DE NOVO CLASSIFICATION REQUEST FOR
BRAINSCOPE AHEAD 100, MODELS CV-100 AND M-100

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Brain Injury Adjunctive Interpretive Electroencephalograph Assessment Aid. A Brain Injury Adjunctive Interpretive Electroencephalograph Assessment Aid is a prescription device that uses a patient's electroencephalograph (EEG) to provide an interpretation of the structural condition of the patient's brain in the setting of trauma. A Brain Injury Adjunctive Interpretive EEG Assessment Aid is for use as an adjunct to standard clinical practice only as an assessment aid for a medical condition for which there exists other valid methods of diagnosis.

NEW REGULATION NUMBER: 882.1450

CLASSIFICATION: CLASS II

PRODUCT CODE: PIW

BACKGROUND

DEVICE NAME: AHEAD 100, MODELS CV-100 AND M-100

SUBMISSION NUMBER: DEN140025

DATE OF DE NOVO: AUGUST 19, 2014

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REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

- The Ahead® 100, consisting of two models, i.e., the Ahead® M-100 and the Ahead® CV-100, is indicated for use as an adjunct to standard clinical practice to aid in the evaluation of patients who are being considered for a head CT, but should not be used as a substitute for a CT scan. This device is to be used for this purpose in patients who sustained a closed head injury within 24 hours, clinically present as a mild traumatic brain injury with a Glasgow Coma Scale score (GCS) of 13-15, and are between the ages of 18-80 years.

- A negative BrainScope® Classification may correspond to brain electrical activity consistent with no structural brain injury visible on head CT in patients presenting as a mild traumatic brain injury, within 24 hours of injury.

- A positive BrainScope® Classification corresponds to brain electrical activity that may be present in both patients with or without a structural brain injury visible on head CT. A positive BrainScope® Classification does not establish the presence of a structural brain injury visible on head CT.

- The Ahead® 100 device is intended to record, measure, analyze, and display brain electrical activity utilizing the calculation of standard quantitative EEG (qEEG) parameters from frontal locations on a patient's forehead. The Ahead® 100 calculates and displays raw measures for the following standard qEEG measures: Absolute and Relative Power, Asymmetry, Coherence and Fractal Dimension. These raw measures are intended to be used for post hoc analysis of EEG signals for interpretation by a qualified user.

- The Ahead® M-100 model additionally stores and displays an electronic version of the Military Acute Concussion Evaluation (MACE) cognitive assessment and user-entered responses to the MACE questions. There is no interaction between EEG-related functionality, including analyzing and displaying brain electrical activity, and the function of storing and displaying MACE information.

- The Ahead® 100 is intended for use by physicians, or under the direction of a physician, who have been trained in the use of the device.

- The Ahead® 100 is a prescription use device.

LIMITATIONS

For prescription use only.

The Ahead 100 should not be used in patients with Glasgow Coma Scale score < 13.

The safety and effectiveness of the Ahead 100 device has not been evaluated in patients who:

- Have forehead, scalp, or skull abnormalities or other conditions that would prevent correct application of the electrode headset
- Have an open head injury
- Are currently receiving sedation medications
- Have a history of brain surgery
- Have Parkinson's Disease
- Have multiple sclerosis
- Have a seizure disorder
- Have brain tumors

- Have a psychiatric disorder for which they take psychiatric medication on a daily basis
- Have chronic drug or alcohol abuse
- Have a history of stroke or TIA within the past year
- Are currently receiving dialysis or are in end-stage renal disease
- Have an active fever defined as greater than 100°F or 37.7°C

The Ahead 100 should only be used by physicians, or under the direction of a physician, who have been trained in the use of the device. To ensure proper device performance, the user must first perform a diagnostic evaluation per the standard of their practice that includes an evaluation using the Glasgow Coma Scale. Ahead 100 interpretations are based on the clinician's initial diagnostic evaluation, the subject's age and the EEG results.

The device should not be used as a substitute for a CT scan or as a stand-alone diagnostic device.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS AND PRECAUTIONS.

