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

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Statistical Analysis Plan
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STATISTICAL ANALYSIS PLAN

1 TRIAL SUMMARY

1.1 Introduction

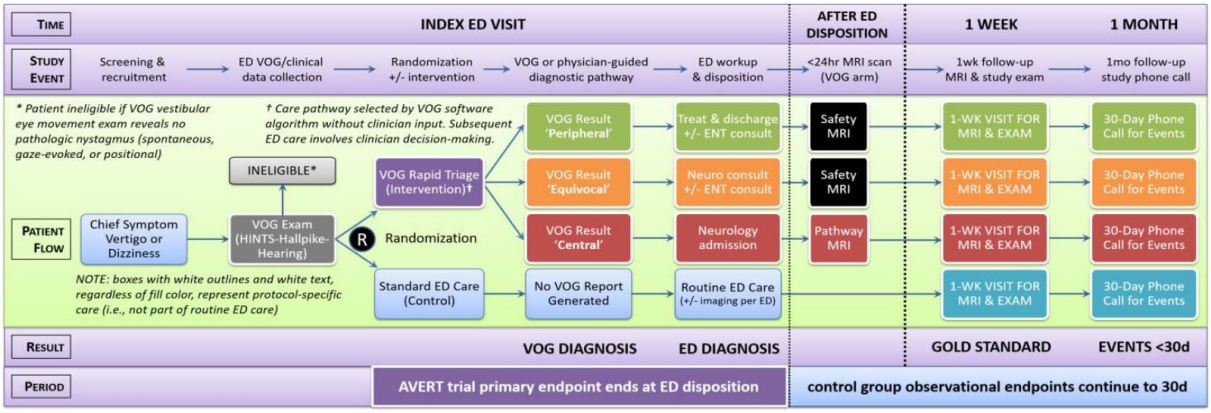
This study seeks to improve clinical care for peripheral and central vestibular disorders by translating recent advances in vestibular physiology to clinical practice. The **AVERT** Trial (**A**cute **V**ideo-oculography for **V**ertigo in **E**mergency **R**ooms for **R**apid **T**riage) is a multicenter, randomized, phase 2 clinical trial of video-oculography (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 five EDs.

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.

1.3 Study design

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.



Trial Arm 1 VRT (intervention arm): VOG-based logic rules determine rapid triage pathway.
Trial Arm 2 Standard Care (control arm): usual ED care plus VOG exam, no VOG report generated.
Observational arm: ED MRI VOG and six-month follow-up.

1.4 Recruitment

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).

2. STATISTICAL ANALYSIS PLAN

2.1 General Design 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: Cohorts will be followed for adverse events and functional outcomes (1wk, 30d). Estimates will be used for phase 3 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.

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.

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 SOC 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.

2.2 Outcomes

2.2.1 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 *i*th 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 SOC 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

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

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 SOC 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 SOC 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

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

where $\overrightarrow{X_\iota}$ 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 1.1-1.2: Diagnosis accuracy for different category groupings and comparisons; the following accuracy comparisons are considered:

1. Expert VOG Six-Category Diagnosis Accuracy (SOC arm, expert VOG vs. ED SOC)

Total diagnosis accuracy adjudicated expert VOG diagnosis vs. ED SOC using 30-day adjudicated final diagnoses categorized in one of six diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Index Expert VOG Diagnosis" and "ED SOC Diagnosis" within the SOC arm based on ED index visit and 30-day follow-up clinical assessments. This within-subject comparison reflects the current potential accuracy of expert VOG-based tele-diagnosis and the targeted maximum diagnostic accuracy performance (i.e., expert level) of future automated algorithms.

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 (including peripheral vestibular, medical, psychiatric, or other central neurologic causes such as multiple sclerosis, traumatic brain injury, epilepsy, or anticonvulsant toxicity).

***Statistical Analysis Plan Secondary Outcomes 1.1-1.2*:** 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.

2.2.2 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]

2.2.3 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 prespecified medical events of interest (PMEIs) occurring between the time of ED index visit disposition and 1-week research follow-up visit among those with correct vs. incorrect ED SOC diagnosis. "Correct" vs. "incorrect" diagnoses are categorized in one of six possible diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). PMEIs will include ED revisits, falls, 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 PMEI (correct diagnosis vs. misdiagnosed) adjusting for demographic and clinical variables.

Specifically, define S_i = 1 if the *i*th subject experience PMEIs 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

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

where $Y_i(0)$ is the variable indicating correct or incorrect diagnoses in SOC arm as defined in Aim 1, $\overleftarrow{Z_\iota}$ 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.

Exploratory Outcomes:

1. 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 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).

2. 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.

3. 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 diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Index VRT Diagnosis" and "ED SOC

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.

4. 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 diagnosis categories (3 peripheral, 1 central, 1 medical/other, 1 non-diagnosis). We will use "Optimized VRT Diagnosis" and "ED SOC 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.

5. 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.).

6. 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.

7. 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.

2.3 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 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

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)

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% VOG 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 3 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 3: We will proceed to phase 3 if phase 2 suggests either the (1) total diagnosis accuracy point estimate for 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 VOG care (Aim 2). Based on scant available data, a phase 3 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.

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

3.1 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 coordinating center 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 coordinating center 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 coordinating center 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.

3.2 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 Coordinating Center (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 Coordinating Center 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 (e.g., 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;
- coordinating center and performance site IRBs;
- direct, ongoing oversight by the coordinating center and PI;
- central image reading providing independent, masked radiographic assessments;
- multidisciplinary panel of outcome adjudicators masked to allocation status;
- automated data quality checks at 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.

3.3 Data and Safety Monitoring Board (DSMB)

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 coordinating center 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 coordinating center 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 coordinating center 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 coordinating center, 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 coordinating center’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 coordinating center 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 coordinating center in this same fashion) data analyses that summarize the study's findings. The coordinating center 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.

3.4 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. 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.

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 (ck), 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]

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