DE NOVO CLASSIFICATION REQUEST FOR ANALYTIC FOR HEMODYNAMIC INSTABILITY (AHI)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Adjunctive hemodynamic indicator with decision point. An adjunctive hemodynamic indicator with decision point is a device that identifies and monitors hemodynamic condition(s) of interest and provides notifications at a clinically meaningful decision point. This device is intended to be used adjunctively along with other monitoring and patient information.

NEW REGULATION NUMBER: 21 CFR 870.2220

CLASSIFICATION: Class II

PRODUCT CODE: QNV

BACKGROUND

DEVICE NAME: Analytic for Hemodynamic Instability (AHI)

SUBMISSION NUMBER: DEN200022

DATE DE NOVO RECEIVED: April 3, 2020

SPONSOR INFORMATION:

Fifth Eye Inc.
110 Miller Avenue, Suite 300
Ann Arbor, MI 48104

INDICATIONS FOR USE

The Analytic for Hemodynamic Instability (AHI) software is intended for use by healthcare professionals managing in-hospital patients 18 years or older who are receiving continuous physiological monitoring with electrocardiography (ECG).

AHI provides a frequently updated binary output over time based on pattern analysis of a lead-II ECG waveform intended to describe a patient's hemodynamic status and indicate if a patient is showing signs of hemodynamic stability or instability. Signs of hemodynamic instability are defined as hypotension (systolic blood pressure <90 mmHg or mean arterial pressure (MAP) <70 mmHg) combined with tachycardia (heart rate ≥ 100 bpm).

The goal of this adjunctive monitoring method is to enable identification of patients who are showing signs of hemodynamic instability and to allow clinicians an opportunity to increase vigilance. This device is intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy.

LIMITATIONS

The following reflect the limitations of the underlying dataset that AHI was trained on as well as specific physiological conditions that may affect the ECG-II features that AHI analyzes and might produce an incorrect output. AHI's performance has not been validated on patients with these conditions:

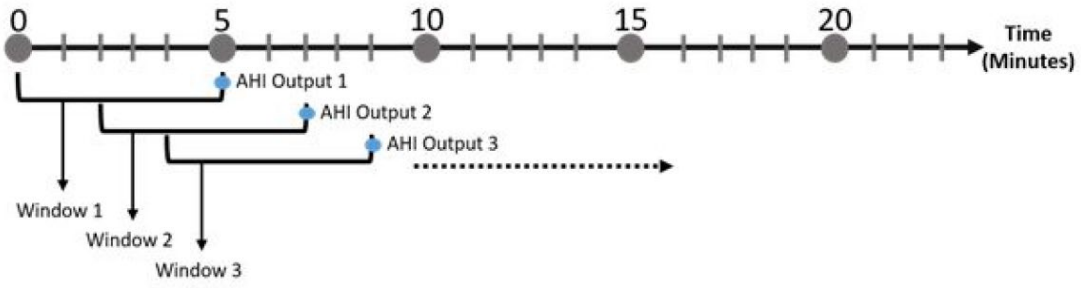
- Less than 18 years of age
- Cardiac transplant
- Ventricular assist device (VAD)
- Sustained atrial or ventricular arrhythmia
- Pacemaker dependent during AHI data collection
- On comfort/palliative care, or Do Not Attempt Resuscitate (DNAR) status

The sale, distribution, and use of the Analytic for Hemodynamic Instability (AHI) are restricted to prescription use in accordance with 21 CFR 801.109.

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

DEVICE DESCRIPTION

Analytic for Hemodynamic Instability (AHI) is a software as a medical device (SaMD) that analyzes Lead-II ECG signals to identify patients who are showing signs of hemodynamic instability. Signs of hemodynamic instability are defined as low blood pressure (BP) and high heart rate (HR). The device processes 5 minutes of continuously recorded Lead II ECG data to determine the presence of a combination of HR ≥ 100 bpm and SBP < 90 mmHg/MAP < 70 mmHg within a 2-minute sliding window as shown in the figure below. The system normalizes input signals and assesses signal quality prior to data analysis.