DEVICE DESCRIPTION

The Ahead 100 is a portable EEG system consisting of two models: the Ahead M-100 and the Ahead CV-100. As stated in the Indications for Use above, the only functional difference between the M-100 model and the CV-100 model is that the M-100 stores and displays an electronic version of the Military Acute Concussion Evaluation (MACE) cognitive assessment and user-entered responses to the MACE questions in addition to all other device functionality as discussed below.

The Ahead 100 device is comprised of the following main components:

1. The Ahead 100 Handheld Unit
2. The Electrode Headset
3. The Patient Interface Cable
4. The Compact Flash Card (CF Card)

The Handheld Unit, Patient Interface Cable, and Electrode Headset (Figures 1 and 2) interface together to facilitate the collection of EEG data from the patient. The Electrode Headset includes 8 wet gel electrodes integrated into a single use, disposable headset that allows for electrode placement over the following frontal locations: Fp1, Fp2, Fpz, AFz, F7, F8, A1, and A2 as defined by the standardized International 10-20 Electrode Placement System (Figure 3). The Patient Interface Cable connects the Electrode Headset to the Handheld Unit and contains a preamplifier that prepares the electrical signals measured by the Electrode Headset for processing by the Handheld Unit.

Figure 1. Handheld Unit and Patient Interface Cable

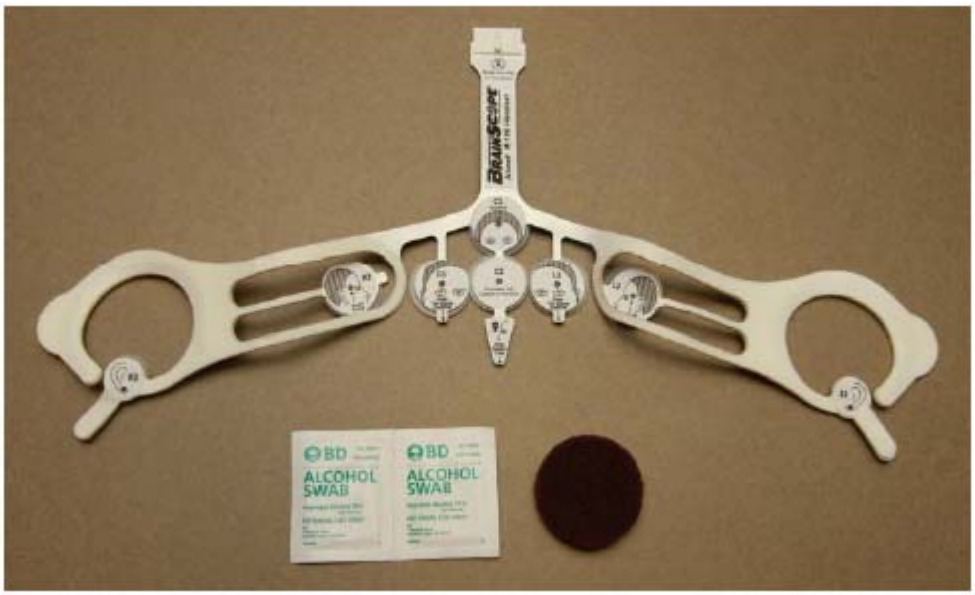

Figure 2. Electrode Headset

Figure 3. Patient wearing an applied Electrode Headset

The Handheld Unit employs a color, touch-screen user interface and utilizes proprietary software to perform real-time analyses of the collected EEG data. Using the Handheld Unit, the user is able to review the raw EEG data, view spectral plots, and view a number of calculated quantitative EEG (qEEG) measures including Absolute and Relative Power, Asymmetry, Coherence and Fractal Dimension.

The software utilized by the Handheld Unit also processes the collected raw EEG to produce the final Ahead 100 classification. This data analysis includes filtering the raw EEG, performing artifact reduction, computation of a variety of qEEG features across specific frequency bands, normalization of these computed features, a quality check to identify potential outliers, integration of these features to determine the appropriate classification, and finally a graphical display of this classification to the user. The algorithm used to integrate the computed features and determine a classification was pre-established in a separate study, prior to validation in the B-AHEAD II study.

