedside with greater accuracy than MRI brain scans in the first two days after the onset of acute, continuous vertigo or dizziness. This approach has been validated in over 200 patients. Similar, well-established bedside techniques (e.g., Dix-Hallpike test) work to diagnose intermittent, position-provoked vertigo. Unfortunately, these eye movement tests are unfamiliar to most ED providers and even to many specialists. A video-oculography (VOG) device that measures these eye movements quantitatively has the potential to transform diagnosis of acute dizziness and vertigo. The device is easy to use, measures eye movements accurately, and requires no more patient cooperation than a routine bedside exam of the cranial nerves by a specialist. We have shown initial proof that the device correctly diagnoses acute vestibular strokes.

The **AVERT** Trial (**A**cute **V**ideo-oculography for **V**ertigo in **E**mergency **R**ooms for **R**apid **T**riage) is a multicenter, randomized, Phase II clinical trial of VOG-guided vs. standard care to improve diagnosis and initial management for patients with a chief symptom of vertigo or dizziness suspected to be of vestibular cause. We will recruit 226 adults from four EDs. We will perform bedside VOG and hearing testing on all subjects, who will then be randomized to VOG-guided vs. standard care. In the VOG arm, patients will be diagnosed and treated according to a standard, predefined protocol guided by VOG results using automated, evidence-based decision rules. We will compare the impact of this VOG-guided care pathway relative to standard care on ED diagnoses, diagnostic resource utilization, costs of diagnosis, treatments applied, and short-term outcomes. A logistical pilot study will be conducted to refine study test procedures and data collection tools prior to initiation of the main trial.

We hypothesize that VOG-guided rapid triage (VRT) will accurately, safely, and efficiently differentiate peripheral from central vestibular disorders in ED patients presenting acute vertigo or dizziness, and that doing so has the potential to improve post-treatment clinical outcomes for these patients.

1.2 OBJECTIVES

1.2.1 To measure the impact of VRT on diagnosis and initial management in ED vertigo/dizziness.
1.2.2 To measure the impact of VRT on initial diagnostic work-up costs in ED vertigo/dizziness.
1.2.3 To compare short-term clinical outcomes in those correctly diagnosed vs. those misdiagnosed.
1.2.4 To develop a training library of educational materials related to eye-movement interpretation.
1.2.5 To measure the diagnostic accuracy of expert interpretation of VOG in ED vertigo/dizziness.

2. BACKGROUND

Rapidly differentiating acute central from peripheral vestibular disorders is a major public health problem relevant to NIDCD[1] and NIH.[2] There are ~4.4 million US emergency department (ED) visits for vertigo or

dizziness at a cost of ~$10 billion/yr.[3] The ~1 million with peripheral vestibular causes are over-tested,[4] misdiagnosed,[5] and undertreated.[6] Hundreds of millions of dollars are spent on brain imaging trying to rule out dangerous central vestibular causes such as stroke,[3] yet one third of vestibular strokes are missed initially.[7]

ED physicians rank vertigo as a top priority for developing better diagnostic tools.[8] Misconceptions[9,10] drive ED clinical practice, resulting in both overuse and underuse of diagnostic tests.[4] Patients with inner ear conditions such as vestibular neuritis (or labyrinthitis) and benign paroxysmal positional vertigo (BPPV) are often imaged and admitted unnecessarily[4] instead of being treated and discharged. Patients with dangerous brainstem or cerebellar strokes may be sent home without critical stroke treatments, sometimes resulting in serious harm.[11]

Over the past decade our team has documented the problem and built solutions to help close this quality of care gap.[2-7,9,10,12-43] Multiple research studies, systematic reviews, and guidelines confirm that correct diagnosis for vestibular neuritis,[44-46] BPPV,[47-51] and vestibular stroke,[4,21,29,38] should be based on vestibular eye exams. We have developed a clinical decision rule based on such eye exams that distinguishes central from peripheral causes in acute vertigo more accurately than early MRI.[4,21,38] Unfortunately, eye findings (e.g., head impulse, nystagmus type) require visual interpretation and can be subtle. Many clinicians are unfamiliar with their use.[5]

A device measuring these eye movements could transform diagnosis of vertigo in the ED. A portable video-oculography (VOG) device is approved by the FDA for vestibular testing. Its technical performance has been validated in the lab,[52,53] and it is already routinely used in the assessment of peripheral vestibular patients in otolaryngology clinics.[54-56] We recently showed that it can accurately diagnose strokes in the ED.[33] Integration of this device into daily ED practice could allow rapid and accurate diagnosis of vestibular neuritis, BPPV, and stroke—in total accounting for roughly one third of ED dizziness patients.[57,58]

3. STUDY PROCEDURES

Randomized controlled trial (individual patient randomization), parallel design (1:1) (Figure 1). Patients screened but not eligible for randomization will be enrolled in an observational arm that undergoes limited follow-up to ascertain for clinical outcomes, particularly stroke events.

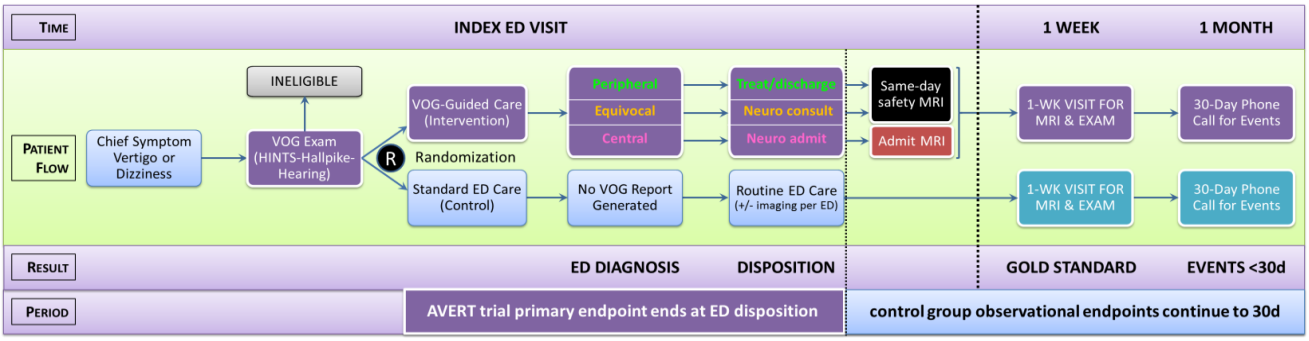

Figure 1. AVERT Trial patient flow. R = randomization. The VOG-guided rapid triage (VRT) algorithm selects a predetermined care pathway using decision rules. If the VRT algorithm diagnosis is peripheral, the patient will be slated for treat and discharge from the ED, followed by same-day safety MRI. ED providers may go 'off protocol' and insist on admission for safety, and may choose to consult another provider (e.g., ENT physician, vestibular physical therapist) for treatment of BPPV or vestibular neuritis if study treatment procedures appear ineffective. If the VOG diagnosis is equivocal, a neurology consultation is required, with subsequent management determined by ED provider and consultant(s) working together. The requirement for neurology consultation may be waived in cases where doing so could not feasibly be accomplished within a reasonable time frame; in such a case, the ED provider would determine subsequent management without the assistance of a neurologist. If the VOG diagnosis is central, the research team will request that the ED provider order a neurology consultation, neuroimaging (MRI), and admit the patient for further evaluation and testing, even if the ED provider believes the patient has a peripheral cause; a note to this effect will be placed in the patient's medical chart as part of the research record. The ED provider will make the final decision whether to admit the patient. If the ED provider elects to discharge the patient, this would be documented as a protocol deviation. Funds permitting, we will also obtain 6-month phone follow-up.

The logistical pilot study is being conducted to refine study test procedures, data collection tools and examine VOG-guided rapid triage (VRT) reports prior to initiation of the main AVERT Trial. Study coordinators will verify that VOG quantitative outputs are complete and accurate before results are submitted to the clinical trials data warehouse. A designated centralized eye movement expert will review all VOG tests (videos, tracings, summary values and the automated algorithm classification) after VOG data collection and provide an eligibility determination and diagnostic classification, independent of the automated VRT algorithm result. The expert human interpretation will either agree or disagree with the eligibility and classification determined by the automated algorithm. If disagreement occurs, the human expert classification will determine eligibility (for all) and VRT pathway of care (for those randomized to the VRT arm of the study). These findings will be compared to the automated results output from the VOG device for quality assurance and to evaluate testing accuracy and sensitivity of the VOG-guided results. This process will continue in the main trial, if necessary, until confirmation of VOG testing result accuracy is established and verified. Subjects enrolled in the logistical pilot study may undergo some, but not all, study procedures scheduled for the main trial.

4. ENROLLMENT CRITERIA & PROCESS

Performance sites are Johns Hopkins University (Bayview Medical Center [ED], Johns Hopkins Hospital [ED, clinic]), University of Michigan Hospital [ED, clinic], University of Illinois (OSF St. Francis Medical Center [ED, clinic]), The Mount Sinai Hospital [ED, Clinic], The Massachusetts General Hospital [ED], Massachusetts Eye and Ear [Clinic].

4.A. MRI standardization subjects

Healthy volunteers, up to 4, were recruited for the purposes of standardizing MRI machine settings and image acquisition protocols across sites. Some of the volunteers were staff traveling from the Coordinating Center (CC) to the performance sites in order to have the same person(s) undergo MRI scanning at each site to enhance MRI standardization across sites. Adults 18 years or older who were able to undergo MRI were recruited and granted their consent either under this protocol or in association with other locally IRB-approved protocols, depending on the study center. Prospective volunteers with a health condition that made it unsafe for the participant to have an MRI, including people with certain metal or foreign objects in their bodies, and pregnant women were excluded. Non-study staff volunteers were recruited in accordance with local IRB policies.

4.B. Dizziness subjects (ED patients at one of 5 academic-affiliated hospitals; consecutive sample during shifts)

For the main clinical trial, we expect to enroll (randomize) approximately 226 participants recruited from the ED across the five sites, approximately 75 per site (the Johns Hopkins and University of Michigan will each recruit a total of 75 subjects from all of their institutional ED sites combined). Recruitment will be consecutive during shifts (generally scheduled during the time window 8AM to 7PM weekdays). For the logistical pilot study, participants from the ED were screened and granted consent for participation across the three sites in a convenience sample to maximize effectiveness of trial procedure development.

4.1 Inclusion criteria

Adult (18 years and older) ED patients with all of the following (all determined pre-randomization):

1. VESTIBULAR SYMPTOMS: presenting symptom of “vertigo” OR “dizziness” OR “unsteadiness” (as defined by consensus expert definitions in the International Classification of Vestibular Disorders[25])
2. RELEVANT EXAM SIGNS*: pathologic nystagmus (spontaneous, gaze-evoked, or positional) by bedside VOG testing OR pathologic ataxia (gait, trunk, stance, limbs) by bedside ataxia examination
3. RECENT ONSET: symptoms AND signs* appear to be new or markedly worse in the past month

** Exam signs are required for randomization, but not for the observational arm*

4.2 Exclusion criteria

(Frequency and reasons for exclusion will be compiled and examined to plan for a follow-on Phase III trial)

Excluded from Pre-Randomization Screening

- Level 1 trauma or critical illness
- Altered mental status (e.g., delirium, dementia) that would preclude active study participation (this includes patients with abnormal mental state due to alcohol intoxication or illicit substance, which are known, easily-recognized causes of dizziness or vertigo presentations to the ED)
- Non-English speaking (enrollment of non-English speakers is not feasible given the logistics of identifying a translator and the need for rapid recruitment and randomization in the AVERT study; furthermore, the terms vertigo, dizziness, and unsteadiness may have different meanings in other languages[15])
- Known pregnancy (all women of childbearing age who are enrolled will undergo a urine or serum beta-HCG pregnancy test prior to MRI to confirm no pregnancy, per local institutional guidelines)
- Unable or unsafe to participate in screening, including VOG tests (as deemed by specific pre-enrollment risk assessment questions or ED provider and/or Study Coordinator judgment) including, but not limited to:
    - visual impairment sufficient to prevent visual fixation during the VOG testing
    - clinically-perceived risk to patient of participating in study (ED provider or staff concerns)
    - clinically-perceived risk to research staff (e.g., violence, blood/body fluid/respiratory precautions)
    - unstable cardiac status (given a single reported case of bradycardia with impulse testing[61])
    - acute cranio-cervical trauma or other condition (e.g., rheumatoid arthritis) that might lead to instability of the cervical spine that would be a contraindication to neck rotation during VOG testing
- Obvious general medical cause (as judged by treating ED provider) including, but not limited to, acute myocardial infarction, pulmonary embolus, pneumonia, urinary tract infection, drug intoxication, etc.

Excluded from Randomization (Eligible for Observational Arm Follow-up)

- Patient previously randomized in the AVERT Trial (*previously screened but not randomized are eligible*)
- Unable to participate fully with study follow-up (particularly MRI) including, but not limited to:
    - unable to return for follow-up testing within 30 days
    - unable to undergo MRI because of contraindications (e.g., pacemaker, metallic foreign body, pregnancy) or other reasons (severe claustrophobia, too large or too heavy for MRI scanner)

4.3 Study enrollment procedures

4.3.1 Sampling: Consecutive during shifts. Recruitment shifts will be Monday to Friday during peak hours (window between 8AM–7PM). Total ~35 hours per week.

4.3.2 Identification & Recruitment: A full-time study coordinator (SC) at each site will screen, recruit, and collect clinical data. The SC will be stationed in the hospital to systematically identify potential subjects and maximize early recruitment, using both active and passive (notified by ED staff) surveillance. We will actively pre-screen chief complaints under a HIPAA waiver, and approach potentially eligible patients for pre-screening and consent. After granting consent, patients will undergo VOG testing to determine trial eligibility.

4.3.3 Documentation for Ineligibility: Patients with a chief presenting symptom of vertigo, dizziness, or unsteadiness, whether eligible or not, who have been screened by study personnel at participating hospitals will be documented in the VISION Electronic Data Capture (EDC) system. All reasons for exclusion for each

patient not entered into the trial will be recorded. Each participating hospital will enter screening data into the VISION EDC system using a standardized electronic data capture procedure (see 'Digivey' below). Subjects completing the screening procedure will be identified as ineligible (a pre-screen or screen failure) or will be randomized. Monthly reports of subject accrual (pre-screened, screened, randomized) and other protocol compliance data will be maintained by the CC and monitored for site performance.

4.3.4 Logistical Pilot Subject Recruitment for Training: During the trial start-up period, each site was approved to obtain consent from up to approximately 250 subjects to collect preliminary data in order to test the data collection procedures and logistics. For the logistical pilot trial, enrollment occurs at the time of consent. These subjects who consented also served to test the VRT algorithm, and as training for site personnel in the administration of the VOG test and additional clinical exams. Consent was obtained from pilot subjects for participation, including 1-week and 30-day clinical follow-up. A sample pilot study consent document is found in v3.2 of the AVERT protocol document, but has been removed from the main trial protocol (v4.0). The consent procedure for these pilot study subjects differs from the full study participants, and the consent form and procedure identified the specific aspects of the study in which the patients were participating (which varies during the pilot period). The rationale for having a flexible pilot protocol was twofold: (1) *staged beta testing of data collection instruments and procedures* – for the initial patients we did a very limited data collection to test the consent procedures, electronic data capture forms and data transfers; subsequent patients went through the full 1-month data collection protocol, including follow-up; the final group of patients will complete the entire protocol, including randomization to VOG care; (2) *availability of funds for follow-up testing* – we sought to test the procedures for scheduling and conducting these exams at each site, but did not have sufficient funds for all pilot participants to complete the full protocol with follow-up advanced testing (MRI, vestibular lab tests).

4.3.5 Consent/Ethics: Patients will be offered enrollment using a standard written consent procedure. A sample AVERT (main) trial consent is provided in the Appendix. For the main trial, consent will be obtained during screening with enrollment into the trial occurring at the time of randomization. The testing involves minimal risk, identical to that in routine specialty care (neuro-otologic exam). Randomization is ethical because we are in research equipoise: (1) eye movement approaches to diagnosis are established[63]; (2) the VOG device has proven measurement accuracy[52,53,64,65]; but (3) the impact of VOG on clinical management and outcomes is uncertain. We will obtain VOG in all patients, then randomize to disclosure (VRT) or non-disclosure (standard care). The ethical nature of non-disclosure in diagnostic trials has been discussed in detail by Fost and Farrell.[66] The key reasons why such trials are considered ethical are that (1) patients are not being denied anything of known value, (2) disclosure may cause harm, and (3) subjects consented to the conditions of non-disclosure.[66] Trial risks and safety of head impulses (routine in specialty care) are summarized in Section 7 Risks.

Study personnel will obtain consent at two different time points for patients who are enrolled at St. Joseph Mercy Health System. The first consent will be obtained at the St. Joseph Mercy Health System for activities that take place at St. Joseph Mercy Health System. The second consent will be obtained at the time of the approximately 1-week follow-up visit at the University of Michigan for the University of Michigan activities. This is because the two sites operate under different IRB structures, despite their institutional affiliation.

4.3.6 Randomization: Patients who meet all of the inclusion and exclusion criteria using the above screening procedures and who provide consent will be randomized. AVERT randomization will initially assign each patient to a block size of 2 or 4, with a 50-50 probability; all site personnel will be masked to this block assignment. Then, when the patient is determined to be eligible for the study, the patient will be randomized using VISION's randomization framework, stratified by site and block size, so that all patients assigned to size "2" are randomized in blocks of 2 and all patients assigned to "4" are randomized in blocks of 4 at each site. In this way, it would be difficult for the site personnel to predict the next assignment, as they will not know which patients are in which block.

VISION's just-in-time randomization framework generates each random treatment at the moment a patient is randomized, instead of reading from a pre-computed table of treatments. This automatically compensates for

imbalances caused if a previously-randomized patient drops out of the study or accidentally receives the wrong treatment. When a random choice is made, VISION uses a cryptographically-strong SecureRandom random number generator. The SecureRandom algorithm computes the SHA-1 hash over a true-random seed value concatenated with a 64-bit counter, which is incremented by 1 for each operation. From the 160-bit SHA-1 output, only 64 bits are used. As a result, there is no known computer analysis which is able to predict the next "toss" better than 50% of the time.

4.3.7 Masking (blinding): Allocation will be known to SC, ED provider(s), and patients (VOG result added to the medical record in the intervention arm), in order to guide management in the ED. This allocation will also be known to a small number of personnel at the CC, including members of the biostatistics team. The Investigator will become unmasked to allocation status for patients who have completed their final diagnosis adjudication as part of the iterative VRT algorithm refinement process (see Section 5.1.1). Since this is a diagnostic (not therapeutic) trial, masking is most crucial for outcome assessors, who will adjudicate final diagnoses 'offline,' masked to allocation status. Procedures will be used to ensure maximal masking of the Final Diagnosis Adjudication Committee (FDAC) members to trial allocation. In particular, all testing protocols are the same between the two arms of the study other than the required "safety MRI" in the VRT arm (Figure 1). The risk of unmasking of allocation therefore relates to patients in the standard care arm who do *not* undergo clinical MRI. The FDAC process will proceed in two discrete stages separated in time: (1) based solely on ED index visit data *without* the safety MRI; (2) based on all clinical data through the 30-day follow-up. Study radiologists will be masked to the index visit scan purpose/type ("safety MRI" vs. "pathway MRI" vs. "clinical MRI"), so the presence or absence of an imaging study will not cue them to the allocation during the first stage of FDAC review. During the second stage of review, study radiologists will reference any prior imaging studies using standard language that prevents disclosure to the other FDAC members whether a prior imaging study was or was not available (e.g., "The present study was compared to any prior studies, if available, and revealed no evidence of interval change."). The actual FDAC review will occur approximately 1 month after these images are interpreted, so the neuro-radiologist, when reviewing this summary, will generally not recall which subjects did or did not have MRI imaging prior to the definitive, 1-week research MRI. If they do recall this information for a particular subject, they are instructed not to indicate this to the remaining FDAC members.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

5.1.1 Study Structure & Flow: Detailed study flow is illustrated in Figure 2 and Table 1 below, highlighting safety aspects where care in either arm differs from usual care, and the roles of ED providers and consultants in patient care in the intervention arm. The 30-day follow-up period after ED Index Visit will be the time window for analysis of primary endpoints. Although the VRT diagnosis and pathway decision will occur in real time, final adjudicated (correct) diagnoses will be determined by a masked, multidisciplinary panel of physicians using clinical data from the ED Index Visit, 1-week, and 30-day follow-up. Data from the 6-month follow-up (*funds permitting*) will not be used for primary trial outcome measures.