Rationale for Vital Sign Thresholds

Vital Sign Measure	Thresholds for 'Normal Range' Vital Sign(s) Label	Thresholds for 'Out of Range' Vital Sign(s) Label	Rationale for Selection of Vital Sign Thresholds *These traditional vital signs have well-established and accepted ranges of normal, as described in the referenced peer-reviewed literature below.*
Heart Rate	HR <100 bpm	HR ≥ 100 bpm	According to the American Heart Association, a normal range for heart rate is between 60 and 100 beats per minute. They also state that although resting heart rate could be below 60 for consistently active individuals, it seldom is above 100 for adults (American Heart Association 2018). Therefore, a resting heart rate above 100 is indicative of hemodynamic distress as also recognized in the Modified Early Warning Score (MEWS) which is designed to identify patient at risk of clinical deterioration (Subbe et al. 2001).
Systolic Blood Pressure	SBP ≥ 90 mmHg	SBP <90 mmHg	Systemic Inflammatory Response Syndrome (SIRS) criteria as defined by American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) uses systolic blood pressure less than 90 mm Hg as one of four rules indicating hemodynamic instability (Dellinger et al. 2013; Bone et al. 1992). Furthermore, in a study by Pierson et. al. one of the criteria used as a trigger for a rapid response team activation was when the systolic blood pressure fell below 90 mm Hg for any patient (Pierson 2013). Similarly, a study by Fagan et. al. also considered systolic blood pressure below 90 mm Hg as vital sign abnormality to trigger rapid response team (Fagan et al. 2012). The most common hemodynamic variable associated with shock is hypotension, typically "defined as systolic arterial pressure less than 90 mm Hg or mean arterial pressure less than 70 mm Hg with associated tachycardia" (Vincent and De Backer 2013)
Mean Arterial Pressure	MAP ≥ 70 mmHg	MAP <70 mmHg	The most common hemodynamic variable associated with shock is hypotension, typically "defined as systolic arterial pressure less than 90 mm Hg or mean arterial pressure less than 70 mm Hg with associated tachycardia" (Vincent and De Backer 2013). "As a single value less than 70 mmHg or a series of successive measurements trending downward toward 70 mmHg, MAP provides an objective assessment of hypotension that may precede hemodynamic decompensation." (Henry et al. 2002)

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

The sponsor provided documentation according to "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidance for Industry and FDA Staff" (5/11/2005). The software was determined to be a moderate level of concern. The documentation included unit (module or component) level testing, integration level testing, and system level testing. The following test suites were performed to demonstrate the software functionality:

Test Name	Test Description
User Acceptance Test Suite	Verified that the software behaved as expected based on the requirements accessible to a person using the software.
End-to-End Test Suite	Verified component integration, application stability, and end-to-end functionality.
Algorithm System Test Suite	Verified component integration, AHI algorithm functionality, and application stability.
Component Test Suite	Used unit, code quality, and coverage tests to provide individual validation of low-level functions and scenarios to verify that units performed as expected at the function level on the specific product components.
Software Performance Test Suite	Verified component integration, AHI algorithm functionality, and application stability.
Browser Compatibility Test Suite	Verified the software performed acceptably across the range of specified operating systems and browsers.
Amazon Web Services (AWS) OTS Platform Capability Test Suite	Verified the cybersecurity and managed services capabilities that are not tested automatically.
Labeling Test Suite	Verified the software user documentation met labeling requirements.
Installation Guide Test Suite	Verified the software documentation met the installation guide requirements.

Fifth Eye's approach to cybersecurity addressed each of the elements identified in the guidance document "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" (2014).

HUMAN FACTORS/USABILITY

A formative usability study followed by a (b) (4) participant (including Registered nurses, Nurse Practioners, Physician Assistants & MD prescribers) simulated use validation study was conducted according to the guidance document "Applying Human Factors and Usability Engineering to Medical Devices" (2016). The summative validation study was conducted in a simulated-use format in which intended users performed the tasks that are necessary to use AHI as intended. Participants had access to AHI itself, the AHI Indications for Use (IFU), and any relevant accessories. Human factors specialists observed participants as they performed various tasks and documented difficulties and use errors. The following critical tasks were assessed in the summative study:

- Determine if participants can correctly interpret patient exclusions and understand how to correctly change patient exclusion status.
- Associate AHI output to correct patient
- Interpret the AHI outputs correctly in the user interface
- Apply filter views to correctly interpret which patients are shown and hidden
- Determine if participants can correctly interpret Indications for Use, including the importance of using AHI outputs as an adjunct to other parameters and patient information and not being used to solely direct therapy.

Comprehension questions were used to address critical knowledge tasks or interactions that could not be evaluated through simulation. The results of the human factors validation study were analyzed to identify root causes of any difficulties or use errors observed during testing. Uncertainty regarding comprehension of the vital signs components termed signs of hemodynamic instability was addressed by prominently displaying this definition in the user interface.

The results of the human factors validation study demonstrated that mitigations addressing use-related risk were effective. Human factors researchers conducted a root cause analysis to identify the root causes of each difficulty and use error that was observed. Across the (b) (4) validation study participants, a total of 960 critical performance and comprehension task interactions were attempted. Among these attempts, there was an overall (b) (4) success rate, (b) (4) difficulty rate ((b) (4) observed difficulties), and (b) (4) use error rate (b) (4) observed use errors). The findings from the validation study demonstrate that the vast majority of simulated-use and comprehension tasks were completed without use error or difficulty.

SUMMARY OF CLINICAL INFORMATION

The sponsor conducted a prospective, single-center, observational study to investigate the performance of AHI for identifying out-of-range (OOR) vital signs with respect to ECG and invasive BP reference standards. The study collected data from (b) (4) consecutive patients

admitted to the critical care and emergency room units November 26, 2019 through January 29, 2020 at the University of Michigan Medical Center. The data included all patients monitored with an ECG monitor in all units capable of monitoring patients with an arterial line. All data from patients who were not excluded due to the limitations of the training dataset (see above) and underwent both continuous ECG and continuous arterial line blood pressure monitoring were included in the analysis. After these exclusions, 222 patients contributed data for the primary analysis. The demographic information for these patients is summarized in the table below.