The Ahead 100 device provides one of two potential classifications of the patient's recorded EEG data (Figure 4):

1. "May correspond to brain electrical activity consistent with no structural brain injury visible on head CT in patients presenting as a mild traumatic brain injury, within 24 hours of injury." or,
2. "Corresponds to brain electrical activity that may be present in both patients with or without a structural brain injury visible on head CT. A positive result does not establish the presence of a structural brain injury visible on head CT."

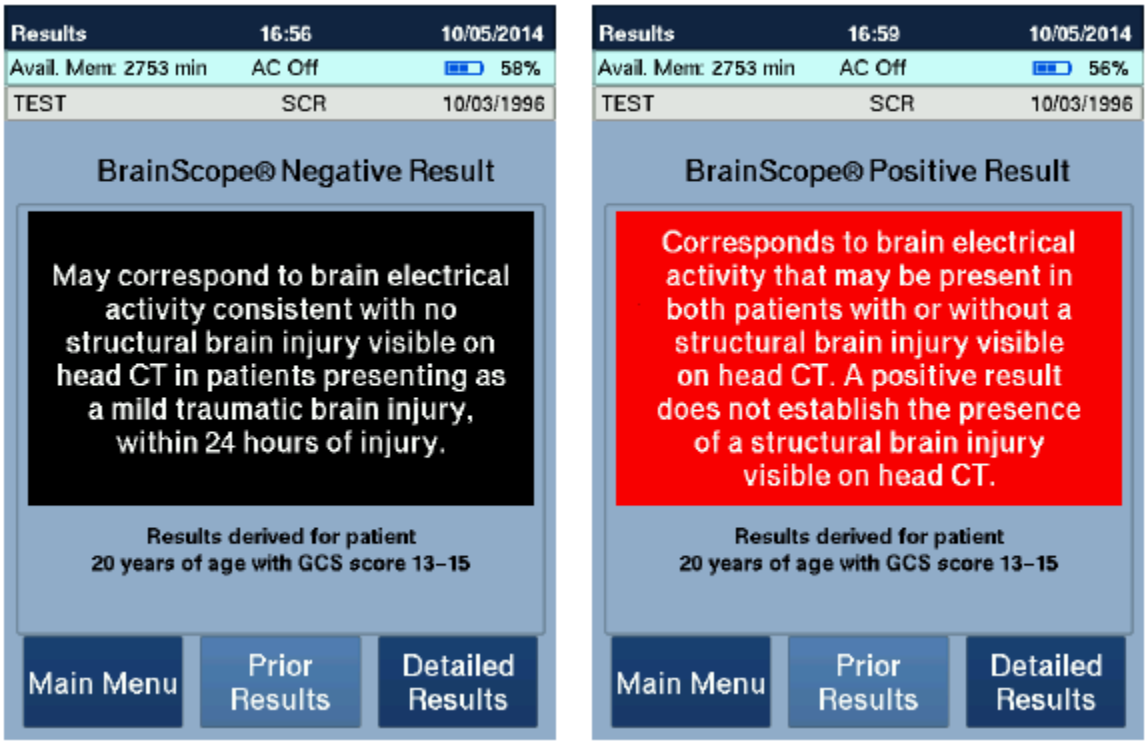

Figure 4. BrainScope Device Classification of the Patient's EEG data

SUMMARY OF NONCLINICAL/BENCH STUDIES

The sponsor conducted a series of bench testing to demonstrate that the Ahead 100 device would perform as anticipated. Please refer to the sub-sections below for a discussion of each of the types of non-clinical testing performed.

BIOCOMPATIBILITY/MATERIALS

The patient contacting materials packaged as part of the Ahead 100 are the electrode headset and skin prep kit. The electrode headset provided with the Ahead 100 is manufactured and procured from Techprint, Inc. and Vermed, Inc. Biocompatibility testing according to ISO 10993 has been provided that demonstrates safety of the electrode headset for the intended single use and not for use over broken skin. Cytotoxicity for the hydrogel and adhesive used in the headset were Grade 1 and Grade 2, respectively. Primary Irritation Index for the hydrogel and adhesive were 0.0 and 0.9, respectively. Neither component exhibited signs of causing delayed dermal contact sensitization. This information is sufficient.

SHELF LIFE/STERILITY

The Ahead 100 is not provided sterile nor are any of the components to be sterilized by the end user. Cleaning and maintenance instructions for the handheld component of the Ahead 100 are included in the labeling.