It is pre-specified that the VRT algorithm will be adjusted during the study period. Because this algorithm has not been used before in this specific study population, optimal cut points for various algorithmic parameters can only be approximated prior to the trial. The plan for adapting the algorithm will be refined during the logistical pilot study phase, in close concert with the study's biostatistical team. The general plan is to adapt the algorithm frequently near the beginning of the trial, and progressively less frequently during the course of the trial. The algorithm will be adapted during the logistical pilot phase as frequently as necessary to identify cut points that maximize total diagnostic accuracy. The algorithm will be adapted during the main trial at pre-specified intervals that will be identified in the statistical analysis plan following the logistical pilot phase. In the event of

coding issues or algorithm malfunction, the system will default all patients to the Equivocal arm and the expert human VT double-check will ensure an appropriate VRT pathway is selected for the patient (see section 5.1.3).

5.1.2 Study Flow (timing): Patients will be directly engaged at three or four time points: (1) ED Index Visit, (2) 1-week clinic follow-up, (3) 1-month phone follow-up, and (4) 6-month phone follow-up. After consent, screening data collection burden early in the ED Index Visit is anticipated to be ~30-45 min. Additional research data will be gathered after patients are randomized (another ~30 min). In our prior observational studies,[15] we have gathered research data from patients up to 60 min continuously. Total patient data collection burden in follow-up is anticipated to be approximately 6 hours, the bulk of which will occur during an on-site 1-week 'gold standard' follow-up visit: <1.5 hours for MRI; <3 hours for VOG, vestibular expert exam, repeating survey instruments; 1 hour for round trip travel; and 0.5 hours for 30-day telephone surveys. For scheduling purposes, the 1-week follow-up testing may be performed over two half days. Additional data will be gathered from the ED chart and electronic health record for the index visit and subsequent 30 days of follow-up. An additional phone follow-up will be made at 6 months to ascertain stroke diagnoses (*funds permitting*).

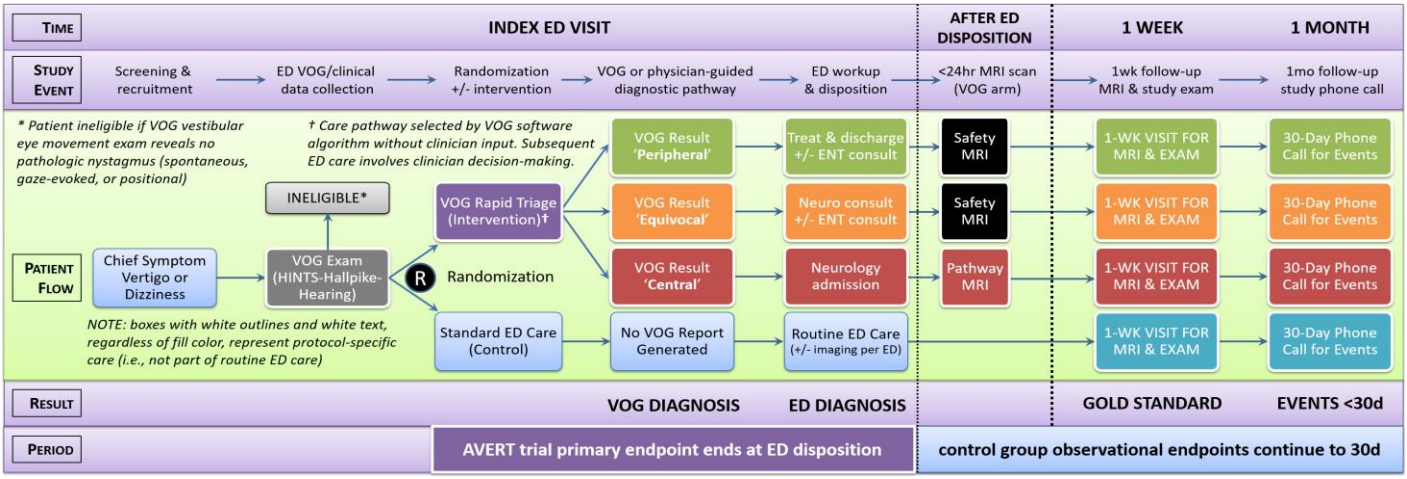

Figure 2. AVERT Trial flow (expanded). ED = emergency department; ENT = ear, nose, and throat physician; R = randomization; VOG = video-oculography; WK = week. VOG-guided rapid triage (VRT) selects one of three predetermined care pathways using decision rules implemented as a computer-based algorithm (detailed rules to be used and modified as needed):

a) If the VOG algorithm diagnosis is *peripheral*, the research team will request that the ED provider treat and discharge the patient, followed by same-day safety MRI. Treatment will be applied for VOG-based BPPV diagnoses by study personnel, while recommendations for medical therapies will be made for those with VOG-based other peripheral diagnoses (e.g., vestibular sedative treatments with or without steroid therapy for vestibular neuritis). ED providers may choose to go 'off protocol' and insist on admission for safety, and may choose to consult an ENT physician, vestibular physical therapist, or other provider (optional) for treatment of BPPV, vestibular neuritis, or other peripheral vestibular disorder. Safety MRIs will occur after an ED disposition decision is made (discharge, observation, admission). To optimize integration of VOG care pathways into local care delivery mechanisms, decisions regarding precise timing and location of immediate, same-day MRIs (<24 hours) were adapted to each site's specific needs during the pre-trial logistical pilot phase.

b) If the VOG diagnosis is *equivocal*, the research team will request that the ED provider order a neurology consultation, with subsequent management determined by ED provider and consultant together. The requirement for neurology consultation may be waived in cases where doing so could not feasibly be accomplished within a reasonable time frame (e.g., at a site where on-site neurology consultation is not routinely available); in such a case, the ED provider would determine subsequent management without the assistance of a neurologist. ED providers may choose to go "off protocol" and consult an ENT physician, vestibular physical therapist, or other provider (optional) for treatment of BPPV, vestibular neuritis, or other peripheral vestibular disorder if they believe the patient has an inner ear disease.

c) If the VOG diagnosis is *central*, the research team will request that the ED provider order a neurology consultation, neuroimaging (MRI), and admit the patient for further evaluation and testing, even if the ED provider believes the patient has a peripheral cause; a note to this effect will be placed in the patient's medical chart as part of the research record. The ED provider will make the final decision whether to admit the patient. If the ED provider elects to discharge the patient, this would be documented as a protocol deviation. The neurology consultation may be obtained after inpatient admission, if logistical circumstances in the ED or hospital so dictate. ED providers may choose to go "off protocol" and consult an ENT physician, vestibular physical therapist, or other provider (optional) for treatment of BPPV, vestibular neuritis, or other peripheral vestibular disorder if they believe the patient has an inner ear disease.

Table 1. Assigned care pathway group and associated VRT pathway and routine clinical care events

Assigned Clinical Pathway Group	Neurology consult at ED Index Visit	ENT or PT consult at index visit	Hospital admission at ED Index Visit	Same-day MRI (for safety)	Vestibular exam (1 wk)	Research MRI (1 wk)
VOG (peripheral)	Routine	Routine	Routine	Pathway (required)	Yes	Yes
VOG (equivocal)	Pathway (required*)	Routine	Routine	Pathway (required)	Yes	Yes
VOG (central)	Pathway (required*)	Routine	Pathway (required)	Pathway (required)	Yes	Yes
Standard care	Routine	Routine	Routine	Routine	Yes	Yes

ED = emergency department; ENT = ear, nose, and throat physician; PT = physical therapist; wk = week

* The requirement for neurology consultation in equivocal cases may be waived in cases where doing so could not feasibly be accomplished within a reasonable time frame; in such a case, the ED provider would determine subsequent management without the assistance of a neurologist..

Both Trial Arms (pre-randomization & follow-up): VOG exam determines eligibility

- patient approached for consent as early as possible during ED visit; randomization occurs after VOG testing
- algorithm exam protocol (HINTS-Hallpike-Hearing) is a ~20-minute data collection in the ED by the SC
- uses commercially-available recording equipment (portable VOG device, audiometer, tablet computer)
- examination protocol is standard in neuro-otologic specialty practice
- systematic 1-week (visit), 30-day (phone, records), follow-up post randomization

Trial Arm 1 VRT (intervention arm): VOG-based logic rules determine rapid triage pathway

- report includes direct device output (physiologic traces, quantitative measures) plus most likely diagnosis, category, and clinical trial care pathway (peripheral, equivocal, central) instructions
- the VOG results become part of the patient's clinical record

The roles of the ED provider in the care of patients in the VOG arm will be as follows:

- assess illness severity and appropriateness of the patient for VOG testing and the study protocol
- exclude obvious general medical conditions
- take over diagnostic decision-making for patients in whom VOG is equivocal (with consultant input, if available)
- intervene to deviate from VRT pathway if they are concerned about safety for patients in the VOG arm

Note: these are the same roles anticipated for ED providers if the VOG device were used for clinical practice

Trial Arm 2 Standard Care (control arm): usual ED care plus VOG exam, no VOG report generated

- no VOG automated interpretation or summary report will be generated; the computer-based randomization algorithm does not generate a VOG report or pathway using logic rules in the control (standard care) arm

The roles of the ED provider in the care of patients in the standard care arm will be as follows:

- assess illness severity and appropriateness of the patient for VOG testing and the study protocol
- exclude obvious general medical conditions
- all diagnosis, consultation, treatment, and disposition decisions will be made by the treating ED provider(s)

5.1.3 Expert Human VRT Double-Check: The VRT algorithm outputs in the intervention arm will be double-checked by expert neuro-otology fellows or faculty in real time to ensure accuracy; human judgment will "trump" VRT if there is disagreement (or if, for technical reasons, the real-time algorithm is not able to be generated – for example, as with internet connectivity problems or during development). The expert human double-check procedure will be in place at the start of the main trial, and we anticipate it will remain in place until the VRT algorithm is refined (as per pre-specified adaptations during the trial period) such that it appears accurate and safe.

Procedurally, the patient will be randomized electronically, with their VRT algorithm diagnosis determined electronically. If the patient is randomized to the VRT (intervention) arm, the on-call expert reviewer at the Coordinating Center will be notified (regardless of site) and the entire VOG recording will be available for immediate review and playback, in real time, along with key historical data. The review process is expected to take ~10-15 minutes. The review includes viewing a room camera of the test procedures, eye camera of the eye movements, and quantitative traces of eye and head. If necessary, the reviewer may contact the study coordinator to seek additional information. The double-check expert review procedure will NOT apply to those in the standard care arm (only those in the VRT arm).

In the VRT arm, the selected diagnosis is linked to the prespecified management recommendation per diagnosis. If the ED provider has any concerns with VRT-diagnostic category or specified management, they will be given the opportunity to talk with the reviewing vestibular specialist, if applicable, and if so desired. For as long as this human double-check procedure remains in place, any VRT-arm care recommended by the expert reviewer and endorsed by the ED physician will be considered clinically-indicated for billing purposes. For example, if the VRT algorithm suggests the patient has a vestibular neuritis, but the human reviewer changes the category to stroke, then the prespecified management pathways (including the stroke-related care) is considered clinically-indicated (e.g., ED index visit MRI, hospital admission). Alternatively, if the VRT algorithm returns an "equivocal" result and the expert reviewer changes the category to a specific vestibular condition, then the prespecified pathway for the vestibular condition (e.g., requires vestibular function testing for Menière's disease) will also be considered clinically-indicated.

6. CLINICAL AND DEVICE-BASED TESTING

6.1 Schedule of Evaluations

Test/Procedure	Screening & Recruitment	ED Index Visit & Hospitalization	1-Week* Visit Follow-up (+/- 3 days)	Phone Follow-up 30 days (+/- 7) & 6 months (+/- 1)
Consent	X			
Symptom History				
Structured Symptom History	X		X§	X§
Vertigo Symptom Scale (VSS-SF)		X§		X§
ABCD[2]	X			
Neurological Examinations				
NIH Stroke Scale (NIHSS)	X		X§	
Scale for the Assessment and Rating of Ataxia (SARA)	X		X§	
Calibrated Finger Rub Auditory Screening Test (CALFRAST)	X		X§	
Subjective visual vertical (SVV)		X§	X§	
Portable VOG (HINTS-Hallpike)	X		X	
Portable audiometry (air, bone hearing)		X§	X§	
Health Status Measures				
General Self-Rated Health	X		X	
Dizziness Handicap Inventory-Screening (DHI-S)		X	X	X
Modified Rankin Scale (smRSq)		X	X§	X
Neuro-QoL (multiple short form items)			X§	
RAND 36				X§
Charlson Comorbidity Index (CCI)		X§		X
MRI pre-screen	X		X (per local policies)	
MRI		X† (VRT arm)	X*	
Hospital admission		X‡ (VRT-C subarm)		
Neuro-otology examination			X	
Laboratory-based vestibular testing			X§	
Laboratory-based audiometry			X§	
EDPEC (satisfaction with overall experience)		X§	X§	
Resource utilization review		X	X§	X
Medical record review	X	X	X	X
Canalith repositioning treatment for active BPPV		X (VRT-P subarm)	X	
National Death Index review				X#

* Optimal timing for the follow-up Research MRI is days 3-7 after onset of symptoms, so timing of "1-week" follow-up will be scheduled accordingly.
§ Time permitting. Time constraints may make some of the testing, especially during the ED index visit, unrealistic under certain circumstances.
† MRI required for all participants in the VRT care arm (pathway MRI in VRT-C; safety MRI in VRT-P or VRT-E) unless ordered clinically; slinical MRI may or may not be ordered by the clinical care team for participants in the Standard ED-care (control) arm.
‡ Hospitalization may or may not be ordered by the clinical care team for any patient in either arm, but is pre-specified in the VRT-C subarm.
# For patients lost to follow-up at 6 months, we will search the National Death Index to ascertain their vital status and cause of death, if available.

6.2 Timing of Evaluations

6.2.1 Screening & Recruitment: Screening & recruitment is the start of the screening process and begins when the study team identifies or is notified of a potentially eligible subject. Consent will be obtained prior to performing VOG to determine trial eligibility. The potential research subject will be informed as part of the consent discussion that the screening procedures will determine eligibility for the trial and that signing the consent form does not constitute enrollment into the trial.

6.2.2 ED Index Visit & Hospitalization: The acute phase of the protocol is defined as day one (day of randomization) through ED discharge or hospital admission. All subjects randomized to the VRT arm will undergo study-specific procedures as outlined in Table 1 above. Randomization, which is determined by the Vision EDC, will occur immediately after eligibility screening if all eligibility criteria are met.

6.2.3 1-Week Clinic Follow-up: The follow-up phase of the protocol begins during the week following the ED Index Visit. All enrollees will undergo a 'gold standard' battery of tests during week 1 that will be used in

determining final diagnoses. The tests will include a vestibular exam by a neuro-otologist, repeat VOG, caloric testing, formal audiometry, and MRI as applicable. The timing of the Week-1 visit will be determined based on optimal MRI sensitivity for detecting stroke and logistical constraints. The optimal MRI timing window for diffusion-weighted images to detect stroke is roughly 3-7 days after the onset of continuous dizziness or vertigo symptoms, although MRI-DWI detects acute stroke with high sensitivity out to 14 days or longer. We will define "T0" (time zero) as the time when dizziness symptoms began or most recently worsened, leading to the ED index visit. We will define "T1" as the ED registration time at the ED index visit. Follow-up MRI should not occur prior to 72 hours after 'T0' to reduce the odds of a false negative follow-up MRI scan for those with stroke. The target window for MRI is 3-7 days after T0, but up to 14 days will be considered acceptable for the purposes of inclusion in the primary outcome analysis (see Statistical Analysis Plan below). If T0 is unknown or uncertain, we will use time from T1 to determine the appropriate follow-up window. For scheduling purposes, the 1-week follow-up testing may be performed over two half days, separated in time. Regardless of exact timing, this visit will be known as the "1-Week" or "Week-1" follow-up visit.

6.2.4 30-Day Phone Follow-up: All subjects will complete a phone interview 30 days (+/- 7 days) after the ED Index Visit. In the event that no 6-month follow-up is possible (e.g., due to funds limitations), the subject will be instructed that this is the final visit. 30-day phone follow-up (~20-30 min) will repeat symptom and quality-of-life measures (see Schedule of Evaluations) and determine hospitalizations or doctor visits for stroke-related diagnoses (e.g., stroke, aneurysm, heart attack). We will review relevant medical records for vascular events, outpatient visits (particularly neurology or otolaryngology), ED visits, hospitalizations, and neuroimaging. Regardless of exact timing, this visit will be known as the "30-Day" or "1-Month" follow-up visit.

6.2.5 6-Month Phone Follow-up: Funds permitting, all subjects will complete a phone interview 6 months (+/- 1 month) after the ED Index Visit. The subject will be instructed that this is the final visit. The 6-month phone follow-up and record review will be similar to the 30-day phone follow-up and record review in structure, but may be abbreviated. This visit is intended to provide data for a future Phase III trial with more longitudinal patient outcomes, and data at this time point will not be part of the AVERT Trial primary outcomes. For any patients lost to follow-up at this time point, we will search the National Death Index (http://www.cdc.gov/nchs/ndi/index.htm) using the patient's social security number or other identifiers to determine the patient's vital status and cause of death, if available.

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Consent: The informed consent process will occur during pre-screening, and must be completed prior to screening VOG testing. A signature on the consent form does not translate into enrollment in the study. Only after informed consent has been signed ***and*** all relevant inclusion/exclusion criteria have been met can a patient be randomized or enrolled in the observational arm of the study.

Informed consent must be obtained from the patient. Patients will not be enrolled if consent cannot be obtained.

The study center will document the informed consent process and the signing of the consent form in a written progress note, place a signed copy of the consent form in the hospital medical record, and keep the signed original consent form in the study subject file. A signed copy must be given to the subject as well. The study monitor will review and confirm the signed consent form while reviewing subject data collection forms and/or during monitoring visits (which may be conducted remotely or on site).

6.3.2 Structured Symptom History: SCs will gather standard identifying, demographic, and meta-data (e.g., triage severity); key clinical parameters related to dizziness (e.g., symptom onset, timing, triggers, type[42]), associated symptoms (e.g., tinnitus, hearing loss, other neurological symptoms), and key past medical history.

6.3.3 Vertigo Symptom Scale – short form (VSS-SF[166]): The VSS-SF incorporates two sub-scales with 8 items relating to vertigo-balance and 7 items relating to autonomic anxiety symptoms. Severe dizziness is defined as ≥12 points on the total scale. Subjects will complete the VSS-SF at baseline and 1-month visit.

6.3.4 ABCD^2 Vascular Risk Score[167]: The ABCD^2 score will be calculated to determine the risk for stroke in the days following the ED index visit. This measure will likely be incorporated into the initial diagnostic algorithm.

6.3.5 NIH Stroke Scale (NIHSS): The NIHSS will be done by a certified examiner during screening or shortly after randomization and then repeated at the 1-week visit.

6.3.6 Scale for the Assessment and Rating of Ataxia (SARA): SARA is an 8-item clinical scale that will be used to assess cerebellar signs. The scale assesses gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test. The SARA evaluation will be done during screening or shortly after randomization and then repeated at the 1-week follow-up visit.