The disposable electrodes are single use, so cleaning instructions for the electrodes have not been provided.

Neither the Ahead 100 nor any of its components are provided sterile. Using a real time aging protocol, the estimated product life of the Handheld Unit is 5 years and the single-use disposable Electrode Headset has a shelf life of 12 months. Based on the nature of the system components, this estimation of product life is acceptable.

ELECTROMAGNETIC COMPATIBILITY (EMC) AND ELECTRICAL SAFETY

The Ahead 100 device was tested in accordance with the following consensus standards and passed the following EMC, immunity, electrical, mechanical, and thermal safety tests:

Standard	Name
IEC60601-1: 1988 +A1: 1991 +A2: 1995	Medical Electrical Equipment; Part 1: General Requirements for Safety
IEC60601-2-26: 2002	Medical Electrical Equipment Part 2-26: Particular Requirements for the Safety of Electroencephalographs
IEC60601-1-2: 2007	Medical electrical equipment; Part 1-2: General Requirements for Safety - Section 2: Collateral standard: Electromagnetic compatibility - Requirements and tests.
IEC60601-1-4	Medical Electrical Equipment; Part 1-4: General Requirements for Safety - Collateral Standard. Programmable Electrical Medical Systems.
IEC/UL 60950-1	Information technology equipment - Safety - Part 1: General requirements.

SOFTWARE

Software for the device consisted of proprietary software. The software is consistent with a 'MODERATE' level of concern, as discussed in the FDA document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.

PERFORMANCE TESTING – BENCH

The sponsor provided sufficient bench testing and all results demonstrated acceptable performance. Non-clinical testing included functional verification testing of the following:

- Battery charge and discharge according to specification
- Impedance measurement and display
- EEG signal measurement and display
- Noise performance

- Common mode rejection ratio (CMRR)
- Frequency and phase response within EEG frequency bands
- Repeatability and reliability testing demonstrating consistency of the device outputs when testing is administered by a variety of physicians as well as when testing is administered on the same subject at multiple different times
- Artifact reduction
- qEEG feature calculation
- Discriminant score calculation and final classification that demonstrates the algorithm performs predictable and repeatable calculations given a fixed or known set of input data
- Human factors engineering/usability that obtains either data or feedback from users of the device in order to verify adequate use and operability of the device
- Software verification and validation testing as mentioned above that includes a complete device hazard analysis

SUMMARY OF CLINICAL INFORMATION

Clinical Study Design

A prospective, controlled, non-randomized, pivotal study was conducted to validate the EEG-derived BrainScope Ahead 100 device classification in the discrimination between subjects suspected of having a traumatic brain injury (TBI) who have a structural brain injury on CT scan (CT+) and subjects who either have no structural injury on CT scan or in whom a CT scan was not indicated (CT-). Subjects were to be 18-80 years of age admitted to an Emergency Department (ED) with suspicion of TBI and with a GCS > 8. The injury was specified to have occurred within 24 hours of presentation to the ED. The study was not designed to include a separate "control" group of non-head-injured subjects in the statistical analysis, though such subjects were recruited and enrolled as a separate cohort. A head-injured control group who were suspected of or sustained a head injury but did not report or manifest symptoms (e.g., presented with facial lacerations or whiplash) was recruited and included as well. Exclusion criteria included

- forehead, scalp, or skull abnormalities or other conditions that would prevent correct application of the electrode headset;
- dementia,
- Parkinson's Disease,
- multiple sclerosis,
- seizure disorder,
- brain tumors,
- history of brain surgery,
- chronic psychiatric history or taking daily psychiatric drugs,
- drug or alcohol abuse,
- fever,
- currently receiving dialysis or in ESRD,
- condition listed as "critical",
- open head injury,
- advanced airway management,

- receiving sedatives, and
- pregnancy.