6.3.7 Calibrated Finger Rub Auditory Screening Test (CALFRAST): CALFRAST is a rapid bedside assessment for hearing loss using finger rubbing. Results of this test at the ED Index Visit will be used as part of the diagnostic algorithm. The test will be followed post-randomization by portable audiometry in the ED to confirm the accuracy of the clinical assessment. We will obtain formal, lab-based audiometry at 1-week follow-up, in addition to repeating the CALFRAST test during the follow-up bedside exam, for comparison to audiometry.

6.3.8 Subjective Visual Vertical (SVV): Measurement of the patient's SVV is a routine part of bedside and laboratory vestibular testing. This psychophysical test assesses the patient's perception of verticality. At the ED Index Visit, testing will be accomplished using a standard 'bucket test.'[174] In the bucket test, the examiner holds a large bucket in front of the patient's face so that they are peering at the floor of the bucket. A straight line is displayed in the floor of the bucket. As the examiner rotates the bucket slowly, the patient is asked to notify the examiner when they believe the line to be completely vertical (i.e. parallel to gravity). The bucket is pre-calibrated, and the examiner records how far from true vertical the bucket line is when the patient believes the line is vertical. The test will be repeated at the 1-week follow-up. Depending on site-specific procedures, tests may be performed using the bucket, a mechanical light bar (see Laboratory-based vestibular testing), or both.

6.3.9 Portable VOG – HINTS-Hallpike: Using the ICS Impulse 3-dimensional VOG (horizontal-vertical-torsional channels), trained SCs will record eye movements, including VOR gain (horizontal head impulses); nystagmus—spontaneous (with, without fixation), gaze-evoked, positional (Dix-Hallpike [Nylen-Bárány] plus supine roll positional tests[50]), head shaking[104]; and eye alignment (alternate cover for skew deviation[60]).

As per standard practice, testing will occur under conditions of visual fixation and with vision denied. Vision will be denied using the manufacturer's FDA-approved disposable occluder and eyepatch or a study-designed drape affixed to a simple plastic headband. The manufacturer's disposable vision denied solution is comprised of one sticky patch that is fully opaque for the non-test (left) eye and a cup inserted into the goggles frame that allows the infrared camera to record eye movement in the recording (right) eye. Both pieces have a mild adhesive backing and are applied to the orbital rim of each eye. The materials have passed biocompatibility testing. After testing, the patches are gently removed by slowly releasing the adhesive from the skin. The study-designed external drape is intended to speed testing during recruitment by eliminating the need to remove the goggles, affix the adhesive patches, replace the goggles, recalibrate, and then remove the adhesive patches.

During testing, we will record video images of the eye movement examination for the following purposes: (1) final diagnosis adjudication for the main trial outcome of diagnosis accuracy; (2) monitoring adherence to trial examination protocols; (3) additional research questions (e.g., concordance between expert eye movement interpretation and results of quantitative recordings and algorithmic interpretation; assessing head tilt and ocular counter-roll as signs of central vs. peripheral disease); and (3) generating an educational library of teaching videos, as articulated in the AVERT grant proposal. Images will include the following: eye-only videos (non-

identifiable), room camera videos of most test procedures (potentially identifiable), partial-face close-up eye movement exams (potentially identifiable), and full-head/face images for head tilt (identifiable).

Identifiable images will only be used outside the research study team (e.g., for education or academic publication) if the subject elects this option when signing the consent.

6.3.10 Portable Audiometry: SCs will use portable audiometry headphones to record hearing in each ear (air and bone conduction thresholds). SCs will be properly trained in hearing testing and assessment (e.g., conductive vs. sensorineural loss). Tympanograms/acoustic reflexes will be obtained at 1-week formal audiometry follow-up. Repeat portable audiometry may be performed for test-retest reliability and validity relative to lab audiometry.

6.3.11 General Self-Rated Health Status: We will use two single-item general self-rated health measures to assess current health status and recent changes in health status at baseline, 1-week, and 1-month.

6.3.12 Dizziness Handicap Inventory – Screening (DHI-S[169]): The DHI-S is a 10-item, self-reported, screening version of the full DHI and will be used to identify difficulties that the subject may be experiencing because of dizziness or unsteadiness. Subjects will complete the DHI-S at baseline, the 1-week visit and the 1-month visit.

6.3.13 Simplified modified Rankin Scale questionnaire (smRSq): The smRSq is a shorter, telephone-enabled version of the standard modified Rankin stroke-related disability score. The smRSq will be assessed at baseline and at the 1-week and 1-month follow-up visits to determine a mRS score.

6.3.14 Neuro-QoL: The Neuro-QoL is a set of self-report measures that assess health-related quality of life by evaluating symptoms, concerns, and issues that are relevant across different neurological disorders. Subjects will complete multiple short form items from the Neuro-QoL at the 1-week visit.

6.3.15 RAND 36-Item Health Survey (RAND-36[168] v1.0): The RAND-36 uses 36 questions to measure functional health and well-being. Subjects will complete the RAND-36 at the 1-month follow-up. This instrument is made up of the same 36 questions as the Medical Outcomes Study Short Form (MOS SF-36) but uses a different scoring algorithm (http://www.rand.org/health/surveys_tools/mos/36-item-short-form.html).

6.3.16 Charlson Comorbidity Index (CCI): The CCI is a composing scoring measure of medical comorbidity based on the presence or absence of 19 specific conditions and the patient's age. The CCI will be assessed at the ED Index Visit and updated at 1-month based on medical chart review.

6.3.17 MRI pre-screen: All patients will complete an abbreviated set of questions related to magnetic resonance (MR) pre-procedure screening during the Screening & Recruitment period to determine eligibility. Patients with known contraindications to MR imaging will be excluded from the trial. For those randomized, standard MRI pre-screening will occur per local institutional policies prior to safety (ED Index) or research (1-week) MRI.

6.3.18 MRI: ED Index Visit MRIs differ from Week-1 research follow-up visit MRIs (Table 2). To maximize trial safety, all patients in the VOG arm of the study will undergo stroke protocol (safety; 1.5 Tesla) MRI with non-contrast MRA to minimize risk that a patient is erroneously discharged with a stroke. VRT-arm subjects with suspected central lesions will be admitted for stroke care and undergo clinical stroke protocol MRI with MRA as part of the required trial care pathway. VOG care patients slated for discharge will undergo same-day safety MRI if they have not had a clinical MRI. Stroke-protocol images (for safety or based on pathway VRT-C) will not be specifically adjusted or harmonized for the research study; they will use standard clinical protocols, so as to minimize clinical disruption in the ED and radiology department. Although the protocol requests a non-contrast MRI/A (to minimize total contrast dose, in light of Week-1 contrast-enhanced MRI), the patient's clinical providers may request contrast-enhanced imaging be added if clinically indicated for patients without contraindications to contrast. All enrollees will undergo a Week-1 gold-standard (3 Tesla with or without contrast) MRI (stroke, internal auditory canal sequences pre-/post-contrast, if applicable). A 1.5 Tesla basic stroke protocol MRI will be obtained if scheduling conflicts or institutional policies prevent the use of a 3T scanner. The Week-1 MRI protocol has been optimized to include images to detect posterior fossa stroke as

well as other posterior fossa and vestibular lesions (e.g., demyelinating lesions, cerebellar tumor, acoustic neuroma). The Week-1 research MRI acquisition protocol was adapted at the start of the study for each site's MRI technology (GE vs. Siemens, 3 Tesla) by the principal study neuroradiologist. The optimal MRI window is described in 6.2.3.

The rationale for obtaining the delayed gold-standard MRI is that the sensitivity of MRI for detecting stroke is much greater at days 3-7 than in the first 72 hours after onset of symptoms. MRI sensitivity (using diffusion-weighted imaging [DWI] optimized for stroke detection) rises sharply in the first few hours after the onset of stroke symptoms. False negative scans are more frequent in the first 24 hours after onset of posterior fossa stroke symptoms than in the subsequent period from 24-72 hours after onset. MRI sensitivity is about 80%[29] <24 hours and about 86%[73] <72 hours. Maximal MRI sensitivity (~99%[73]) is achieved after about 72 hours, and is maintained at a high level until ~14 days after onset of symptoms, then declines to a nadir around 1 month.[107] Accordingly, only those whose gold-standard MRI scans were obtained within the 14-day period will be included as part of the primary analysis for the main trial outcome (see Statistical Analysis Plan below).

Oral anxiolytic therapy may be offered to subjects per local institutional policy who have MRI anxiety. This will be documented in the subject's record and same-day follow-up assessments that may be affected by anxiolysis (e.g., vestibular testing) must be completed prior to anxiolytic administration.

MRIs will be read by two independent, masked study neuro-radiologists. For safety, all 1-week study MRIs will also be read clinically as an urgent ED scan by on-site clinical radiologists.

Standardization MRIs (normal volunteers, occurred only during protocol refinement phase): The MRI acquisition protocol was adapted for each of the study center's MRI technology (GE vs. Siemens, 1.5 Tesla vs. 3 Tesla) by the principal study neuroradiologist in collaboration with an MRI physicist. To ensure that MRIs for the 1-week gold standard study were harmonized across sites, the MRI personnel from the CC visited each study center and collaborated with the local MRI personnel. This process involved scans obtained from both a "phantom" (non-human or animal impregnated gel) and 1-4 human volunteer subjects (inclusive of study staff from the CC to allow for the same person(s) to undergo MRI scanning at each site to enhance MRI standardization across sites). Each volunteer underwent MRI (see Table 2 for sequences) for 60-180 minutes depending on the progress of the harmonization process. Scanner settings were adjusted during this time until optimal settings were obtained. This protocol differed from the final protocol for the patients enrolled in the AVERT Trial; no gadolinium was used, negating the need for IV access and assessment of kidney function.

Table 2. Major MRI sequences obtained as part of the standard MRI protocols in the AVERT Trial

Time Point	Stroke Images	Posterior Fossa, Internal Auditory Canal (IAC) Images	Approximate Length	Image Strength
Immediate safety MRI obtained in all VOG patients before being released from the hospital	**Stroke protocol MRI** (using non-contrast clinical protocol for each site, whether or not it includes an MRA)	*none*	30 min image acquisition time (total time ~45 min)	3.0 Tesla or 1.5 Tesla
Gold standard MRI (1 wk)	**Stroke protocol MRI** with diffusion-weighted, T2 FLAIR, susceptibility-weighted images for stroke **Stroke protocol MRA** with contrast and special T1 sequences for vertebral artery or basilar dissection	**IAC protocol MRI** with pre- and post- contrast images,[108] including axial and coronal T1 as well as CISS sequences with thin cuts through the posterior fossa, including the vestibular (8th) nerve complex for patients without contrainidcations to contrast	90 min image acquisition time (total time ~90 min)	3.0 Tesla or 1.5 Tesla
Standardization MRI (normal volunteers only)	**same as above**	**same as above but without contrast use or post-contrast sequences**	60-180 minutes	3.0 Tesla

6.3.19 Hospital admission: The ED provider determines if admission is necessary for the standard care pathway. The research team will request that the ED provider admit eligible subjects randomized to VRT whose VOG diagnosis is 'central' at the ED Index Visit. Those whose VOG diagnosis is 'equivocal' will have hospital admission determined by the ED provider in consultation with a neurologist, when available. Those whose VOG diagnosis is 'peripheral' will be discharged after safety MRI, unless the ED provider decides to admit 'off protocol' for safety.

6.3.20 Neuro-otology examination: All subjects will undergo a focused neuro-otology examination at the 1-week visit to evaluate ongoing and new clinical symptoms since the ED Index Visit, to assess the likely diagnosis, and to provide any necessary referrals or communication with other providers.

6.3.21 Laboratory-based vestibular testing: All subjects will undergo formal vestibular testing at the 1-week visit. This standard clinical vestibular testing battery (~3 hours) will include the following:

1. Subjective visual vertical (SVV) testing

   This test requires the patient to re-position a mechanical light bar so it is oriented upright. Depending on site-specific procedures, this may occur using the 'bucket test' (described above).
2. Video-oculography (VOG) saccade accuracy testing

   This test requires the patient to look from side to side.
3. Video-oculography (VOG) head impulse testing (vHIT), 6 semicircular canal planes.

   This test involves ~15 rapid head rotations in the plane of each semicircular canal.
4. Video-nystagmography (VNG) with caloric testing.

   This test involves a series of maneuvers designed to elicit nystagmus. These include looking side to side, blocking visual fixation, passive head shaking, positional tests (Dix-Hallpike, supine roll), and bithermal caloric testing (warm and cold water instilled into the ear canal) while supine.
5. Vestibular-evoked myogenic potentials (VEMPs), cervical (c-VEMPs) and ocular (o-VEMPs).

   Both tests are performed supine and using non-invasive, surface electrodes to measure neck and eye motor responses to auditory, vibratory, or forehead 'tapping' stimuli. The c-VEMPs test requires patients to lift or turn their heads against resistance to activate the sternomastoid muscle; they may also be asked to clench their teeth to activate the jaw muscles and to look at a fixed target. The o-VEMPs test does not require any sustained patient effort. Tone bursts will be presented unilaterally to the test ear through a calibrated audiometric speaker or bone conduction vibrator at a varied stimulation rate to obtain thresholds for response. In order to test utricular function, VEMP responses to midline forehead taps will be measured. The stimulus consists of a brief acceleration of the head imparted to the forehead with a neurological reflex hammer or a mechanical device (a short-distance tapping instrument that can give a repeated tap at set time intervals).

SVV, VNG with caloric testing and VEMPs will be performed at all sites where clinical appointments are readily available, and at the same location as the rest of the follow up visit. Sites with logistical constraints for getting these tests will perform them on a time permitting basis at follow-up.

6.3.22 Laboratory-based audiometry: All subjects will undergo formal audiometry testing at the 1-week visit. Pure tone thresholds at 500 Hz through 8000 Hz will be measured in addition to speech reception threshold and speech discrimination score. Testing will be performed in a sound-proof booth with a clinical audiometer. Tympanometry (test of middle ear compliance during changes in external auditory canal pressure and during comfortable-level sounds applied by an audiometer speaker so as to assess stapedius/acoustic reflex function) will also be performed.

6.3.23 Emergency Department Patient Experiences with Care (EDPEC): An abridged version of the EDPEC survey (https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/CAHPS/ed.html) using questions focused on overall experience will be completed by subjects at the ED Index Visit and 1-week follow-up visit to provide their perspectives on the care they received during the ED Index Visit.

6.3.24 Resource utilization: SCs will record the number and type of brain imaging studies, consultations, and admissions, as well as ED length of stay. They will note key process measures such as whether patients are treated with anti-vertigo medications or undergo specific canalith repositioning therapy.

We will track use of higher-cost services likely to be impacted by VOG care at ED visit and in follow-up (radiology/lab tests, physician consultations, admissions). Costs will be based on national average Medicare reimbursement (commonly used in cost analyses[170]), or, as needed, average consortium costs.

6.3.25 Medical record review: Medical records will be accessed at the ED Index Visit to identify relevant medical conditions related to inclusion/exclusion parameters or critical study covariates. SCs will review medical records for baseline medical comorbidities (and any acquired during the 30-day follow-up period), ED/hospital/outpatient healthcare visits, and major medical events (falls, hip fractures, vascular events [stroke, myocardial infarction, venous thromboembolism], and test or treatment complications related to studies/interventions during the study period (ED Index through 1-month).

6.3.26 Canalith repositioning treatment for BPPV: For patients in the VRT arm with an algorithmic, VOG-derived diagnosis of BPPV, SCs will provide standard, evidence-based guideline-recommended canalith repositioning treatments.[49,50] These maneuvers are simple and routinely performed by vestibular physical therapists and nurses in clinical practice. All SCs will be trained to provide canalith repositioning for posterior canal BPPV via the modified Epley canalith repositioning maneuver (a 270 degree rotation from the Dix-Hallpike test position). SCs with more experience will also perform horizontal canal canalith repositioning treatments (e.g., the Lempert roll maneuver, which is similar to the Epley but with the chin tucked forward rather than head hanging back). No treatments for anterior canal BPPV will be applied by SCs, as our current VOG algorithm dictates that patients with positional downbeat nystagmus are diagnosed as presumed to have central lesions until proven otherwise by neuroimaging; if this aspect of the VOG algorithm is modified during the course of the study, only SCs with adequate experience or training in treatment of anterior canal BPPV will apply the appropriate maneuvers. Our standard approach will be the one typically used in subspecialty practice: to apply the treatment maneuver up to three times or until the nystagmus has resolved on positional testing. The treatments will be provided under VOG guidance—the VOG tracks the three-dimensional position of the head in space, and notifies the user if the patient's head angles are not in the appropriate planes/locations. This will increase the accuracy of treatments by SCs with less experience. It will also provide an internal check on accuracy and effectiveness of treatment procedures, as the VOG traces and videos from the treatments will be reviewed by neuro-otologists for correct technique and correct results (based on nystagmus patterns). At any time, the ED provider may go 'off protocol' for any safety or treatment effectiveness concerns and request an ENT or physical therapy consultant to perform the maneuvers instead of (or in addition to) the SC. Similar treatments will be applied at the 1-week follow-up visit if patients have BPPV symptoms and findings.

7. RISKS

This is a low-risk study whose properties generally do not exceed that typically encountered in routine clinical care (bedside exam using the standard of care in neuro-otology/vestibular neurology; MRI brain imaging using standard clinical protocols). Other than the risks of contrast MRI, there are no specific procedures, situations, or materials that pose serious hazards to patients or personnel. Additional small risks relate to misdiagnosis and risks from subsequent inappropriate testing or treatments. While we hypothesize that the intervention (VOG-guided care) will substantially reduce the risks of misdiagnosis, we are in equipoise regarding the possibility that it may not, on average, prove beneficial (or that individual patients could be harmed).

Risks to human subjects fall into seven broad categories that affect both arms of the trial:

I. **Risks of disclosure of protected health information (PHI)** [*equal risk in both arms*] (very low)
II. **Risks from delays in care due to VOG testing** [*equal risk in both arms*] (rare)
III. **Risks of video-oculography (VOG) with head impulse testing (HIT)** [*equal risk in both arms*] (rare)
    a. Discomfort (increased dizziness, nausea) (infrequent)
    b. Symptomatic bradycardia (rare, single case report[62])
    c. Minor soft tissue neck injury (rare, with no known cases of any significant injury)
    d. Minor discomfort or loss of facial (eye brow or eyelash) hair upon adhesive eye patch removal
IV. **Risks of MRI testing with contrast (both arms)** [*similar risk in both arms*] (rare)
    a. Inadvertent imaging of patient with contraindication (rare with standard screening procedures[68])
    b. Risks of flying metallic objects (rare with standard precautions[69,70])
    c. Risks of auditory injury (rare with standard precautions[69,70])
    d. Risks of difficulty with cardiac resuscitation (unstable cardiac patients will be excluded)
V. **Risks of missed diagnoses or undertesting** [hypothesis to be tested: *potentially differential risk*]
    a. Missed stroke (estimated ~30% in standard care arm; hypothesized ~1% in VOG-guided arm)
    b. Missed treatable vestibular disorders (~50% standard care; hypothesized ~1% VOG)
VI. **Risks of incorrect diagnoses or overtesting** [hypothesis to be tested: *potentially differential risk*]
    a. Imaging or admission for stroke evaluation (~50% standard care; hypothesized ~15% VOG)
    b. Inappropriate medications (~30% standard care; hypothesized ~1% VOG)
VII. **Risks to ED providers of medicolegal liability** [*unknown differential risk across the two arms*]

EACH OF THESE TRIAL RISKS IS DESCRIBED FURTHER BELOW

7. I. Risks of disclosure of PHI

These risks are minimal, since data security protections (described in Data and Safety Monitoring below) are in place and the data we are gathering will, in general, not be of a particularly sensitive nature.

7. II. Risks from delays in care

A theoretical risk is that clinical care will be delayed because of interference by study data collection. As in all of our previous ED-based studies,[4,15,21,33,71-74] clinical care needs will always take precedence over our research investigations. SCs will be trained to stop their testing immediately if clinical care is needed. **There will be no delay in administration of any treatment or procedure, including administration of thrombolytic medications for stroke, should this be the ED provider's management decision**. Since testing will all happen 'in situ' within the ED, there will be no delays associated with patient transport. Likewise, since we will only recruit during shifts when SCs are stationed in the ED, there will be no delays incurred related to SC notification or travel prior to assessing the patient as part of the study protocol.

Another theoretical risk is that care will be delayed because the VOG test results are part of the diagnostic process for VOG care. The total testing time for pre-randomization screening is expected to be about 30-45 minutes, but this will occur 'around' the usual ED care by physicians, providers and nurses, as described in the prior paragraph. The VOG component of the testing will take approximately 20 minutes continuously, but could be interrupted for clinical care. In other words, **VOG care will not lengthen the time of an ED provider's initial assessment or management, or delay its onset**. The VOG diagnosis may identify a stroke missed by

the clinician. In such cases, VOG could speed identification of stroke (i.e., relative to waiting for neurology consultation or neuroimaging), shortening (not lengthening) the time to early stroke therapies.

7. III. Risks of VOG with HIT

7. III. 1 Overview of Video-oculography (VOG): VOG has been used for 20 years (since the early 1990s) to measure eye movements during vestibular testing both in a laboratory[75] and clinical setting.[76] The technology is relatively simple in that it involves sending a video picture of one or both eyes to a computer, which then processes the image to detect eye position (usually through algorithms that recognize and track the location of the pupil). The pupil location, representing eye position, is then tracked in horizontal and vertical directions (some systems, including ours, track torsional eye movements, but real-time torsional measures are not as accurate[77]). This is generally accomplished using a set of goggles with a small, infrared camera pointed at the eye. Prior iterations of such goggles looked similar to a large dive mask. More recent iterations are more compact and look more like swim goggles. These have enabled new forms of testing, described further below.

Eye movement exams for specific forms of nystagmus during positional testing represent the gold-standard diagnostic tool in BPPV.[48,78] This process is easily accomplished with standard VOG technology. [56,164]

Bedside differentiation of vestibular neuritis from stroke, however, has required technical developments that matured over the past 25 years. Scientific advances have made device-based diagnosis of stroke attainable:

1. HIT (1988): Halmagyi and Curthoys developed the horizontal head impulse test (h-HIT) of vestibulo-ocular reflex (VOR) function to assess vestibular disorders.[79] The test could be performed qualitatively (expert examiner, visual inspection of eye movements) or quantitatively (lab-based recording devices).[79] The test has now been adapted to assess all semicircular canals.[80]

2. HINTS (2008): Newman-Toker and colleagues demonstrated the utility of the qualitative h-HIT by experts in differentiating vestibular neuritis from vestibular stroke or other central causes in patients with acute, continuous dizziness (the 'acute vestibular syndrome').[16,21] Our team recognized that strokes involving both the brain and labyrinth could mimic inner ear disease when relying solely on the h-HIT,[21] so we created a 3-step eye exam battery to capture the remaining cases. We labeled the beside qualitative eye examination 'H.I.N.T.S. to I.N.F.A.R.C.T.'[42] and showed it outperforms acute MRI in the first 48 hours after onset.[4,29,73]

3. VOG-HINTS (2009): MacDougall et al. built a portable VOG device lightweight enough to measure the h-HIT without goggles slippage.[52,64,81] This invention allowed our team to be the first to demonstrate in a small, proof-of-concept study that device-based differentiation of vestibular neuritis and stroke was indeed possible.[33] We have since confirmed this approach in another dozen patients with acute vestibular syndrome and have published detailed quantitative results and technical analyses.

4. **HINTS 'Plus' (2013)**: Newman-Toker et al. showed that a minor modification of the HINTS decision rule is more sensitive for detecting stroke while losing only a small amount of specificity.[73] This 'HINTS plus' counts new unilateral hearing loss in those with acute, continuous vertigo or dizziness as a predictor of stroke involving the inner ear (i.e., combined cochleo-labyrinthine infarction). This occurs because vestibular neuritis is generally without hearing loss, while the blood supply to the inner ear derives from the vertebrobasilar circulation, generally via the anterior inferior cerebellar artery (AICA) giving rise to the internal auditory artery.

The ICS Impulse device (http://icsimpulse.com/) that will be used in the AVERT Trial is a lightweight, modern adaptation of standard VOG technology; it received FDA approval in February, 2013 via a 510(k) mechanism that demonstrated it to be substantially similar to predicate VOG devices measuring vestibular function (http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/510kclearances/default.htm).

Since VOG devices can now measure the h-HIT, nystagmus (BPPV or central-type), and vertical eye position (skew deviation), VOG testing can now diagnose BPPV, vestibular neuritis, and stroke.

Note on Commercial Relationships and Choice of Device: No one on the research team had any commercial or financial interest in the ICS Impulse device (or any other VOG system) at study start; any new commercial relationships (e.g., licensing the AVERT algorithm) will be disclosed per institutional policy. Here we describe the rationale for our choice of the ICS Impulse device (http://icsimpulse.com/) over competitor products such as the EyeSeeCam (http://eyeseecam.com/; http://www.interacoustics.com/us/vhit) or Video Head Impulse Test Ulmer (http://www.synapsys.fr/en/p-video head-impulse-test-ulmer-vhit-ulmer-48.htm). Our choice to focus on using the ICS Impulse device was made for scientific reasons. To our knowledge, only the ICS Impulse and EyeSeeCam devices have been validated against magnetic scleral search coil recordings (the gold standard in eye movement recording techniques) and are currently FDA approved for clinical use in the US. Companies producing these two devices have loaned them to our research group for research purposes. The EyeSeeCam has greater eye movement measurement flexibility in its current hardware and software configuration, but the ICS Impulse has a simpler, unibody design without moving or detachable parts; it is also more comfortable for patients to wear. We believe these features make the ICS Impulse device more likely to be widely disseminated in an ED environment, so we chose to focus our initial efforts on using this particular device. We are currently using the EyeSeeCam preferentially for laboratory-based studies. As long as the particular device can give similar measurements as described in this trial, the results should be applicable to all similar VOG devices.

7. III. 2 The Impulse Maneuver: The horizontal head impulse test (h-HIT) of vestibulo-ocular reflex (VOR) function, as originally described in 1988,[79] is a rapid, passive head rotation from lateral (10-20 degrees) to center head position as a subject fixates at a central target (e.g., the examiner's nose). For the test to work, the head rotation must be passive (i.e., conducted by the examiner), rather than active (i.e., deliberate head turn by the patient).[82] Although it the h-HIT is often performed from center to lateral in research studies, we will use the original maneuver and displace the head laterally first before rotating the head back to the center position.[21] This approach reduces any theoretical risk of vertebral artery injury with neck over-rotation by an overzealous, inexperienced examiner, and is the technique we have used successfully in our prior studies. **In the AVERT Trial, all examiners will be well trained. We have shown that high-quality technique is achieved in less than 1 hour of training (Fig.3)**.

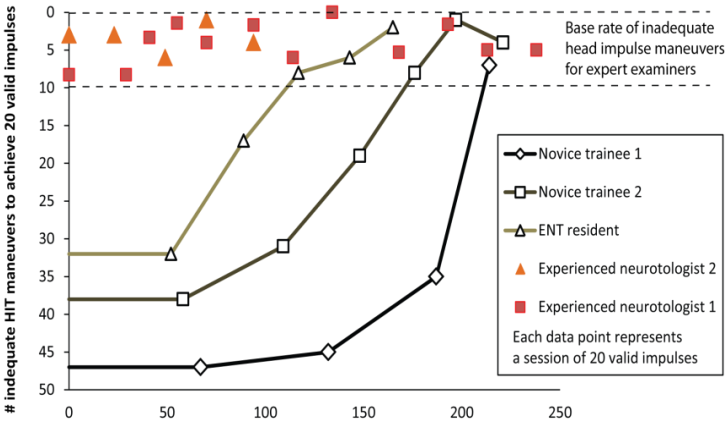

Figure 3. Novices learn correct HIT technique in <1hr with VOG

The HIT technique is now considered a standard part of the routine clinical exam in patients presenting with dizziness or vertigo.[63,83] The evidence supporting its use in experienced hands is substantial.[4,21,29,73,84] Our systematic review concluded there was strong evidence (GRADE system[85]) for adequately-trained providers to use these findings for stroke diagnosis in AVS.[29] Not performing the technique in a patient with acute, continuous dizziness or vertigo would now be considered inappropriate care by most vestibular specialists.

7. III. 3 Side Effects of HIT: It is reasonable to expect that patients with dizziness or vertigo could have an exacerbation of their symptoms during the HIT, as they might with any head movement. As a consequence, patients may feel greater dizziness, nausea, or unsteadiness during testing or for a few seconds or minutes after testing is complete. The maneuver could provoke vomiting or other vagal responses. Since 1988 there has been one case report of bradycardia after HIT,[62] but no other reported complications, to our knowledge.

Our 75 AVS patients enrolled in our observational VOG studies have easily tolerated 20-40 impulse maneuvers at a session, often many more. We have found that patients experience more symptoms from sitting up from a recumbent position in bed than from the HIT itself. This is likely because the amplitude of the HIT movement is so small and the stimulus duration so brief, that it does not cause major symptoms.

Those with neck arthritis (or baseline neck pain or headache) could experience mild, transient increase in pain during the head rotation. None of these symptoms are expected to last more than a few seconds and none of these symptoms will be greater than those expected to be brought out by the routine process of clinical care (e.g., during typical Dix-Hallpike positional testing for nystagmus, which, unlike the HIT, is more commonly applied by ED providers in the course of routine clinical care for patients with dizziness or vertigo).

7. III. 4 Theoretical Complications of HIT: Millions of HITs have been performed by dozens of investigators worldwide over the past 25 years.[4,21,44,45,52,64,79,81,82,86-90] To our knowledge, no complications of HIT testing have ever been reported other than the transient side effects described above.

Some who have observed the HIT performed have likened it to chiropractic neck manipulation and expressed concerns about the possibility of causing a vertebral artery dissection or exacerbating a pre-existing one. The HIT differs mechanically from cervical spine manipulations which combine far lateral rotations (>45 degrees) with full neck extension in order to immobilize the joint at its end range of motion before applying a sudden, high-velocity head rotation as a therapeutic maneuver (http://www.youtube.com/watch?v=CAVxOFftqxg, http://www.youtube.com/watch?feature=endscreen&v=NVuY5vqoGyU&NR=1).

The theoretical risk of vertebral artery injury is with far lateral (>45 degree) neck rotations (as may occur with cervical spine manipulation, but not HIT), since studies suggest that physical traction on the vertebral artery only begins to occur when the head is rotated more than 30 degrees laterally, and is only substantial when the head is rotated beyond 45 degrees laterally.[91,92] This mechanical risk may be further increased in chiropractic cervical spine manipulation by combining far lateral rotation with full neck extension (also not done in HIT), thereby placing the vertebral arteries at additional biomechanical risk.[93]

The correct h-HIT procedure as applied in this study will be to displace the head 10-20 degrees laterally (**less of an excursion than typically used as part of routine auscultation of the carotid artery**) and return the head rapidly to center (100-200 degrees per second) (http://content.lib.utah.edu/cdm/singleitem/collection/ehsl-dent/id/6, video time point 4:29 for close-up demonstration of the head impulse as performed properly).

For vertical HIT (v-HIT) testing in the RALP (right anterior, left posterior semicircular canal) and LARP (left anterior, right posterior semicircular canal) planes, we will displace the head 30-40 degrees laterally[53] (**roughly the excursion typically done as part of routine auscultation of the carotid artery**) and rotate the head rapidly in flexion and extension by 10-20 degrees.[53]

Despite the lack of biomechanical similarity between chiropractic neck manipulation and HIT testing, we are mindful of concerns about the possible relationship between sudden neck movements and dissection expressed by thoughtful physicians.[94] It is important to note that **a direct causal relationship between chiropractic neck manipulation and stroke linked to cervical (carotid or vertebral) artery dissection has been postulated,[95] but remains controversial**.[96,97] Population-based case control studies have shown that vertebrobasilar artery dissection and stroke is associated with a three to five-fold increase in likelihood of having been exposed to recent chiropractic neck manipulation among patients age <45 years but not those over that age.[98,99] The risk of having visited a primary care physician in the weeks before dissection/stroke diagnosis, however, is the same as the risk of having visited a chiropractor.[99] These findings suggest the association could be spurious, reflecting "confounding by indication" or "reverse causality bias" ('vertebral dissection' causes 'neck pain' which causes 'chiropractic or primary care visit'… rather than 'neck disease' causes 'neck pain' causes 'chiropractic visit' which causes 'vertebral dissection').[96,99] Even those asserting a real association accept the absolute risk of dissection is low.[97] The maximum estimated risk is 1 dissection per 20,000 manipulations,[100] though others

suggest the risk is much lower, between 1 per 400,000 and 1 per 1.3 million manipulations.[98] Also, the presence of a vertebral artery dissection often has a favorable outcome when treated appropriately.[36]

Assuming the theoretical risk of dissection with the HIT is the same as the risk for cervical manipulation (which is unlikely based on the biomechanics described above), with a maximum of 180 impulses per patient (20 per canal, 2 canals at ED index and 6 at 1 week), the total risk of a dissection would be approximately 0.01-0.9%. By contrast, the risk of **not** performing the HIT in an ED patient with acute, continuous dizziness or vertigo presenting in the first 24 hours confers a 20% risk of missed stroke, even if every such patient is sent for an MRI. The 20% risk is of a false-negative MRI,[29] currently considered the best available test (other than HIT). Many ED patients get CT rather than MRI, so their risk of a missed stroke is probably 58-93%.[101-103] Those whose strokes are initially missed appear to be at much higher risk of death (40% in one case series[11]) so the absolute risk increase of death due to a misdiagnosis (as a consequence of **not** performing the HIT) could be as high as 35% relative to a correctly-diagnosed patient. Thus, the absolute risk of death due to missed stroke in typical ED care (by **not** performing the HIT) in a patient population like ours (~10-20% strokes) may be ~1%.

If we have 15% strokes in our subject pool, then even if the excess risk of death due to a delay in ED cerebellar stroke diagnosis is only half that reported in the literature,[11] the risk of stroke-related death due to misdiagnosis from NOT performing the HIT is likely greater than any hypothetical risk of vertebral artery dissection from actually performing the HIT to help diagnose stroke in these patients.

7. III. 5 Risks of other vestibular testing (positional tests,[49,50] side-to-side head shaking[104]): These standard vestibular tests used to provoke vertigo, dizziness, or nystagmus are used routinely in specialty clinical practice.[42,105,106] Aside from an increase in symptoms (dizziness, nausea, or vomiting), there are no known risks of these tests. If a patient wishes not to continue with the test protocol, they may stop at any time.

7. III. 6 Risks of vestibular treatments (canalith repositioning maneuvers): These standard vestibular treatments are used routinely in specialty clinical practice and form the basis of at least two clinical practice guidelines.[49,50] Aside from an increase in symptoms (dizziness, nausea, or vomiting), there are no known significant risks of these procedures (Cochrane Review doi: 10.1002/14651858.CD003162.pub3). The modified Epley maneuver for posterior canal BPPV is effective in approximately 80% of acute cases, with a number needed to treat ~1.4-2.4 from two Class I randomized trials.[50] Similar results have been found for horizontal canal BPPV treatments, albeit from lower-quality studies.[50] If a patient wishes not to continue with the treatment protocol, they may stop at any time. If an ED provider prefers treatment by another provider, they may go 'off protocol.'

7. IV. Risks of MRI testing

Overall, the risks of MRI, even with contrast administration, are extremely low. None of the risks in this study exceed risks typically encountered in clinical care for patients with vertigo undergoing MRI. Contrast administration is a recommended element of MRI imaging for patients with vertigo and hearing loss.[108]

7. IV. 1 Inadvertent imaging of patients with contraindications: This complication is rare with standard pre-MRI screening procedures,[68] which will be followed in the AVERT Trial. People who have known metallic foreign bodies in the head or eyes, or who may have been exposed previously to metal fragments in their work, such as welders or metal workers, will be excluded from the study in the initial screening review for eligibility. As described in the consent form, those with remote exposure who have previously been cleared by skull x-ray or CT scan of the head (i.e., confirmed *NOT* to have metal fragments) will, however, be eligible. Eligibility will be confirmed at each site using the standard clinical or research pre-screening MRI questionnaires/checklists, per local institutional policies (including a negative pregnancy status for all women of childbearing potential prior to MRI). Patients will be pre-screened for claustrophobia and treated with anxiolysis in advance as appropriate; if refractory anxiety develops during the MRI, we will stop the scan.

7. IV. 2 Risks of flying metallic objects: This complication is rare with standard precautions in the conduct of MRI testing,[69,109,110] which will be followed in the AVERT Trial.

7. IV. 3 Risks of auditory injury: This complication is rare with standard precautions,[69,109,110] which will be followed in the AVERT Trial. All patients will receive hearing protection. While some clinicians consider immediate MRI in a patient with sudden hearing loss to be contraindicated (for risk of further noise-induced damage), our data suggest that patients with combined audio-vestibular presentations to the ED are more likely to be the result of stroke than peripheral vestibulopathy (i.e., labyrinthitis or cochleo-vestibular neuritis).[73] This means that the risks of further hearing loss from MRI are likely outweighed by the risks of missed stroke.

7. IV. 4 Inadvertent risks of difficulty with cardiac resuscitation: Risks of difficulty with cardiac resuscitation are minimal since critically ill and unstable cardiac patients will be excluded.

7. IV. 5 Risks of gadolinium-based contrast agents: [Note that this risk did not apply to the MRI standardization volunteers because gadolinium was not administered.] Gadolinium helps identify brain, blood vessel, and cranial nerve pathology by demonstrating pathologic tissue enhancement and by enhancing the contrast between diseased arteries (e.g., due to cervical artery stenoses or dissections), and the surrounding soft tissues. Contrast administration is important in this study to identify correct etiologies for dizziness, including active multiple sclerosis, inflammatory balance nerve lesions, small neoplasms (e.g., cerebellar metasteses), and vascular stensoses responsible for stroke. At 1-week, contrast therefore maximizes accuracy of the gold standard.

Overall risks are minimal in patients with normal renal function[70] (defined as GFR >30 mL/min/1.73 m^2). For patients without contraindications, we will use a gadolinium-based contrast agent to be administered intravenously at a dose of 0.1 mM/kg body weight using a power injector at a rate of 2cc/sec. This agent has been approved by the FDA and is widely used for clinical MRI exams. The amount is considered a "single dose", and is typically the lowest dose used for clinical applications. We will minimize excess dosing by conducting safety or admission MRIs without contrast.

Insertion of an intravenous catheter for injection may cause minor pain, bruising and/or infection at the injection site. Transient side effects of gadolinium administration may include discomfort during the injection of contrast, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arms, nausea, or headache. These symptoms occur in less than 1% and resolve quickly. There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction (anaphylaxis) occurs in less than 1 in 300,000.

People with moderate to advanced renal failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). NSF/NSD causes thickening of skin and connective tissues that can result in pain, reduced joint mobility, and in some cases leads to death.[70] The risk of developing NSF/NFD is 3-7% in subjects with moderate to advanced renal failure,[70] but these patients will not receive gadolinium. The disorder has not been reported in patients with normal renal function.[70]

7. IV. 6 Risks of incidental findings: Research MRI images or other tests obtained for research purposes may disclose incidental abnormal findings. In some cases, these findings may benefit the patient, in others, pursuing them may prove harmful.[111] These findings will be shared with the patient, as described in the written consent form and in the incidental findings plan (http://braininjuryoutcomes.com/documents/viewdownload/82/592).

7.IV.7 Risks of Anxiolysis: Optional anxiolytic medications given prior to MRI typically produce temporary drowsiness, dizziness, and mild cognitive impairments, all reversible. In patients who metabolize these medications slowly, these side effects may persist for several hours, and, in rare instances, longer. Operating a motor vehicle while suffering from such side effects may be dangerous. To mitigate this risk, patients will not be administered these agents if they must operate a motor vehicle later that day; as appropriate, transportation assistance may be offered to participants if necessary. There are also rare risks of serious allergic reactions.