Subjects who received a head CT and met the New Orleans Criteria (NOC) were used for the truth assessment of structural injury. Subjects who presented with GCS = 15 and did not meet the NOC were considered CT negative. If a head CT was performed on a subject with GCS = 15 and no clinical findings, then the CT results were used as the truth. The final head CT readings were reviewed by a panel of 3 blinded neuroradiologists, and classification was determined by a majority of the panel. Data acquisition by the subject device was to occur in the ED. All treating physicians were to be blinded to the output of the Ahead 100 device. A follow-up visit 72-96 hours after initial visit was conducted in person or via telephone to determine the subject's level of injury recovery as well as if additional brain imaging (e.g., CT Scan or MRI) was conducted.

The primary endpoint of the study is the sensitivity and specificity of the device in discriminating structural brain injury on CT scan (CT+) in patients suspected of head injury from those who either have a head injury without CT findings or no head injury (CT-). A lower one-sided 95% confidence limit greater than 78% for sensitivity and a lower one-sided 95% confidence limit greater than 50% for specificity were defined as the pre-specified performance endpoints. The study also included a secondary objective to compute the negative and positive predictive values (NPV and PPV, respectively) for a range of prevalence of CT+ subjects, although no performance goals were specified.

Clinical Study Results

A total of 817 subjects were enrolled at 11 study sites in the US and were included in the intent-to-treat (ITT) population, of which 552 subjects were included in the analysis of diagnostic accuracy per the intended use. Of the 265 subjects not included in the analysis, 142 subjects were non-head injured controls that were not part of the intended use population and were excluded, and 123 subjects had missing data in the form of either a missing clinical classification or a missing device classification.

The clinical classification and Ahead 100 device classification results are provided in Table 1. The specificity, sensitivity, PPV and NPV are provided in Table 2.

Table 1. Classification results of the Ahead 100 device versus Clinical Classification

Ahead 100 Classification	Clinical Classification			Total
	CT+	Missing	CT-	
Positive	91	6	224	321
Missing	20	19	70	109
Negative	25	8	212	245
Total	136	33	506	675

Table 2. Performance results for the Ahead 100 classification

	Estimate	95% Confidence Interval
Specificity (%)	48.6% (212/436)	(43.8%, 53.4%)
Sensitivity (%)	78.5% (91/116)	(69.9%, 85.5%)
PPV (%)	28.9% (91/315)	(23.9%, 34.2%)
NPV (%)	89.5% (212/237)	(84.8%, 93.1%)

For PPV (positive predictive value) and NPV (negative predictive value) reference, the study prevalence of the positive condition (structural abnormality confirmed on CT scan) was 21% (116/552).

Conclusions

While the clinical study failed to meet the predefined primary endpoints, the use of the Ahead 100 device may provide adjunctive information about patients when the clinician does not deem it necessary to order a CT scan, adding confidence in the clinical decision path. Ahead 100 device performance has been established by the measured NPV in the clinical investigation. With a study prevalence of 21%, the NPV was 89.5%, demonstrating an 89.5% probability that patients with a negative device classification had no structural injury identifiable on head CT. A negative classification may correspond to brain electrical activity consistent with no structural brain injury visible on head CT in patients presenting as a mild traumatic brain injury, within 24 hours of injury.

Ahead 100 device safety has been established. Physical use of the device has been shown to be safe. EEG collection is a non-invasive procedure. No adverse device events and no unanticipated adverse device events were reported in the clinical investigation.

LABELING

The *Ahead CV-100 System User Manual* and *Ahead M-100 System User Manual* are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device (see *Ahead CV-100 System User Manual* and *Ahead M-100 System User Manual*). The labeling satisfies the requirements of 21 CFR § 801.109 Prescription devices. The labeling for the Ahead 100 includes:

1. A warning that the device is not to be used as a stand-alone diagnostic.
2. A detailed summary of the clinical performance testing, including any adverse events and complications.
3. The qualifications and training requirements for device users including technicians and clinicians.
4. The intended use population and the intended use environment.
5. Instructions technicians should convey to patients regarding the collection of EEG data.
6. Information allowing clinicians to gauge clinical risk associated with integrating the EEG-based measure of structural brain injury into their diagnostic pathway, including instructions in case the device is unable to provide results for any reason.

The safety characteristics and intended purpose of the device requires training of the end-user (see also *Ahead CV-100 System User Manual* and *Ahead M-100 System User Manual*). Clinicians utilizing the Ahead 100 output report should be physicians who have familiarized themselves with all the manuals and labeling of the Ahead 100.

Warnings include that the clinician must ensure that standard EEG practices are followed in the collection of patient data.

SPECIAL CONDITIONS FOR USE

Ahead 100 interpretation guidelines are based on the clinician's initial diagnostic evaluation, the subject's age and the EEG results. The device user refers to the individual who prescribes device use and performs the initial diagnostic assessment. In order to use the Ahead 100, the user should be physicians who have familiarized themselves with all the manuals and labeling of the Ahead 100. The clinician must perform a diagnostic evaluation per the standard of their practice that includes the administration of the Glasgow Coma Scale (GCS). The clinician's evaluation separates the patients into two groups: 1) patients with brain electrical activity consistent with no structural brain injury visible on head CT, and 2) patients with brain electrical activity that may be present in both patients with or without a structural brain injury visible on head CT. To initiate recording EEG with the device, the clinician enters the GCS score for the patient. If the GCS is less than 13, the Ahead 100 displays a warning statement that the device is intended to be used in patients who clinically present with a GCS score of 13-15 and that the safety and effectiveness of the Ahead 100 in patients with GCS scores less than 13 has not been established. Prior to the presentation of results, the Ahead 100 displays a warning screen that states the Ahead 100 has not been evaluated for safety or effectiveness in the diagnosis of traumatic brain injury (TBI).

RISKS TO HEALTH

Table 3 below identifies the risks to health that may be associated with use of Brain Injury Adjunctive Interpretive Electroencephalograph Assessment Aid and the measures necessary to mitigate these risks.

Table 3: Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Measure**
Adverse Tissue Reaction	Biocompatibility Labeling
Equipment Malfunction Leading to Injury to User/Patient (shock, burn, or mechanical failure)	Electrical safety, thermal, and mechanical testing Electromagnetic Compatibility Testing Labeling
Delay in Treatment or Unnecessary Treatment due to Hardware or Software Failure	Performance testing Hardware and Software verification, validation and hazard analysis Electromagnetic Compatibility Testing

Identified Risk	Mitigation Measure
	Technical Parameters Labeling
False Result due to Incorrect Artifact Reduction	Software verification and validation Labeling
False Result due to Incorrect Placement of Electrodes	Clinical performance testing Labeling
False Result when a Brain Injury Adjunctive Interpretive EEG Assessment Aid Impacts the Clinical Decision	Clinical performance testing Device design characteristics Labeling
Use Error	Clinical performance testing Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Ahead 100 is subject to the following special controls:

1. The technical parameters of the device, hardware and software, must be fully characterized and include the following information:
    a. Hardware specifications must be provided. Appropriate verification, validation and hazard analysis must be performed.
    b. Software, including any proprietary algorithm(s) used by the device to arrive at its interpretation of the patient's condition, must be described in detail in the Software Requirements Specification (SRS) and Software Design Specification (SDS). Appropriate software verification, validation, and hazard analysis must be performed.
2. The device parts that contact the patient must be demonstrated to be biocompatible.
3. The device must be designed and tested for electrical safety, electromagnetic compatibility (EMC), thermal and mechanical safety.
4. Clinical performance testing must demonstrate the accuracy, precision – repeatability and reproducibility, of determining the EEG-based interpretation, including any specified equivocal zones (cut-offs).
5. Clinical performance testing must demonstrate the ability of the device to function as an assessment aid for the medical condition for which the device is indicated. Performance measures must demonstrate device performance characteristics per the intended use in the intended use environment. Performance measurements must include sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with respect to the study prevalence per the device intended use.
6. The device design must include safeguards to ensure appropriate clinical interpretation of the device output (e.g., use in appropriate patient population, or for appropriate clinical decision).
7. The labeling and training information must include:
    a. A warning that the device is not to be used as a stand-alone diagnostic.
    b. A detailed summary of the clinical performance testing, including any adverse events and complications.

c. The intended use population and the intended use environment.
d. Any instructions technicians should convey to patients regarding the collection of EEG data.
e. Information allowing clinicians to gauge clinical risk associated with integrating the EEG interpretive assessment aid into their diagnostic pathway.
f. Information allowing clinicians to understand how to integrate the device output into their diagnostic pathway when the device is unable to provide a classification or final result.