7. V. Risks of Missed Diagnosis

The risks of missed diagnoses are important for treatable peripheral disorders and vestibular strokes. These risks are hypothesized to be substantially higher in the standard care arm. Standard care diagnosis accuracy for peripheral vestibular disorders and vestibular strokes is suboptimal.

Vestibular disorders are not always accurately diagnosed and treated in the ED[4,5,112-114] and other frontline settings.[115-122] About 900,000 (~22%[20] of 4.3 million[123]) patients leave the ED with a non-diagnosis of "dizziness/vertigo, not otherwise specified." The majority may have undiagnosed vestibular disorders.[57,58] Among those diagnosed as peripheral, 81% are misclassified.[5] In those diagnosed with BPPV, appropriate bedside positional testing is documented in only 22% and treatments applied in just 4%.[124]

Harm may also result from missed opportunities to treat peripheral vestibular disorders, even if 'benign.'[115,125] BPPV patients not treated within 24 hours of the ED visit have more than double the recurrence risk (46% vs. 20%, p=0.002)[126] and 6.5-fold greater odds of falling.[115] Prompt BPPV treatment improves health-related quality of life.[127] Dizziness is a risk factor for hip fracture,[128] and increases the risk of a repeat hip fracture nearly 3-fold.[129] It produces subjective functional impairment in 54% of patients and engenders fear of serious medical illness in 46%.[130] Untreated, dizziness decreases health-related quality of life[131,132] and functional capacity.[133] Vertigo or dizziness can lead to a secondary depression or anxiety disorder in 32% of patients.[134]

Vestibular strokes are often missed because clinical findings mimic benign ear disorders.[114,135-137] Misdiagnosis is the most common medical error type found in the ED[138] and may be of special concern with neurologic problems.[137] More obvious stroke symptoms such as hemiparesis are infrequently missed (~4%[139]), but ~30% of vestibular strokes are missed initially.[7,135,136] In the subset of vestibular strokes presenting isolated dizziness/vertigo (i.e., without any other associated neurologic symptoms or signs), representing the majority of patients enrolled in the AVERT Trial, it is possible that as many as 50% of strokes are missed initially.[7]

The prognosis of posterior circulation strokes, if promptly diagnosed and appropriately managed, is usually favorable.[17] When strokes are missed, preventable adverse outcomes result from missed opportunities for thrombolysis,[136,140] early surgery for malignant posterior fossa edema,[17,141] or prevention of subsequent vertebrobasilar infarction (i.e., major stroke following minor stroke or transient ischemic attack).[142-144] Rapid, early treatment improves stroke outcomes[145,146] and lowers repeat stroke risk by up to 80%.[147,148]

Women and minorities are at greater risk of misdiagnosis, as are patients under age 50.[149] We have found that there are racial, ethnic, and sex-related disparities in missed vestibular strokes, with minorities and women at ~20-30% higher risk.[149] Patients <60yo are at especially high risk of misdiagnosis,[149] because stroke is often not considered in young patients.[73]

When vestibular strokes are missed, the risks of death and disability may rise substantially.[29] A small study found a 40% 5-day mortality among those with missed cerebellar strokes.[11] If this is representative, missing the stroke may increase mortality 8-fold — 40% (missed cerebellar stroke) vs. 5% (correctly diagnosed cerebellar stroke).[29] This risk difference (35%) could correspond to as many as ~20-30,000 preventable stroke deaths annually in US EDs. The true attributable risk is probably not quite that high, but even a 10% difference would mean ~5,000-7,000 preventable deaths per year.

7. VI. Risks of Wrong Diagnosis or Overtesting

As in Section 7. V. (Missed Diagnoses), the risks of wrong diagnoses are important for treatable peripheral vestibular disorders and vestibular strokes. As with missed diagnoses, these risks are hypothesized to be substantially higher in the standard care arm than in the VOG-guided care arm.

Benign peripheral vestibular disorders are often mistaken for vestibular strokes.[150] Nearly 1 in 3 vestibular stroke diagnoses turns out to have a misdiagnosed benign ear disorder (n=22/70).[114]

Vestibular strokes are often mistaken for benign peripheral vestibular disorders.[66,77,78] In referral cases, more than half of ED ear diagnoses are revised.[114,150,151] Nearly 1 in 4 given a benign ear diagnosis turns out to have a missed stroke (n=36/160).[114,151]

With wrong diagnosis (especially benign vestibular disorders erroneously pursued for stroke), over-testing (especially neuroimaging or admission), confers special risks, described further below.

- The risks of undergoing unnecessary CT will be far higher in the standard care arm than in the VOG-guided care arm (since CT will not be a recommended strategy in any of the VOG clinical pathways).
- The risks of undergoing unnecessary MRI are probably slightly higher in the VOG arm, since the decision rules (algorithm will be used and modified as needed) are tuned to err on the side of not missing a stroke.
- The risks of unnecessary admission are probably slightly higher in the standard care arm.

Patients with benign inner ear disorders are at risk of being harmed by overtesting or overtreatment in pursuit of a stroke or other neurologic diagnosis.

- CT neuroimaging is ineffective, but frequently ordered in routine care for dizziness: The fraction of ED dizziness patients undergoing neuroimaging to rule out stroke or other central causes has risen steadily from 10% in 1995 to nearly 50% in 2015,[123] and this includes overuse in patients diagnosed with both BPPV and vestibular neuritis.[4] Across the US, ED neuroimaging for these patients is still primarily by CT (~47%) rather than MRI (~3%),[123] despite the known pitfalls of relying on CT to 'rule out' ischemic stroke in the posterior cranial fossa.[11,17,135] The general increase in neuroimaging over time has not led to a corresponding increase in diagnosis of strokes or other important central causes.[27] The same is true for unwanted, wide (1.5-fold), local-area practice variations in ED neuroimaging.[152]
- CT carries meaningful risks: In addition to delays in care, CT risks cancer from radiation exposure[153] and, if contrast is used, systemic allergy (including risk of death from anaphylaxis)[154] or contrast nephropathy.[155]
- MRI carries some risks: *described above in 7. IV. Risks of MRI testing*
- Unnecessary admission carries some risks: Some patients may be admitted to the hospital and unnecessarily exposed to hospital-acquired infections or treated erroneously with medications that have potential side effects or toxicity.[116,118]

7. VII. Risks of Medicolegal Liability for ED providers

We are sensitive to this issue, but we believe medicolegal risks arising directly from the study are very low.

ED providers caring for patients in the control arm will be providing standard care to their patients (i.e., without a VOG results report). They are presumably at no greater risk of making a diagnostic error than if they were providing usual care outside the study protocol. Should a diagnostic error occur, ED providers may be at greater risk for medicolegal liability given the greater clarity of diagnostic documentation and confirmatory testing. The gold-standard testing at 1 week could be used in a malpractice proceeding if a diagnostic error occurred at the ED index visit and an adverse event resulted in the following week. Most such events, however, would have formed the basis of a malpractice case independent of the additional testing. For example, if a patient were discharged as BPPV and returned with a devastating basilar-territory stroke two days later, this case would have ample documentation for a malpractice proceeding without research-related testing. Furthermore, few such cases end in malpractice claims, in part because the ED standard of care is low. Cases resulting in claims are often egregious, involving many neurologic symptoms and signs[156] rather than isolated vertigo or dizziness. To mitigate these risks, we will make available on request aggregate ongoing study information to ED quality assurance and quality improvement processes as well as hospital risk managers.

ED providers caring for patients in the intervention arm (i.e., VOG-guided care) could potentially be held liable for VOG misdiagnoses, since ultimately they are responsible for clinical care decisions. This risk is mitigated almost entirely by safety precautions in the study (opportunity for ED providers to go 'off protocol' for safety at any point; MRIs on all VOG patients; and 1-week gold standard testing). The protocol goes well beyond usual care in terms of safety, so a medicolegal action against an ED provider in this arm is highly improbable. It is much more likely that patients in the VOG arm are less likely to suffer a diagnostic error, thereby lowering the overall risk of medicolegal action for misdiagnosis in this arm of the study relative to usual care. Furthermore, oversight provided by the external Data and Safety Monitoring Board (DSMB) will mitigate any residual risk.

Protection Against Risks

Patient Selection: We will exclude from study participation any patients with prior trauma to the cervical spine or other condition (e.g., rheumatoid arthritis) that might lead to instability of the cervical spine that would constitute a contraindication to neck rotation for the HIT. We will exclude any patients from the study who are pregnant (so as not to expose a fetus to neuroimaging risks), and patients with contraindications to MRI with contrast, including renal insufficiency (GFR < 30 mL/min/1.73 m^2),[70] will not receive MRI contrast.

Pre-Screening: For individuals who may have cervical spinal column problems (e.g., fusion, stenosis), prior to performing manipulations as part of the head impulse testing, treating ED providers will confirm that patients can tolerate these manipulations. Patients will be advised to indicate any discomfort, and research personnel will be prepared to discontinue if significant discomfort is indicated, as described further below. Moreover, our routine testing procedures always include a pre-impulse neck range of motion assessment. The head is rotated slowly from side-to-side to ensure that there are no neck problems prior to HIT testing.

Asepsis prior to the Exam: A procedure for sanitizing the ICS Impulse device will be implemented at all enrolling sites before the first subject is enrolled. The VOG device has a disposable foam insert (produced by the company that manufactures the device) that contacts the patient's skin surface. This foam will be replaced after each patient use to avoid infection related to the device. Other equipment surfaces, including over-the-ear audiometry headphones, will be wiped clean with alcohol swabs or other disinfectant as appropriate.

During the VOG Exam: Patients will be notified prior to any maneuvers necessary to evaluate their condition during the physical examination that might exacerbate their symptoms, so as to alleviate any unwarranted fear of the examination or examiner. We will stop testing at any time at the patient's request. We anticipate no adverse effects of these research examinations. Nevertheless, should patients deteriorate clinically during their assessments, appropriate nursing and/or medical staff will be contacted immediately by research personnel.

HIT Exam Technique: During our HIT procedures, the excursion of the neck rotation will be very small (~10-20°). This technique minimizes potential discomfort or pain during testing, and effectively eliminates any hypothetical risk of soft tissue injury (e.g., vertebral artery dissection, described above in section 7.III.4).

Response to Side Effects of the VOG Exam: All research personnel will be trained and ED site clinical providers will be given a standard set of instructions for how to handle any side effects or complications of testing (See Manual of Operations and Procedures). Emesis basins will be kept at the ready in case the patient should vomit during testing. All EDs will be equipped and ready to handle a bradycardic event, should one occur. For minor pain (or minor increase in nausea/dizziness), VOG testing will stop temporarily and the patient asked if they are able to continue. For significant pain, VOG testing will stop. We have never seen a patient experience pain after impulse testing that lasts more than a few seconds. Nevertheless, if pain persists for more than 5 minutes after cessation of testing, its trajectory will be assessed over the subsequent 30 minutes. For

waning pain, there will be no specific intervention. For persistent pain, treatments will be applied by treating providers (e.g., ibuprofen). Pain that remains persistent at the end of the ED visit will be documented, and these patients will be contacted daily by research personnel to assess their pain and any evolution of interval neurologic symptoms that might suggest vascular injury or cervical spinal cord compression. At the 1-week follow-up neuro-otology visit, pain issues will be addressed, and any necessary referrals or communication with other providers (e.g., primary care) made.

Diagnostic Process: The VRT algorithm will be tuned to err on the side of caution. For example, those with prior inner ear or eye movement disorders risk confounding the results in a way that could potentially harm patients (e.g., patient with prior acoustic neuroma surgery who comes with acute, continuous dizziness due to stroke; in this patient, the exam findings related to prior surgery could lead to an erroneous "benign peripheral" diagnosis). In such cases, the algorithm will incorporate that past history and will be tuned to return an equivocal result, necessitating a neurological consultation, if available. In addition, there will be an expert human double-check for the algorithm output in the VRT arm until it is sufficiently refined (Section 5.1.3)

Identification of Adverse Effects

Safety Assessments: All safety-related assessments will be consistent with generally accepted medical practices and standard-of-care. The following specific assessments will be performed according to the schedule described in the protocol, when it is developed and approved by the DSMB. Adverse events (AEs) recorded in the source documents will be entered into the e-CRF post randomization through the index discharge. Hospitalizations and adverse events reported during the 30-day telephone interview will be recorded, including date and time of resolution, outcome, severity, relatedness and whether or not classified as a serious adverse event.

An adverse event is any untoward medical occurrence in a patient enrolled into the study whether or not it has a causal relationship to the study events. An adverse event can be any unfavorable and unintended sign (including an abnormal lab finding), symptom, or disease temporally associated to the study timeline. The investigators will follow study-related vestibular and stroke adverse events to resolution whenever possible.

If a subject is discontinued from the study for any reason, site personnel must clearly report and document the circumstances and data leading to any discontinuation, using the EDC and whether the early termination was due to an adverse event. For any untoward event(s) the subject will be followed until the event resolves or is explained, with the frequency of follow-up designated by the investigator. Any alarming or unexpected adverse event, including death due to any cause, which occurs, inclusive of the follow-up period (30 days), and whether or not thought to be related to the study, must be reported immediately (within 24 hours of learning of the event) to the CC. Clinical adverse events and study AEs are defined in accordance with the International Conference on Harmonization.

Adverse Event Follow-Up: Follow-up assessments will be repeated to document return-to-normal of any abnormalities (or the establishment of a permanent sequelae with no further improvement expected during the established study period), or to document other outcomes of any adverse events.

VISION™ EDC System: The EDC system will have a robust set of data quality checks that will be executed at the time of data entry at the investigational site. This includes the standard validations available with most EDC systems such as range checks (e.g., to flag timing inconsistencies for symptom inclusion) and data format checks (e.g., to flag an invalid date). Additionally, the VISION™ platform performs sophisticated cross-form computed calculations that would not be available in lesser EDC systems. It will also detect protocol variances and present a list to the investigator and the CC for evaluation and follow-up. Consequently, the EDC system will provide consistency, completeness, and logic checks immediately at the time of data collection.

FDA Guidance for Electronic Data Entry Compliance: The design and development of the VISION EDC system will reflect the FDA Guidance for Industry for Computerized Systems Used in Clinical Trials (April 1999) as well as the Electronic Records/Electronic Signatures rule (21 CFR part 11). A secure, computer generated, time-stamped electronic record allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record. A copy of original information is verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original. A computer data compilation of a series of symbols, executed, adopted, or authorized by an individual is the legal binding equivalent of the individual's handwritten signature. Source documents are retained to enable a reconstruction and evaluation of the study. The system ensures that all applicable regulatory requirements for record keeping and record retention in clinical trials are met with the same degree of confidence as are provided with paper systems. Clinical investigators retain the original copy of all source documents uploaded onto the electronic case report form (eCRF). Query resolution correspondence is maintained and eCRF edits are tracked by the system. Changes to a required record do not obscure the original information. The record clearly indicates the time a change was made and clearly provides a means to locate and read the prior information through the audit trail. This audit trail is in compliance with the 21 CFR 11.10(e). The record, along with supporting documentation, also indicates who made the changes, when, and why changes were made. Security measures are in place to prevent unauthorized access to the system and data. To ensure that individuals have the authority to proceed with data entry, the system is designed to verify the electronic signature (user ID and password) at the start of a user session. The data entry system ensures attributability. Each entry to an electronic record, including any change, is made under the electronic signature of the individual making that entry. A separate electronic signature is not required for each entry or change; a single electronic signature covers multiple entries or changes. Individuals who maintain the electronic record systems as well as the audit trail carry the responsibilities to protect authenticity, integrity, and confidentiality of electronic records. Audit trails will be available for inspectors at the CC or other location where associated electronic study records are maintained. The system will be designed to contain the prompts, lookup values, cross-field validations, flags, and on-line help to encourage consistent use of clinical terminology and to alert the user in case that data entered are out of acceptable range. External safeguards are in place to ensure that access to the computerized system and to the data is restricted to authorized personnel. Servers are stored in a physically secured, guarded data center.

Security Measures: Users at the participating centers are aware of system security measures and the importance of limiting access to authorized personnel. Access to the data at a clinical site is restricted and monitored by the system through required log-on, security verification procedures, and audit trail. The data cannot be altered, browsed, queried, or reported via external software applications without entering through the protective software, although computers at each site may also be used for purposes other than the clinical trial. Because the system is largely through remote access, all data and applications used for the study are logically and physically isolated from the servers in order to preclude unintended interaction with non-study use software. These servers are strictly monitored and maintained by designated administrators; remote sites do not have the ability to change such logical security of the system.

Wireless data transfers will be fully encrypted. In addition, a secure handoff procedure has been developed for the transfer of data from the wireless data (Creoso/Digivey) devices to the VISION™ system via a secure mechanism. This secure procedure will ensure that patient identifiers are disaggregated from any PHI transferred. Research personnel will first conduct a secure patient matching procedure to secure the patient's unique study identifier from the e-patient log, then gather data from patients transferred as an encrypted file, and using only the patient's unique study identifier.

Disaster Prevention for EDC System: The VISION EDC server uses multiple hard drives configured in a RAID array to maintain a continuous backup. A daily backup to external media supplements the RAID system along with weekly backup to offsite secure storage. The server also has redundant separate power supplies. The hosting data center has dual electricity generation systems that can maintain the facility for up to 24 hours

(along with redundant cooling systems) in the event of power grid failure. OnRamp also maintains a second data center at a geographically separated locations (in the event of an attack or disaster that takes down the Austin facility completely) and, further, Prelude has contracted with a second data center in Austin (which is in an underground nuclear-fortified shelter that also serves as a backup for the State of Texas) that can be deployed quickly to ensure continuing operation with minimal downtime.

Limited Access: Each user is assigned an individual account with a unique username and password. The users are required to log into that account to start a data entry session and log out at the completion of the session (the system will time-out following a period of inactivity). Users are legally (per FDA regulation subjecting them to civil and possibly even criminal liability) and contractually prohibited from giving another person access to the system directly or by sharing login account information. Any hacking attempt to guess the password is locked out after ten (10) consecutive failed attempts, and any unauthorized access log-in attempt is recorded in a log file that includes the originating TCP/IP address. Once a hacking attempt is recognized, blocks of IP addresses (say, from a geographic region or top-level domain where there are no participating sites) can be locked-out at the network level.

Users are required to log off the system upon leaving a workstation. Login sessions are protected by an https certificate and session ID, creating a secure tunnel between the authorized user and the server. The computer automatically logs off the current session after 30 minutes of inactivity, deactivating the session ID. On the computers accessing the EDC, as well as the site laptops/tablets temporarily compiling patient data, users are also required (per training and contractual user agreement) to use screensavers with passwords that prevent access to their computer screens after a short period should they step away from the computer.

Audit Trails: All changes made to data in the electronic record are tracked and recorded in the audit trail which is located within the primary database. This audit trail captures the date/time, and the contents of the changes made, and the user's name used to make the change. The audit trail is created incrementally in chronological order, and in a manner such that overwriting of data cannot occur, in accordance with 21 CFR 11.10(e).

Date and Time Stamps: All data are saved in the VISION EDC system on a central server carrying a time stamp, which is documented in the audit trail. The data server uses the participating site's time zone when available and US Central Time otherwise as the server is located in that time zone. The computers in participating sites use the local time where the study site is located. Individual users are unable to change the time on the server.

8. CRITERIA FOR INTERVENTION DISCONTINUATION

At any point of the study, the patient may choose to withdraw.

9. STATISTICAL CONSIDERATIONS & STATISTICAL ANALYSIS PLAN

9.1 General Design and Analysis Issues

***Main trial design*: Randomized controlled trial (individual patient randomization), parallel design (1:1). Results will be used for primary outcome analyses related to diagnosis accuracy at the ED index visit.**

Secondary cohort design: Two cohorts in the standard care arm are defined based on correctness of ED index visit diagnosis. Cohorts will be followed for adverse events and functional outcomes (1wk, 30d). Estimates will be used for Phase III trial planning for the impact of diagnosis accuracy on clinical events and outcomes. The 6-month follow-up time point (if available) will not be part of the primary trial outcomes.