BENEFIT/RISK DETERMINATION

The risks of the device are based on non-clinical data as well as data collected in the clinical study described above. The major risk of the Ahead 100 device is a false negative result. A false negative result may influence the clinical decision maker to not order a CT scan that would have identified a structural injury. The risk of a false negative result may result in delaying treatment for a potential structural brain injury that would require immediate life-saving treatment or neurosurgery. A False Negative Rate of 21.5% was observed in the B-AHEAD II study.

In addition, a false positive result may influence the clinician to order a CT scan that is not required. The risk of a false positive result may result in a potential increase in the incidence of CT scans which can increase radiation exposure. A False Positive Rate of 51.4% was observed in the B-AHEAD II study.

The probable benefits of the device are also based on non-clinical data as well as data collected in the clinical study as described above. The device is intended as an aid in the evaluation of patients who are being considered for a head CT scan following a mild traumatic brain injury. The use of the Ahead 100 device may provide adjunctive information about patients when the clinician does not deem it necessary to order a CT scan, adding confidence in the clinical decision path. This has the potential to aid in the avoidance of unnecessary CT scanning through increased confidence in the clinical decision to not scan a patient. Based on the B-AHEAD II study results and some educated assumptions, we can approximate that about 160 patients in the study may have benefitted from reduced CT exposure based on a negative device output. This corresponds to a reduction of unnecessary CT exposure in (160/552) = 29% patients. The effective radiation dose of a single head CT scan is ~2 mSv, or 8 months natural background exposure.

As an adjunctive tool, the Ahead 100 can supplement the clinical assessment with additional objective information to enhance the clinical decision-making process. While the Ahead 100 device is not indicated for use as a stand-alone diagnostic, and there are no non-imaging devices approved for use as a stand-alone diagnostic for the assessment of brain injury, the reported Ahead 100 specificity of 48% is greater than that of existing standard clinical tools, such as the NOC and CCHR.

Additional factors to be considered in determining probable risks and benefits for the Ahead 100 include:

- Clinical performance data was completed via a multi-site, non-randomized, blinded controlled clinical study. There were concerns related to the conduct and design of the clinical study, specifically related to the amount of missing data as well as the application and adjudication of the NOC for patients and the undefined procedure for determining whether a CT scan was necessary.
- In an effort to mitigate the risks, particularly those associated with the potential false negative device outputs, a number of statements have been included in the labeling, the Ahead 100's IFU, as well as in the user interface of the device itself:
    - The Ahead 100 is indicated for use only in patients with GCS scores between 13-15, corresponding to mild traumatic brain injuries
    - The physician must input the patient's GCS score into the Ahead 100 device prior to initiating the test. This helps ensure that the patient has been evaluated according to the GCS prior to use of the Ahead 100 device.
    - Additional warnings are provided in both the device labeling as well as in the device user interface that state that the intended use of the device is only in patients with GCS scores between 13-15 and that safety and effectiveness of the Ahead 100 device has not been evaluated in patients with GCS <13.
    - The Ahead 100 device is not indicated for use as a stand-alone diagnostic and is not indicated for use as a replacement for CT scanning.
    - Complete results of the clinical study, as well as a chart that provides calculated NPV and PPV results corresponding to a range of disease prevalences, a discussion of the reference database to which the patient data is compared, and a discussion of the missing data from the B-AHEAD II study is provided in the device labeling to aid in the physician's understanding of the clinical utility of the Ahead 100 device.

In conclusion, given the available information above, the data support that for the use of the Ahead 100 device as an adjunct to standard clinical practice to aid in the evaluation of patients who are being considered for a head CT, who sustained a closed head injury within 24 hours, clinically present as a mild traumatic brain injury with a Glasgow Coma Scale score (GCS) of 13-15, and are between the ages of 18-80 years, the probable benefits outweigh the probable risks for the Ahead 100. The device provides benefits, and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* for the Ahead 100 is granted and the device is classified under the following:

Product Code: PIW
Device Type: Brain Injury Adjunctive Interpretive Electroencephalograph Assessment Aid
Class: Class II
Regulation: 21 CFR 882.1450