Observational arm: Patients with vestibular symptoms but no signs or who are not randomized for other reasons (see Inclusion and Exclusion Criteria) will be eligible for a parallel track observational sub-study with limited phone follow-up. Results will support Phase III trial planning and diagnostic algorithm refinement.

Diagnosis adjudication: Prior to adjudication, index VOG results will be interpreted by two independent vestibular experts masked to allocation. They will be given only patient demographic information, a structured summary of dizziness-related history of the present illness, and bedside hearing test results. Using this information, and masked to all other index visit clinical findings, ED physician diagnoses, any neuroimaging, and all follow-up data, they will render an ED index visit diagnosis ("Index VOG Diagnosis"). Prior to adjudication, MRIs will be interpreted by two independent neuro-radiologists masked to allocation and all clinical findings other than demographic information. They will render an index visit diagnosis ("Index Radiology Diagnosis"). A 5-member multidisciplinary panel with ED physician, otolaryngologist, vestibular neurologist, stroke neurologist, and neuro-radiologist will adjudicate diagnoses. The panel will be masked at all times to trial allocation (VRT vs. standard care). Diagnoses will be classified into 1 of 6 diagnostic categories likely to affect ideal ED management and rated as probable or definite based on neuroimaging results and standard clinical criteria. Diagnoses will be rendered in two stages – first based on VOG and all clinical data (including eye videos) from the ED index visit alone, without follow-up data ("Adjudicated Index Diagnosis"); then again after all 1-week testing and 30-day follow-up data are revealed electronically ("Adjudicated Final Diagnosis"). All differences will be resolved by discussion or majority vote.

Algorithm Refinement: It is pre-specified that the VRT algorithm will be adapted iteratively during the trial. The algorithm performance in the VRT arm of the live trial will be monitored from the outset through the use of a human double-check procedure (described above in Section 5.1.3). The human double-check will remain in place until the algorithm performance is sufficient to be considered safe for unattended use, in consultation with the DSMB. The algorithm will be refined as frequently as necessary as long as the human double-check remains in place, and afterwards (if the human double check is removed before trial end) based on a schedule determined by the lead study biostatisticians. In the interest of being able to conduct an end-of-trial analysis using the 'optimized' algorithm, modifications to the algorithm during the trial will be restricted to results from the VRT or observational arms of the trial; in this way, the optimized algorithm can be run on the SOC arm results without concerns for overfitting the algorithm to the data (i.e., a 'split-half' analysis).

Outcome assessment: The ED diagnosis will have been elicited from ED providers by study personnel as a forced choice diagnosis. For the primary outcome, a correct "ED Provider Diagnosis" requires that the "Adjudicated Final Diagnosis" is the same diagnostic category. The VRT diagnosis will be assigned automatically by the online algorithm in real-time. However, as long as the algorithm is being iteratively refined

during this Phase II trial, the human expert double-check procedure will remain in place. In this context, the primary trial outcome will be based on the actual VRT-based care delivered to the patient (regardless of whether that result was generated by the algorithm or modified by the expert human review). This approach is necessary to maintain alignment with the structure of the study as a randomized trial. Additional analyses will test the diagnostic accuracy of both the algorithm as rendered and the end-of-trial 'optimized' algorithm.

Analytic approach: For all primary and linked secondary analyses, we will include only randomized subjects completing the essential elements of the diagnostic study protocol through the end of 1-week follow-up (i.e., with ED index visit VOG test results, follow-up MRI within 14 days, and an in-person neuro-otology visit within 30 days of the index visit). The quality of VOG and MRI testing will be determined by masked, expert raters from the FDAC during an FDAC meeting pre-review process; if either essential test is deemed to be of insufficient quality for analysis (e.g., key VOG tests performed improperly or missing; motion artifact on MRI), such patients will be excluded from the primary and linked secondary analyses of the main trial outcomes. This per-protocol analysis is appropriate for this Phase II study designed to determine the potential efficacy of the VRT intervention on diagnostic accuracy. Without adequate quality VOG and 1-week follow-up data, diagnoses will remain speculative. Subjects lost to follow-up at the 30-day time point (phone follow-up) will be included in these analyses, as 1-month medical record review will generally be sufficient to determine correct diagnoses.

Definitions: For the purposes of all analyses, the term "stroke" refers to any acute cerebrovascular event (ischemic stroke, transient ischemic attack, intracranial hemorrhage), unless expressly specified otherwise.

9.2 Outcomes

9.2.1 Aim 1 (Trial Outcome): Measure the impact of VRT on diagnosis and initial management

Hypothesis 1: The VRT pathway will yield more correct diagnoses by the end of the ED index visit than the standard care (ED provider-determined) pathway.

Primary outcome 1: **Six-Category Diagnosis Accuracy (all, VRT vs. SOC).** Total proportion of correct diagnoses made by VRT vs. SOC among subjects with 30-day adjudicated final diagnoses (the gold standard) categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis).

Statistical Analysis Plan 1:

Primary analysis 1: A generalized linear model with a log link will be used for comparing the true positive rates (TPRs) of VRT and SOC. Without additional covariates, the model based score test is equivalent to a Pearson Chi-square test for unpaired data. The regression model will assess the influence of demographic and key clinical variables as exploratory subgroups. Generalized estimating equation (GEE) [161] method will be used to account for clustering effects by hospital site or provider. VOG non-completers are excluded pre-randomization (randomization occurs post-VOG for all patients).

Specifically, define D_i= 1 if the 30-day adjudicated final diagnosis for the ith subject is categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). Define a test variable as

$$X_{Test} = \begin{cases} 1 & \text{for VRT} \\ 0 & \text{for SOC} \end{cases}$$

Define $Y_i(VRT)$= 1 if the index VRT diagnosis for the *i*th subject is the same as his/her 30-day adjudicated final diagnosis and $Y_i(VRT)$= 0 otherwise. Similarly, define $Y_i(SOC)$= 1 if the ED Provider Diagnosis for the *i*th subject is the same as his/her 30-day adjudicated final diagnosis and $Y_i(SOC)$= 0 otherwise.

The TPR, over the total proportion of correct diagnoses, is defined as follows

$$TPR(X_{Test}) = P[Y_i(X_{Test}) = 1 \mid D_i = 1], \quad X_{Test} = 0, 1.$$

Define the regression model as

$$\log TPR(X_{Test}) = \alpha_0 + \alpha_1 X_{Test} + \overleftarrow{a_\iota} \cdot \overleftarrow{X_\iota}$$

where $\overleftarrow{X_\iota}$ is a vector of additional subgroup variables or other covariates to be explored for assessing the influence of demographic and key clinical variables described in the secondary analysis.

Secondary analysis 1: For each of the six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis), define the gold standard =1 if the 30-day adjudicated final diagnosis is the corresponding category and 0 otherwise. Define test positive respectively for "Index VRT Diagnosis" and "ED Provider Diagnosis" if the diagnosis is the corresponding category and 0 otherwise. Estimate sensitivity, specificity, predictive values and likelihood ratios accordingly for "Index VRT Diagnosis" and "ED Provider Diagnosis". Between-arm comparisons will be performed by the generalized linear model with a log link as described in primary analysis 1a.

Tertiary analysis 1: Subgroups and covariates:

The regression model is

$$\log TPR(X_{Test}) = \alpha_0 + \alpha_1 X_{Test} + \overleftarrow{a_\iota} \cdot \overleftarrow{X_\iota}$$

where $\overleftarrow{X_\iota}$ is a vector of additional subgroup variables or other covariates to be explored for assessing the influence of demographic and key clinical variables described below.

1) Potential Subgroups:
    a. AVS-Only Group: using only patients with acute (continuous) vestibular syndrome >24hr.
    b. Younger-Patient Group: using only patients 49 years of age or younger (i.e., 18-49).
    c. Women-Minority Group: using only patients self-identifying as female, minority, or Hispanic.
    d. NIHSS 0 Group: using only patients with an NIH stroke scale score of zero at ED index visit.
    e. Stands-Independently Group: using only patients who stand without assistance or support.
    f. Normal Hearing Group: excluding any patient with hearing loss (new or old).
    g. Non-AICA Group: excluding any patient with an AICA-territory stroke diagnosis.
    h. Pre-Treatment Group: using only patients with results obtained prior to anti-vertigo meds.
    i. VRT Definite-Only Group: using only 'definite' VRT diagnoses (excluding VRT-E cases).
    j. Specific ED-Only Diagnosis Group: using only 'definite' ED diagnoses (excluding ED O2).
    k. Neuro-otologic Diagnosis Group: using only patients with peripheral or central diagnoses.

2) Potential Covariates:

l. Site: JH vs. UI vs. UM.
m. Age (ordinal): 18-49, 50-59; 60+ years.
n. Age (continuous): for each year.
o. Sex: female vs. male.
p. Race/Ethnicity: minority vs. non-Hispanic white.
q. Symptom Onset (ordinal): 0-24, 25-48, 49-72, >72 hours.
r. Symptom Onset (continuous): time from symptom-onset for each hour.
s. Symptom Type: vertigo vs. dizziness vs. unsteadiness.
t. Symptom Severity: VSS-SF score.
u. Vestibular Syndrome: episodic positional vs. episodic spontaneous vs. acute continuous.
v. Hearing Loss: new hearing loss vs. no new hearing loss.
w. Vascular Risk Severity (continuous): ABCD2 (0-7).
x. Neurologic Severity (continuous): NIHSS (0-42).
y. Ataxia Severity (continuous): SARA score (0-40).
z. Stroke size (continuous): greatest dimension in millimeters.
aa. Stroke location: none, hemispheric-only, posterior fossa (with or without hemispheric).
bb. Confounded: unconfounded vs. potentially confounded (medications or illnesses).
cc. Comorbidities (continuous): Charlson Comorbidity Index (0-56).

Secondary outcomes 1.1-1.7: Diagnosis accuracy for different category groupings and comparisons; the following accuracy comparisons are considered:

1. *Central-Peripheral Diagnosis Accuracy* (all, VRT vs. SOC)

Total diagnosis accuracy VRT vs. SOC using 30-day adjudicated final diagnoses categorized as central (stroke, posterior fossa mass lesion, encephalitis, demyelinating disease, etc.) vs. non-central (includes peripheral vestibular, medical, psychiatric, non-diagnoses, etc.).

2. *Stroke-No Stroke Diagnosis Accuracy* (all, VRT vs. SOC)

Total diagnosis accuracy VRT vs. SOC using 30-day adjudicated final diagnoses categorized as stroke vs. no stroke (includes posterior fossa mass lesion, encephalitis, etc.).

3. *Preventable Six-Category Diagnosis Error* (all, VRT vs. SOC)

Total diagnosis inaccuracy (error) VRT vs. SOC using adjudicated index diagnoses categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). Adjudicated index diagnoses will be determined using only ED index visit data that 'would have been' available clinically (i.e., excluding safety MRI, index hospital admission data, and all follow-up data).

4. *VRT vs. MRI Stroke-No Stroke Diagnosis Accuracy* (VRT arm only, VRT vs. MRI)

Total diagnosis accuracy VRT vs. index imaging using 30-day adjudicated final diagnoses categorized as stroke vs. no stroke (posterior fossa mass lesion, encephalitis, etc.). The VRT arm is chosen here because all VRT arm patients will undergo MRI at the index visit (protocol, clinical, or safety), eliminating diagnostic ascertainment bias that may be present in the SOC arm.

5. *Algorithm-Only VRT Six-Category Diagnosis Accuracy* (all, initial VRT output vs. SOC)

Total diagnosis accuracy "as computed in real time," algorithm-only VRT diagnosis vs. SOC using 30-day adjudicated final diagnoses categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Index VRT Diagnosis" and "ED Physician Diagnosis" compared to the "Adjudicated Final Diagnosis" based on ED index visit and 30-day follow-up clinical assessments. This

outcome measure reflects the weighted average diagnostic accuracy of the various versions of the automated algorithm as it would have been absent human double-check during the course of the trial.

6. *Optimized Six-Category Within-Subject Accuracy* (SOC arm only, optimized VRT vs. SOC)

Total diagnosis accuracy optimized VRT vs. SOC using 30-day adjudicated final diagnoses categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Optimized VRT Diagnosis" and "ED Provider Diagnosis" compared to the "Adjudicated Final Diagnosis" based on ED index visit and 30-day follow-up clinical assessments. Optimized VRT diagnoses will be run using the final (end-of-trial) version of the VRT algorithm. Only SOC-arm subjects are used for this outcome, as VRT patient results will have been used to optimize the algorithm during the trial. VRT diagnoses in the SOC arm (algorithm not run during the trial), will be assigned based on the final, optimized algorithm; for this purpose, the ED SOC diagnosis will be assigned as the VRT diagnosis for algorithm results in the VRT-E group. This outcome measure reflects the estimated diagnostic accuracy of the end-of-trial automated algorithm.

7. *Expert VOG Six-Category Diagnosis Accuracy* (all, expert VOG vs. SOC)

Total diagnosis accuracy adjudicated expert VOG diagnosis vs. SOC using 30-day adjudicated final diagnoses categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Index VOG Diagnosis" and "ED Physician Diagnosis" compared to the "Adjudicated Final Diagnosis" based on ED index visit and 30-day follow-up clinical assessments. This outcome measure reflects the theoretical maximum diagnostic accuracy performance (i.e., expert level) of any future algorithms.

***Statistical Analysis Plan Secondary Outcomes 1.1-1.7*:** A generalized linear model with a log link will be used for comparing the true positive rates (TPRs) of VRT and SOC. Without additional covariates, the model based score test is equivalent to a Pearson Chi-square test for unpaired data. The regression model will assess the influence of demographic and key clinical variables as exploratory subgroups. Generalized estimating equation (GEE) [161] method will be used to account for clustering effects by hospital site or provider.

Secondary outcomes 8-9: Discharge and admission proportions: the following proportions are considered:

8. Central Discharge Proportion (central subgroup only, VRT vs. SOC)

Total discharge proportion of central causes VRT vs. SOC. Central causes determined based on 30-day adjudicated final diagnosis.

9. Peripheral Admission Proportion (peripheral subgroup only, VRT vs. SOC)

Total admission proportion of peripheral causes VRT vs. SOC. Peripheral causes determined based on 30-day adjudicated final diagnosis.

***Statistical Analysis Plan 1.b.2*:** A logistic regression will be used to estimate the odds of discharge in two arms among subjects with central causes determined based on 30-day adjudicated final diagnosis. Similarly, a logistic regression will be used to estimate the odds of admission in two arms among subjects with peripheral causes determined based on 30-day adjudicated final diagnosis.

9.2.2 Aim 2 (Trial Outcome): Measure the impact of VRT on initial diagnostic work-up costs

Hypothesis 2: The VRT pathway is cost saving relative to current ED practice in diagnostic assessments.

Primary outcome 2: Total dollar costs of VRT as compared to SOC for diagnostic tests and consultations obtained during the ED index visit and hospital admission (for those admitted at the index visit). The cost for

VRT arm does not include the costs of protocol safety MRIs or any tests not specified by the pathway but ordered for clinical purposes by ED providers. It does include tests ordered as part of the VRT pathway by consultants or ED providers in the 'equivocal' pathway. Total costs will be calculated by multiplying fixed cost estimates (most recent year available average Medicare reimbursement in US dollars) by utilization rates for each ED index visit service tracked.

Statistical Analysis Plan 2: Analyses will include two-sample comparisons of mean and median costs. Mean of total cost between two study-arms will be compared by modified t-test with unequal variances. Median total cost between two study-arms will be compared by Wilcoxon-Mann-Whitney tests.[162]

9.2.3 Aim 3 (Observational Outcome): Compare clinical outcomes for correct vs. incorrect diagnoses

Hypothesis 3: ED patients with vertigo or dizziness who receive standard care will have better outcomes if correctly diagnosed than if misdiagnosed (*this is an observational outcome in the standard-care arm*).

Primary Outcome 3: Proportion with short-term serious medical events (SMEs) occurring between the time of ED index visit disposition and 1-week research follow-up visit among those with correct vs. incorrect ED provider Diagnosis. "Correct" vs. "incorrect" diagnoses are categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). SMEs will include ED revisits, falls, hip fractures, vascular events (including stroke), and test or treatment complications.

Statistical Analysis Plan 3: A multivariable logistic regression will be used to estimate the odds of an SME (correct diagnosis vs. misdiagnosed) adjusting for demographic and clinical variables.

Specifically, define $S_i = 1$ if the *i*th subject experience SMEs between the time of ED index visit disposition and 1-week research follow-up visit. Following notation used in Aim 1, define the logistic model as,

$$\text{logit}\, P(S_i = 1 | X_{Test} = 0) = \beta_0 + \beta_1 Y_i(0) + \overleftarrow{\beta_2} \cdot \overleftarrow{Z_i}$$

where $Y_i(0)$ is the variable indicating correct or incorrect diagnoses in SOC arm as defined in aim 1, $\overleftarrow{Z_i}$ are additional subgroups variables or other covariates listed in Aim 1.

In addition, standard time-to-event analyses (Kaplan-Meier,[163] Cox regression[164]) will be used to estimate relative hazard ratios, adjusting for demographic and clinical variables listed in Aim 1.

9.3 Sample Size and Accrual

Powering Endpoint: AVERT will be powered to detect a clinically important difference in diagnosis accuracy of 90% vs. 75% (113 per arm). VRT diagnosis is anticipated to be nearly 100% accurate. We have shown that expert eye movement exams have 98.4% (n=187/190) accuracy for differentiating peripheral (vestibular neuritis) from central (stroke) vestibular disorders in acute, continuous vertigo.[73] We have now replicated these findings with the VOG device in 21 acute vertigo patients (100% accuracy). The gold standard

Table 3. Comparison of proportions power estimate (alpha 0.05, power 80%)

VOG Care Correct Diagnoses	Standard Care Correct Diagnoses	Per-arm sample (total study sample)

99%	50%	15 (30)
95%	50%	19 (38)
90%	50%	25 (50)
99%	75%	38 (76)
95%	75%	59 (118)
90%	75%	113 (226)

for BPPV diagnosis is eye movement analysis,[48,78] often by VOG,[51,165] so we conservatively estimate that VOG accuracy across all vestibular conditions will be >90%. Diagnosis accuracy of routine ED care varies, estimated at <20% for BPPV and neuritis[5] and ~70% for stroke, and lower (~50%) if stroke presents with isolated vertigo.[7,135,136] Best estimates suggest an overall correct ED diagnosis rate of about 56% for vestibular patients.[114] In EDs with greater access to specialty consultations or frequent MRI neuroimaging, the proportion of correct diagnoses may range higher. We have powered the AVERT Trial for an anticipated worst case scenario of 90% VRT accuracy and 75% standard care accuracy (Table 3).

Recruitment Capacity: Our 3-site consortium has a total of ~180,000 ED visits per year. Chief symptoms of vertigo/dizziness account for ~3-4% of ED visits.[15,123] Thus, our 3 sites have ~5,400-7,200 ED dizziness visits per year (~5-7 patients per 24hrs per site). Of these, we estimate ~20-30%[20] will meet inclusion criteria (~1-2 patients per 24hrs per site). We will screen during five designated 7-hr shifts weekly, performing VOG on ~3-5 patients per week, enrolling ~2-4 patients per month per site, taking ~3 years to reach 226.

Number of Strokes: With our inclusion criteria, we expect ~10-20% strokes (n=11-23 per arm). This will not yield firm conclusions about VOG stroke accuracy, but should be sufficient for Phase III trial planning.

Interim Analyses: We plan interim analyses to be conducted by the Johns Hopkins Biostatistics Center for review and evaluation by the DSMB (Human Subjects below). The primary concern is risk of misdiagnosis causing harm in the standard ED care arm, since safety MRIs in the VOG arm make harm from misdiagnosis unlikely. Our preliminary plan is to conduct statistical analyses on 30-day clinical events after 75 and 150 patients, but the interim analysis plan will be finalized in concert with the DSMB and institutional IRBs.

Decision Rule for Proceeding to Phase III: We will proceed to Phase III if Phase II suggests either the (1) total diagnosis accuracy point estimate for VRT (or expert VOG) is higher than that of ED standard care (Aim 1); or (2) total diagnosis accuracy is statistically equivalent (Aim 1), but costs are lower for VRT care (Aim 2). Based on scant available data, a Phase III trial using 30-day clinical events would likely need ~1,000-5,000 subjects. Such a trial could be accomplished at reasonable cost with 2-4 years of recruitment at ~10-25 ED sites.

10. BENEFITS

10.1 Direct and Indirect Medical Benefits

We hypothesize that VOG-guided rapid triage (VRT) will help accurately, safely, and efficiently differentiate peripheral from central vestibular disorders in ED patients presenting vestibular vertigo or dizziness, and that doing so has the potential to improve post-treatment clinical outcomes for these patients. The information learned from this study may help others in the future.

For participants assigned (by chance) to receive care guided by the study goggles device, the results may help them get better care in the ED, hospital, and afterwards. The study goggles device has been shown in a small study to accurately diagnose inner ear versus brain causes of dizziness and will be backed up by a human expert double-check during part (or all) of the trial. It is hoped that the study goggles output (including any provided by expert VOG review) will assist doctors with the correct diagnosis for the cause of the participant's dizziness symptoms. If participants are found to have an inner ear balance problem, participants may receive treatments that help them get better faster, with fewer unnecessary tests. If participants are found to have a stroke causing their dizziness, they will get the best possible treatments, and this could reduce their chances of a second stroke or even be life-saving. Participants may benefit from being examined by the dizziness/vertigo/balance specialist

one week after the ED visit and also from the MRI scan and other tests obtained as part of the study. These tests may help them receive a correct diagnosis and correct treatments for dizziness.

For participants assigned (by chance) to receive standard care, there is no direct benefit from the study goggles testing during the ED visit. They may benefit from being examined by the dizziness/vertigo/balance specialist one week after the ED visit and also the MRI scan or other tests obtained as part of the study. These tests may help them receive a correct diagnosis and correct treatments for dizziness, even if these problems were not diagnosed at the first ER visit.

The information learned from this study may help others in the future.

10.2 Payment and Remuneration

Trial participants who complete the Week-1, in-person follow-up testing will be paid $200. The payment structure is based on roughly $25 per hour for time spent at the one-week follow-up visit. It is anticipated that the follow-up visit will take up to 8 hours, for a total payment of $200. If participants complete partial testing, they will receive partial payment based on tests completed ($50 neuro-otology clinical visit, $50 vestibular and audiometric testing, $100 MRI). Payments will not be prorated based on actual hours spent, and a single payment will be issued to the patient after follow-up testing has been completed (within approximately 6-8 weeks of the follow-up visit). In addition, parking vouchers will be provided for free parking for the one week follow-up visit. Transportation assistance may be offered to participants if necessary. For participants scheduled for their follow-up visit overlapping a mealtime, meal vouchers may be available. Neither trial (randomized) nor observational arm patients (not randomized) will receive payment for phone follow-up.

11. RECORD RETENTION, DATA, SAFETY, AND QUALITY ASSURANCE MONITORING, EARLY STOPPING RULES

11.1 Records to be kept:

Participation in this study requires that original study documents be retained for a minimum of 2 years following notification by the study CC that investigations have been discontinued. This standard complies with U.S. FDA regulations (21 CFR §312.62[c]). Records must not be destroyed without first contacting the CC to ensure that the time limits defined in the regulations have been met.

For the purposes of this section, “original study documents” are defined as:

- Subject medical records created at or available to the enrolling center during the subject’s participation in the trial, or any other document that supports entries in the EDC system and represents the original source of that information, including but not limited to applicable sections of medical charts, and patient correspondence, as well as any forms or documents used to compile or maintain original subject data or study procedural information. Intermediary documents and worksheets used to organize and compile original records into a form that facilitates easier transcription into the EDC do not represent original study documents. Certain data may be entered directly into the EDC in which case the EDC system represents the original study document.

- All Essential Regulatory Documents (as defined under Good Clinical Practice Regulations) including: all material communications with the IRB; all communications with the Sponsor that are related to study subjects or which otherwise document material study-related procedures or

safety issues; and, all training records and documentation that all participating staff are suitably qualified and authorized (CVs, 1572, Delegation Log, etc.).

- Archival copies of the data and electronic documents from the VISION-EDC system.

All study documents should be uploaded to the Electronic Trial Master File (eTMF) section of the VISION-EDC system. VISION will be used as the master repository for all site and Sponsor regulatory documents, and all patient source documents with the exception of DICOMs and any records not uploaded to the EDC (perhaps for confidentiality reasons or do to specific site discretion, such as might be suitable for financial contracts), sites generally do not need to maintain duplicate local files unless otherwise mandated by local institutional requirements.

At the conclusion of the study, all entered patient data and uploaded documents (with the exception of DICOMs) in the VISION-EDC system will be archived and provided to the site on DVDs or other digital media. DICOMs submitted to the EDC system will be maintained in the EDC system. Sites will retain DICOMs via their local PACS system (or local copies of CDs). The CC will also maintain a copy.

Regulations require that study documents (including the archive CDs and any study documents not uploaded to the EDC) must be retained in the files of the responsible investigator for potential review by regulatory agencies. The expected retention period is a minimum of 2 years after the final report is submitted to the NIDCD after the conclusion of the overall clinical trial, irrespective of any particular site's participation.

11.2 Data Management:

Data Collection (logistics): SCs will gather data from enrolled subjects in the ED using tablet devices as we have done in the past (NIH/NCRR RR17324-01, AHRQ HS017755-01).[15] We use Digivey™ (Creoso Corporation, Phoenix, AZ) digital survey software platform to create our structured interview, touch-screen clinical data entry forms for use on tablet devices. All data are temporarily stored to local devices, wirelessly synchronized to a central server via encrypted Wi-Fi, and deleted from the local device following confirmed data transfer for optimal security. For VOG data we will use GN Otometrics' OTOsuite Vestibular™ software in the local configuration, and Digivey's Task Manager will securely transfer files to the VISION™ system.

Data Management: Research data will be synchronized to our internet-accessible clinical trials management software platform (VISION™ by Prelude Dynamics, Austin, TX). This system is used by our Clinical Trials CC (BIOS) for rapid and efficient protocol management in large, multicenter, acute stroke trials (30-70 sites).

BIOS Reading Center*:* Once images and videos are received, the BIOS (Clinical Trials CC) Reading Center Technician opens all image and video packets to verify contents. Each is catalogued by the date/time of the scan, the scan modality (MRI, CT, video, etc.), the scan medium (i.e., digital films, hard films, or printouts, etc.), the date received at the Reading Center, and any comments relating to the image packet or specific individual studies. Once the contents have been verified and catalogued, the images are loaded on the study server for archive, and made available for access at the Reading Center workstations.

Data Analysis and Interpretation*:* We will have a safety and data monitoring committee in full compliance with relevant Federal Policies for Data and Safety Monitoring in addition to compliance with all applicable U.S. and international GCP regulations.

- NIH (NOT-98-084) (http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

This program is designed to safeguard the well-being of study participants and to ensure scientific integrity, and will include the following components:

- an externally-appointed, independent DSMB;
- CC and performance site IRBs;
- direct, ongoing oversight by the CC and PI;
- central image reading providing independent, masked radiographic assessments;
- multidisciplinary panel of outcome adjudicators masked to allocation status;
- automated data quality checks at the time of EDC form completion by the investigational site;
- a training program prior to site activation and with continuous communicating and training after trial start-up.

11.3 Data and Safety Monitoring Board: A DSMB will provide an independent review of the research, interim safety and efficacy data, and progress towards achieving the goals of the study. To enable the CC to properly manage the study, the project leadership and key personnel will jointly work on a DSMB plan early in the study start-up process. The externally-appointed DSMB will then approve the plan. The monitoring plan will describe the process for reporting adverse events to the IRB, FDA, and NIH/NIDCD, as appropriate.

FDA Approval and IDE: FDA review of the AVERT proposal has determined that no IDE is required: "FDA has determined that your proposed clinical investigation is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812)." (FDA Letter; available for download from www.braininjuryoutcomes.com).

Data Flow for the Data Safety and Monitoring Board and Final Analyses: Each step in the flow of data for this study is discussed below in regards to its importance in ensuring data integrity and patient safety. The steps are numbered for reference purposes, albeit some steps may occur simultaneously and data for a single patient may be in differing stages in this process.

1. Regulatory Specialist Verification of Study Documentation: Before the site can begin enrolling patients, the CC will verify that all mandatory startup tasks have been completed and appropriate documentation has been uploaded to the electronic data capture (EDC) system's electronic trial master file (eTMF). A parameter in the EDC system will allow the site to enroll a patient and grant user access rights to the online case form. This step will ensure that no site may enroll patients until all regulatory documentation (i.e., IRB approval, investigator qualification), staff training certificates, and contractual requirements are fulfilled. During the study, the CC will work with the site PIs and SCs to maintain the study documentation in the eTMF repository, as all study documentation will be online. At the end of the study, the eTMF content will be provided to the site on compact disks, consisting of all the collected patient data and study documentation, for long term regulatory retention.

2. Data Entry & Source Document Upload: Once a potential patient is identified, the SC will register this new patient via the Digivey backend connection to the VISION EDC system, triggering an automated alert to the CC, reading center, and investigators. Should the patient subsequently fail to qualify for the study, the basic demographic information and reason for screen failure will be used to assess potential selection bias at the site, and for performance tracking and epidemiologic purposes.

Next, the SC will upload copies of applicable de-identified or identified medical records, according to institutional policy, to the eTMF to include the EDC and ambulance records, ED records, progress notes,

medication records, radiology, and other procedure reports, admit and discharge summaries, and adverse event information.

Also, each site will collect CT/MRI data files (as zipped DICOMS) and video images and upload these to the EDC system as well. These will be reviewed by the reading center.

Sites will be expected to enter critical screening data within 24 hours of enrollment, if these are not automatically transferred to VISION from Digivey. The EDC system will be programmed to send automated reminders to the investigator and site managers if sites fail to enter any data in a timely manner.

3. Correction of Automated Errors and Warnings: As data are entered, the EDC system will immediately generate automated warnings (yellow highlights) and errors (red highlights). Warnings will represent data that is outside expected (questionable, but not impossible) limits or where required data are missing. Errors will indicate conditions that are unrealistic (such as an impossibly high age or blood pressure reading) or that indicate data error (such as an invalid date format).

In keeping with FDA requirements for electronic systems, the EDC system will not force an investigator or SC to immediately change the entered data (as that could be misconstrued as encouraging data falsification) but instead the EDC will simply provide feedback via on-screen messages and red/yellow field highlighting. Unresolved warnings may remain, due to patient-specific issues, but will be documented nonetheless. Conversely, red errors must be resolved before the case form page can be advanced in the workflow (i.e., signed by the SC) so the data will be "clean" before it is exported for analysis. The EDC system will also produce various instantaneous reports that are useful for data quality and safety monitoring purposes both by the site staff and the central teams.

4. Source Document Verification and Data Integrity Review: The CC's data quality monitoring team (monitors) will review the online case forms for completeness, logic, and consistency, then verify the entered data against the uploaded source medical records and data collection worksheets. Routine queries identified in this process will be entered into the EDC system (triggering an automated notice to the site). A monitor will then work with the SCs to obtain correction of all data errors and resolution of the corresponding queries. Random sampling will be used to select primary data for 100% source verification. Should the data accuracy for a patient/site exceed certain minimum expectations in this step, or if any material data integrity or regulatory compliance issues are identified, additional data from a patient/site will undergo intensive monitoring and the site referred to the Study PI for corrective action.

5. Data Analyst Verification & Preliminary Compilation: Once the data are entered, source-verified, and safety-reviewed, they will be exported to a statistical analysis package (Stata or SAS) and subject to additional offline edit checks. Expanding upon the patient-oriented monitoring and automated verifications, this step will focus on cross-study evaluation of the data and identify outliers and notable trends.

6. Final Data Listing Review: After a patient is complete and all data are final, a report (tables and graphs) of the important data points will be generated. The data manager will perform a final check on the data to assess data completeness, consistency, and logic in preparation for final data lock.

7. Report-to-Database Verification Audit: A random sample (approximately 10%) of the data in the final data listing will be 100% visually verified against the EDC entries to ensure there are no systematic or sporadic errors generated in the export, analysis, and compilation tasks. This quality control audit will be documented for the study files.

8. Investigator Signoff and Final Data Lock: Finally, after completion of all data cleaning, safety reviews, and QA activities, the investigator will be asked to sign-off on the final patient data and then the case record will be locked. Once locked, the case forms will no longer be editable.

9. Data Collection and Submission to Statistical Center: Data will be entered digitally at the bedside as described above and synchronized to a secure central server. The study database (EDC system) contains raw data entered by SCs and investigators at study sites; it has pre-programmed exports to extract specific data sets for analysis. New exports can be built as may be necessary. The export routine is fully tested and documented as part of the overall EDC validation (in accordance with FDA Part-11 guidance). For data analysis and reporting, the data forms will be finalized through a specific time point (e.g., all data entered, cleaned, signed-off, and locked to prevent further changes). The database is then exported (maintaining appropriate security, change-tracking, and chain-of-custody controls and a record (snapshot) is kept of data to be used for specific reports and analyses, such as for DSMB reports our routine data quality audits. These snapshots are considered interim, as the patient data are subject-to-change while the study is ongoing. StatTransfer (Seattle, WA) or a comparable package is used to export data from tables and queries of the local copy of the database in a format that can work with the statistical software (Stata or SAS) or be used for cost or cost-effectiveness analysis using standard software (TreeAge, http://www.treeage.com/). The outputs are then analyzed, and if graphical presentation is needed, Ploticus, Stata, or SAS are used to generate charts and graphs. The CC will prepare routine interim reports of data analyses and reports summarizing patient screening and selection, protocol adherence, and data quality. After the final full database lock at the conclusion of the study (and for any formal interim analyses stipulated in the protocol), the Statistical Center will develop (using final data exports that are generated by the CC in this same fashion) data analyses that summarize the study's findings. The CC will work with Statistical Center to prepare the final reports summarizing the overall performance of all sites with respect to the protocol and the quality of the data generated.

10. Statistical Analysis and Study Reporting: Final, locked data will be used for the protocol-defined and exploratory statistical analyses and generation of the final study report and associated study publications.

10.4 Interim Analyses for Harm (Early Stopping Rules): We plan two interim analyses to statistically assess for harm in either trial arm (VOG care [active intervention] or standard care). These will be finalized in concert with the externally-appointed DSMB and institutional IRBs, but our initial plans are described here.

Analyses will be conducted by the principal study statistician with oversight by the Johns Hopkins Biostatistics Center for review and evaluation by the DSMB. The first interim analysis will occur at the one-third-way point in the trial after the first 75 patients have been randomized. The second interim analysis will occur at the two-thirds-way point after the first 150 patients have been randomized. If it is determined at either interim analysis that patients are suffering significant harms differentially across the two arms, the DSMB will determine if the trial should be modified (e.g., by adding a safety MRI to the standard care arm) or discontinued.

Potential risks of harm are described in detail in Human Subjects Section above, and adverse event detection and reporting in the Data and Safety Monitoring Plan (below). The primary concern is risk of misdiagnosis and resulting harm in the standard ED care arm, since safety MRIs in the VOG arm make harm from misdiagnosis unlikely. The rationale for allowing a 'no safety MRI'-standard care arm is that immediate safety MRIs for the standard care arm would be non-standard, since only 1-2% of all ED patients with dizziness nationally undergo MRI.[123] Further, we could not measure clinical outcomes of usual care to estimate sample size for a Phase III study. Although the primary concern is risk of harm in the standard care arm, it is also possible that there would be instead be harms from overtesting in the VOG care arm (7. VI. Risks of Wrong Diagnosis or Overtesting).

The DSMB will consider all NIH/NIDCD-defined serious and non-serious adverse events occurring within 30-days

NIH Adverse Event Definition (http://grants.nih.gov/clinicaltrials_fdaaa/definitions.htm):

> "Unfavorable changes in health, including abnormal laboratory findings, that occur in trial participants during the clinical trial or within a specified period following the trial. Two types of adverse event data are to be reported: "Serious" and "Other (Not Including Serious)" adverse events.

- *Serious Adverse Events* include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect. Other important medical events, based upon appropriate medical judgment, may also be considered Serious Adverse Events if a trial participant's health is at risk and intervention is required to prevent an outcome mentioned.
- *Other (Not Including Serious) Adverse Events* are those that are not Serious Adverse Events that exceed a frequency threshold."

These two interim analyses will be based on group sequential methods that control for the effects of 'multiple looks' at the data, as described by Piantidosi.[171] To create the stopping rule, we will use cutoff points (c_k), as described in Jennison and Turnbull,[172] for construction of repeated confidence intervals for a hazard ratio. These critical cutoff points allow for the calculation of relative hazard of adverse events between the two trial arms using Cox regression[164] and assuming O'Brien-Fleming boundaries.[173]

12. HUMAN SUBJECTS

All subject participation will be in accordance with applicable Federal and international Good Clinical Practice (GCP) requirements regarding protection of human subjects, to include 45 CFR Part 46, 21 CFR 50, and the Declaration of Helsinki. All research will be under the review of the IRBs at the respective sites, to include IRB approval at the JHU BIOS CC (JCCI), operating in accordance with 21 CFR Part 56.

The HIPAA Privacy Rule, 45 CFR Parts 160 and 164, will govern the protection of individually identifiable Protected Health Information (PHI). No PHI will be collected without first obtaining a HIPAA waiver and subject informed consent. Access to PHI will be restricted to authorized staff, and only after signing confidentiality, patient privacy, and security agreements. All key personnel, BIOS staff, and all investigative team members at the enrolling sites will provide proof of training on the protection of human research participants and maintenance of patient confidentiality. All certification documents will be required on e-file before a site is activated and its first research participant enrolled. The conduct of this study will be in accordance with NIH's Policy for Data and Safety Monitoring (NOT-98-084).

12.1 Institutional Review Board (IRB) Review and Informed Consent: This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation.

The informed consent documents will meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a) and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study.

The sample consent forms (Appendices 1 and 2) along with the protocol will be provided to study centers for adaptation to conform to local IRB requirements. Performance site consent forms will be submitted to the CC for approval before the initial IRB submission and each time the document is modified. The protocol and informed consent document must be submitted to the IRB for review and approval before the study is initiated

at each respective study center. The final IRB letter of approval and approved informed consent document will be provided to the CC along with other pertinent regulatory documentation.

The sample consent form contains language that subjects' demographic and medical data may be disclosed to specific agencies or persons for their use as part of the AVERT Trial in accordance with HIPAA. All study centers will be required to comply with its individual institution's HIPAA requirements including but not limited to institution-specific HIPAA authorization documents separate from the informed consent document and/or HIPAA waivers for screening patients and the transfer of screening data of enrolled and non-enrolled patients to the CC.

12.2 Study Modification/Discontinuation: The study may be modified or discontinued at any time by the DSMB, NIDCD, or IRB as part of their duties to ensure that research subjects are protected.

13. PUBLICATIONS

The Steering Committee will develop a detailed publications policy. Copies will be distributed to all Clinical Site PIs and the NIDCD Project Scientist. The goals of this policy are to (1) assure and expedite orderly and timely presentation to the scientific community of all pertinent data resulting from the AVERT study; (2) have accurate and scientifically sound presentations and papers; (3) assure that all investigators, including those of junior faculty rank and other professionals have the opportunity to participate and be recognized in study-wide presentations and the preparation of AVERT papers; (4) assure that press releases, interviews, presentations, and publications are accurate and objective, and do not compromise the collaborative trial and the acceptance of its results; and (5) establish procedures for review and approval of ancillary study applications.

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Appendix: Sample Main AVERT Trial Consent Form

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title:	**AVERT_Acute Video-oculography for Vertigo in Emergency Rooms for Rapid Triage**
Application No.:	[insert local IRB number]
Sponsor:	**National Institutes of Health (NIH); National Institute on Deafness and Other Communication Disorders (NIDCD)**
Principal Investigator:	**[insert local PI name and contact information]**

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1. What you should know about this study:

- *You are being asked to join a research study. This consent form explains the research study and your part in the study.*
- *Please read it carefully and take as much time as you need.*
- *Ask your study doctor or the study team to explain any words or information in this informed consent that you do not understand.*
- *You are a volunteer. If you join the study, you can change your mind later. You can decide not to take part or you can quit at any time. There will be no penalty or loss of benefits if you decide to quit the study.*
- *During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.*
- *If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout [insert your institution name]. Doctors outside of [insert your institution name] may not have access to this information. You can ask the research team to send this information to any of your doctors.*
- *A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.*
- *If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.*
- *During this study, you will not have access to certain medical information and test results collected for study purposes. If an emergency occurs while you are in the study, medical information needed for your treatment can be made available to your study physician and other physicians who treat you. When the study is completed, all the information in your medical record will be available to you.*

2. Why is this research being done?

This research is being done to learn more about the diagnosis of stroke in Emergency Room (ER) patients who are experiencing new dizziness or other balance problems.

Sometimes doctors are not able to figure out whether the dizziness or balance problem is coming from a problem with the ear or a problem with the brain (like a stroke). We are trying to make sure doctors in the ER don't miss the chance to recognize and treat strokes early, since strokes that cause dizziness are easy to miss. Specialists can diagnose strokes by looking at tiny movements of the eyes in people with recent dizziness. We are using a non-invasive device that is similar to a pair of swimming goggles that fits over a person's head and takes a video picture of their eyes to study these tiny eye movements. These goggles are already routinely being used to care for patients with vertigo, dizziness and balance problems in specialty clinics and in some ERs.

We want to see if using the information from the goggles helps give better treatment to people with dizziness or balance symptoms. To do this, we need to compare people whose treatment was guided by the information from the goggles to people who receive standard ER care. This study is a "randomized trial." Everyone will be tested with the goggles, but not everyone's doctor will be told the results. The choice of whose doctor gets the goggles test results will be random (by chance, like the flip of a coin). For some participants, the study goggles test results will guide the care they receive and become part of their medical record. For other participants, the results will not be given to their ER doctor, and they will get the same care in the ER that they would have gotten if they did not join the study.

The video goggles in this research study are approved by the United States Food and Drug Administration (the FDA) for measuring balance function. The use of the video googles in this study is investigational. The word "investigational" means that they are not approved by the FDA for diagnosing stroke. The FDA has reviewed its use in this study and determined that it presents a non-significant risk to you and other participants.

Adults, 18 years and older who speak English and are not pregnant, coming to the ER with dizziness, vertigo, or other related balance problems may join this study.

How many people will be in this study?
Roughly 2,000 people are expected to take part in the screening part of this study, but only about 226 will complete the randomized trial, including about 75 at [insert your institution name].

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

NOW, AT THE ER VISIT: After signing this consent form, you will answer some basic questions about your health, including how much your dizziness is affecting you now. Put on a pair of study goggles (like swimming goggles) that measure eye movements and a brief clinical exam will be performed. The goggles have a small camera built into the frame to record a video of your eye movements during this exam. This video technology finds more abnormalities than visual observation alone. It is important to do a portion of the exam in complete darkness and your eyes will be covered temporarily using sticky patches that block light or a drape that covers your face. This should take about 20 minutes. We believe this will help doctors get the right diagnosis and treatment for your dizziness. During the exam, we will ask you to look from side to side, move your head around, and lie down on the bed. We will test your hearing, your balance when standing or walking and some other routine clinical tests of brain function. We will record a video of these tests using a room camera. These video recordings are an essential part of the research study. Without agreeing to them, you cannot join the study. You may request that the video recording be stopped at any time, but this will end your participation in the trial.

By allowing doctors and researchers to view these video recordings of your examination, doctors can use the information to learn and perform the tests in a more consistent manner. We want to use the video recordings of the clinical examination performed today and at the follow-up visit to educate other doctors so they can provide the best possible care for other patients like you. This includes teaching during lectures and eye movement training courses, some of which may be posted to the internet so that physicians anywhere in the world can learn. Most of the videos and other images recorded in the study will not be identifiable (for example, a close-up video picture of your eye). Signing this consent to participate in this trial means you agree to have these unidentifiable images used for the purposes of training, teaching, and scientific publication.

Some images for the research study will include a picture of your face that might be recognized. In order for us to use these identifiable recordings to help educate other doctors around the world, we are asking for your permission below. You do not have to allow us to use these recordings to take part in the study. You may still take part in this study no matter what your decision. These videos will be used for the purposes of training, teaching and scientific publications. These materials will not be used for any other purposes, such as marketing.

□ Yes, I agree for my identifiable images in the video recordings to be used for training, teaching, and scientific publications.
  - □ Yes, I understand that I can request that the video recording be stopped at any time and that by doing so, this will end my participation in the trial.
  - □ Yes, I understand that I have the right to withdraw my consent before the video recordings or my images are shared with the public.

□ No, my identifiable images in the video recordings may not be used for training, teaching, or scientific publications. I understand that my identifiable images in the video recordings will still be seen and analyzed as part of the research study.

At the end of the initial testing, the results of the eye exam with the goggles and other tests will determine if you are eligible for the trial. Even if you are not eligible for the trial, you are still eligible for the part of the follow-up study.

If you are eligible for the trial, you will be randomly assigned to one of two groups. It is like tossing a coin. If you are assigned to the first group, your care in the ER will be guided by diagnostic information from the study goggles. If you are assigned to the second group, you will receive standard care in the ER.

GROUP #1 (STUDY GOGGLES CARE)

a) The study goggles will determine your care. In some cases, your goggles results may be double-checked by a specialist doctor who is an expert in dizziness. If the specialist doctor disagrees with the goggles result, the specialist doctor's opinion will be used to guide your care. The study coordinator doing the goggles testing will tell you whether the specialist will be reviewing your goggles and other test results.

b) If the study goggles (or specialist doctor's review) suggest your dizziness or vertigo probably indicates a stroke, you will be admitted to the hospital to confirm the diagnosis and be treated. This will include a brain scan (magnetic resonance imaging [MRI]) and other standard tests. The length of your hospital stay (usually about 2-3 days) will depend on test results and treatments you need. If tests confirm you have a stroke or other brain problem, you will be given standard treatments for that problem. If tests confirm an inner ear problem, you will be given standard treatments and sent home. If your ER doctors believe you do *not* need hospital care and the hospital stay confirms this, then the research study will pay for the hospital care. If your ER doctors believe you should be admitted to the hospital or if you are found to have a problem that would typically require you to stay in the hospital, the study will not pay for your care.

c) If the study goggles (or specialist doctor's review) suggest your dizziness or vertigo is from an inner ear problem, you will be treated in the ER and sent home. You will be given standard treatments for your inner ear problem such as medications to reduce dizziness or nausea. As an added precaution before you leave, we will obtain an MRI brain scan (details below) to make sure you do not have a stroke.

GROUP #2 (STANDARD CARE)

You will have the study goggles test, but the results will not be given to you or your doctors. The care you receive in the ER will be the same as you would if you were not part of the study.

AFTER TODAY'S ER VISIT: If you are eligible for the trial, there will be one more in-person study follow-up visit and two follow-up phone calls: (1) Week 1 (in person); (2) one month (phone); and, in most cases, (3) six months (phone). If you are not eligible for the trial, there will only be two phone calls. Each appointment is described below.

WEEK-1 IN-PERSON VISIT (TRIAL PARTICIPANTS ONLY): We will ask you to return for an in-person follow-up visit to [insert your institution name]. You will be paid $200 for the completion of the Week-1 follow-up testing that includes a visit with a dizziness specialist and an MRI brain scan. This visit will take about 6-8 hours and may take place in two half days or one full day, depending on scheduling. Free parking and transportation assistance may be offered to participants who need it. For those participants scheduled for their follow-up visit in one day, meal vouchers may be available.

A dizziness specialist will examine you and perform standard clinical tests related to dizziness and balance function. The study goggles test will be performed again. As before, we will take a video recording of your eye movements and use a room camera to record the clinical exam. Standard balance tests, including a caloric test (water in the ear test) and a complete hearing test will be performed. A repeat MRI brain scan (*see below*) will be performed to confirm your diagnosis, since early MRI can sometimes be wrong. Unless these tests were recommended as clinically necessary by doctors at the ER visit (including any specialists, if involved), the tests will be paid for by the research study.

ONE-MONTH & SIX-MONTH PHONE FOLLOW-UP (ALL PARTICIPANTS): You will be called by a member of the research team about one month (and, in most cases, again about six months) after your ER visit to ask some questions and see how you are doing. Each call will take about 20 minutes. We will also check to see if you were back in the ER or the hospital since your last in-person visit with a similar problem. To do this, we will look at specific parts of your medical record that relate to dizziness or strokes, like whether you saw an ear doctor (otolaryngologist) or a brain doctor (neurologist).

DETAILS ABOUT MAGNETIC RESONANCE IMAGING (MRI) BRAIN SCANS:
As part of your participation in this research study, you will have a MRI brain scan to look for stroke or other brain disease that might be the cause of your dizziness or vertigo. If you have known reasons why you cannot have an MRI brain scan, you cannot take part in the trial, but you may still take part in the phone follow-up study. If you agree to join the study, we will ask you questions to make sure you are able to have an MRI. If you are accepted into the trial, before your MRI exam, the

MRI staff will ask you to complete a standard questionnaire that asks similar, but more detailed questions. The purpose of this questionnaire is to be totally sure that you are able to safely enter the MRI area.

After you are cleared as safe and ready to begin, the full MRI exam will take about 90 minutes to complete. To start your MRI test, you will lie on a padded table. A head/neck "coil" frame will be placed around your head, face, and neck (close to your face, but not touching you directly). The coil frame is necessary to help the MRI machine take pictures. The table on which you are lying will be moved to the center of an MRI magnet, which looks like a long narrow tube. Even though the tube is open, some people feel confined in small places. If this bothers you, please notify the MRI staff. You may end your participation in this study at any time by telling the MRI staff. When MRI pictures are taken, radio-signals and magnetic fields are used. When this happens, it is normal for the MRI machine to make loud, banging, and clicking noises. You will be asked to wear earplugs or headphones for your comfort during the exam, and to protect your hearing.

During the exam, the MRI staff can see and hear you. You will be able to hear the MRI staff. The MRI staff will be talking to you during your MRI exam and may give simple instructions to hold your breath, maintain your position, etc. You will generally be requested to lie perfectly still throughout the exam. Again, you may ask the MRI staff to stop at any time. If your MRI is with contrast, at some point during your MRI exam the MRI staff will interrupt the scanning procedure in order to give a "contrast agent" (sometimes called a "contrast dye"). Giving contrast allows us to take more accurate pictures of the balance organs and blood vessels. The agent is given through a needle placed (an IV) in your arm. The IV will be placed using standard hospital techniques. The research study requires an MRI at the 1-week follow-up visit; if you do not wish to receive a MRI, you cannot participate in the trial, but you may still participate in the phone follow-up study.

Incidental Findings

The MRI you are having as part of this research study will be reviewed by a qualified physician just as when having the MRI as part of your routine medical care. There is a possibility that while reviewing your MRI we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding." We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home. A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding. If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, it may affect your current or future life or health insurance coverage. This risk will vary depending on the type of insurance plan involved.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

How long will you be in the study?

The entire study will last for about 5 years. You will be in this study for about six months.

4. What are the risks or discomforts of the study?

- You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.
- You might experience some increased dizziness or feel sick to your stomach during the examination, although most of our patients and research participants do not.
- The sticky patches on your eyes, if used, may cause some brief discomfort when removing.
- There is a rare risk of neck pain or slowed heart rate during the examination.
- There is a rare risk of discomfort from the audiology tones during the examination.
- The risks of the MRI are the same as in routine brain scans for dizziness/vertigo.

MRI Brain Scan

The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia) or by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the MRI scanner. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, including metal in your eye.

The contrast agent you will receive is FDA-approved and used routinely for MRI exams. It contains a material called gadolinium. The injection of contrast may cause discomfort, tingling or warmth in the lips, metallic taste in the mouth, tingling in the arm, nausea, or headache. These symptoms occur in less than 1% (less than 1 in 100) of people and go away quickly. Insertion of the needle and intravenous catheter (small plastic tube often referred to as an "IV") to give you gadolinium may cause minor pain, bruising and/or infection at the injection site. There is a small risk of an allergic reaction to gadolinium; however, a severe allergic reaction occurs in less than one in 300,000 people.

People must have normal kidney function to receive gadolinium during the research MRI in this study. People with severe kidney failure who receive gadolinium are at risk of developing Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD). This (NSF/NFD) is a serious progressive disease and can result in death. There are no confirmed cases of this complication (NSF/NFD) occurring in individuals with normal kidney function (GFR $\geq$ 30 mL/min).

All subjects will undergo the standard, institutionally required clinical prescreening tests, including MRI questionnaire and blood or urine test for kidney disease or pregnancy, per policy. Please notify a doctor, nurse, or technologist if you are allergic to gadolinium, if you have any kidney problems, or if you experience any of these or other side effects.

A physician will be available during the procedure to administer any necessary care if side effects do occur, and to determine when or if the injection of the gadolinium should be stopped.

Unexpected Diagnosis or Future Diagnostic Tests: In this study you will get special diagnostic tests that you would not normally get. These tests could identify brain diseases that you have but did not know about, such as stroke or multiple sclerosis. Finding this out could make you upset. It could also lead to other tests or treatments outside the study that might have side effects, risks, or costs to you. These tests could also be wrong, which might lead to unnecessary tests or treatments.

Confidentiality: There is always a risk that information about you may become known to people outside this study. We will do everything we can to make sure that everyone who needs to see your information uses it only for the study and keeps it confidential.

Randomization (Coin Flip): The study goggles results (or specialist doctor's opinion after reviewing them) might lead your ER visit doctor(s) to choose tests or treatments that they might not have chosen. We believe those choices will benefit you, but we cannot be sure. For example, a common situation is that the study goggles results might require a brain scan that your ER doctor wouldn't have ordered. The tests could show an important medical condition, like stroke, but it might also turn out that these other tests don't reveal anything, making them unnecessary. We believe the goggles lead to tests that are medically necessary and decrease unnecessary tests, but we cannot be sure this will happen for you.

5. Are there risks related to pregnancy?

Pregnant women may not take part in this study because of unknown MRI/gadolinium risks for an embryo or fetus. Women of childbearing potential may have a urine or blood pregnancy test, per institutional policy, to confirm they are not pregnant.

6. Are there benefits to being in the study?

You may or may not benefit from being in this study. The information learned from this study may help others in the future.

If you are assigned (by chance) to receive care guided by the study goggles device (that might include input from a dizziness/vertigo specialist), the results may help you get better care in the ER, hospital, and afterwards. The study goggles device has been shown in a small study to accurately diagnose inner ear versus brain causes of dizziness. We believe the study goggles will help your doctor get the correct diagnosis for the cause of your dizziness symptoms. If you are found to have an inner ear balance problem, we believe you may receive treatments that help you to get better faster, with fewer unnecessary tests. If you are found to have a stroke causing your dizziness, you will get the best possible treatments, and

these could reduce your chances of a second stroke or even be life-saving. You may benefit from being examined by the dizziness/vertigo/balance specialist one week after the ER visit. You may benefit from the MRI scan or other tests obtained as part of the study. These tests may help you receive a correct diagnosis and correct treatments for dizziness.

If you are assigned (by chance) to receive standard care, there is no direct benefit to you from the study goggles testing during the ER visit. You may benefit from being examined by the dizziness/vertigo/balance specialist one week after the ER visit. You may benefit from the MRI scan or other tests obtained as part of the study. These tests may help you receive a correct diagnosis and correct treatments for dizziness, even if these problems were not diagnosed at the first ER visit.

7. What are your options if you do not want to be in the study?

You do not have to join this study. If you do not join, your care at [insert your institution name] will not be affected.

8. Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet). This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. Will you be paid if you join this study?

You will be paid $200 if you are eligible for the trial and complete the Week-1 follow-up visit. It is expected that the follow-up visit will take up to 8 hours. You will also receive free parking for the follow-up visit. Transportation assistance may be offered. For participants scheduled for their follow-up visit overlapping a mealtime, meal vouchers may be available. If you complete part of the follow-up visit, you will receive partial payment based on the tests you completed. You will receive payment by check about 6-8 weeks after completing the study follow-up. There is no additional payment for the phone follow-up, regardless of whether you are eligible for the trial or only the phone follow-up study.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from [insert your institution name] exceed $600 per year, [insert your institution name] will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us. Your social security number may also be used at the 6-month follow-up to make sure you're still alive if we cannot reach you. Although your name and birthdate can be used to check government records, your social security number is the only reliable way for us to make sure we know it's you.

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, [insert your institution name] may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

11. Why might we take you out of the study early?

You may be taken out of the study if:

- You fail to follow instructions.
- You become pregnant prior to your one-week follow-up visit.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, [insert your institution name] may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

12. How will your privacy be protected?

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the diagnostic tests described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records. This could include information about sensitive health conditions (such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment) if they might be linked to your dizziness.

The research team will know your identity and that you are in the research study. Other people at [insert your institution name] may also see or give out your information, particularly your doctors, who may need this information for your clinical care. We make this information available to your doctors for your safety.

People outside of [insert your institution name] may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration or National Institutes of Health), Johns Hopkins, safety monitors, and other sites involved in the study. We will not give out your information unless it is necessary for the study or required by specific rules or regulations.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside [insert your institution name] who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that it will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other health care providers. You may be asked to give us a list of other health care providers that you see.

14. What treatment costs will be paid if you are injured in this study?

[insert your institution name] and the federal government do not have programs to pay you if you are hurt or have other bad results from being in the study. However, medical care at [insert your institution name] is open to you as it is to all sick or injured people.

- If you have health insurance: The costs for any treatment or hospital care you receive as the result of a study-related injury will be billed to your health insurer. Any costs that are not paid for by your health insurer will be billed to you.

- If you do not have health insurance: You will be billed for the costs of any treatment or hospital care you receive as the result of a study-related injury.

By signing this form you will not give up any rights you have to seek compensation for injury.

15. What other things should you know about this research study?

a. What is the Institutional Review Board (IRB) and how does it protect you?

The [insert your institution name] IRB is made up of:

- Doctors
- Nurses
- Ethicists

- Non-scientists
- and people from the local community.

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is (**local IRB phone number**). You may also call this number for other questions, concerns or complaints about the research.

b. What do you do if you have questions about the study?
Call the principal investigator, **[local PI name]** at **[local PI phone number]**. If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at **[local IRB phone number]**.

c. What should you do if you are injured or ill as a result of being in this study?
If you think you are injured or ill because of this study, call [local PI name] at [local PI phone number] during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call 911. Once stable, notify [local PI name] at [local PI phone number] during regular office hours or at [24-hour phone number] after hours and on weekends.

d. What happens to Data that are collected in the study?
[insert your institution name] and our research partners work to understand and cure diseases. The data you provide are important to this effort.

If you join this study, you should understand that you will not own your data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy (insert your institution name) may share your information with our research sponsors and partners.

16. What does your signature on this consent form mean?
Your signature on this form means that:

- you understand the information given to you in this form
- you accept the provisions in the form
- you agree to join the study

You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

_____

Signature of Participant (Print Name) DateTime

_____

Signature of Person Obtaining Consent (Print Name) DateTime

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO [local EPIC fax number]; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE [insert your institution name] LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS. IF THIS CONSENT FORM DOES NOT HAVE A [insert your institution name] LOGO, DO NOT USE IT TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.