Table 1: Study Patient Demographics

Characteristic Statistic	Primary Analysis Set N=222
Gender	
Male, n (%)	125 (56.3%)
Female, n (%)	97 (43.7%)
Age (Years)	
Mean (SD)	58.8 (15.3)
Median (Q1, Q3)	61 (47, 70)
Minimum, Maximum	19, 92
Race, n (%)	
American Indian or Alaska Native	0 (0%)
Asian	9 (4.1%)
Black or African American	24 (10.8%)
Native Hawaiian and Other Pacific Islander	0 (0%)
White	175 (78.8%)
Other	9 (4.1%)
Unknown or not reported	5 (2.3%)
Ethnicity	
Hispanic	10 (4.5%)
Non-Hispanic	203 (91.4%)
Unknown or not reported	9 (4.1%)

Of (b) (4) minute windows from these 222 patients, (b) (4) were flagged by the system as AHI Noisy. When the window was flagged as AHI Noisy, the reference standard was not available (b) (4) of the time, normal range vital signs (b) (4) of the time, and out-of-range vital signs (b) (4) of the time. Therefore, the AHI Noisy flag was infrequent and did not appear to mask hemodynamic instability events according to the reference standard.

Using all of the windows in the Eligible Patient Set (b) (4), the percentage of windows that were flagged as AHI Missing was (b) (4). When the window was flagged as AHI Missing, the reference standard was not available (b) (4) of the time, normal range vital signs (b) (4) of the time, and out-of-range vital signs (b) (4) of the time. Therefore, the vast majority of the time an AHI Missing flag reflects patients not being monitored by ECG or arterial line.

(b) (4) of the (b) (4) windows contained valid paired data for comparison. (b) (4) of ineligible windows were due to the BP reference standard being unavailable.

The primary analysis was performed on a per-window basis, and each patient contributed at most data from 150 windows. The performance results are summarized in the table below. The results met the predetermined acceptance criteria.

Table 2: Primary Analysis of Windows-Based Primary Study Endpoints

Windows-Based Performance Measure	Observed Estimate	95% one-sided confidence interval [1]	Acceptable Threshold [2]
Sensitivity	95.6%	2.5% LCB: 88.9%	>85%
1-Specificity	15.1%	97.5% UCB: 19.7%	<25%
Specificity	84.9%	n/a	>75%

[1] Bootstrap confidence interval based on 100 samples with replacement from Primary Analysis Set patient data (note: not re-sampling windows within a patient). LCB = lower confidence bound; UCB = upper confidence bound; 1-specificity = false positive rate

[2] The null hypothesis is rejected and we conclude that sensitivity > 85% and 1-specificity < 25% (equivalently, specificity > 75%) if 2.5% LCB is > 85% and 97.5% UCB is < 25%.

Two key risks of the AHI output are false negatives and false positives. A false negative means that a clinician will see an 'AHI Stable' output when the patient is actually unstable according to the reference standard for that particular 5-minute window and will maintain standard of care. If hemodynamic instability progresses unrecognized, there is risk of a failure to rescue a patient. The observed sensitivity (95.6%) in the study means there were few false negatives (Type-II error), and thus fewer instances of missed hemodynamic instability. The false negative rate was (b) (4).

Negative predictive value is the probability that any window classified as 'AHI Stable' also is labeled as Normal Range according to the conservative vital signs-based reference standard. The negative predictive value was (b) (4) The high negative predictive value is partially due to the low prevalence of OOR windows, is reassuring for clinicians that when AHI says the patient is hemodynamically stable, the patient is very likely hemodynamically stable.

A false positive means that a clinician will see an 'AHI Unstable' output when the patient is stable according to the reference standard for that particular 5-minute window and will increase vigilance. The consequences of increasing vigilance on a stable patient (false positive) are distraction from higher priority patients and potential for alarm fatigue. As clinicians increase their vigilance on that patient, since the patient is actually stable, the results of increased vigilance will not confirm that the patient is unstable. Since AHI is adjunctive information intended to be used in conjunction with other information, the clinician will be considering the total picture of the patient's condition in determining the course of care. The observed specificity (b) (4) in the study means there were relatively few false positives (Type-I error). The false positive rate was (b) (4)

Positive predictive value is the probability that any window classified as 'AHI Unstable' also is labeled as OOR according to the vital signs-based reference standard. In the study, the positive

predictive value was (b) (4) reflecting in part the influence of the low prevalence (b) (4) of OOR windows on these statistics.

When using AHI in a clinical setting, the recommended action based on an AHI Unstable window is to increase vigilance in monitoring the identified patient. As an adjunctive device, clinicians will consider an AHI Unstable window in the context of the trend of other AHI outputs as well as with other clinical context information to determine the appropriate clinical action which may include waiting for additional clinical confirmation of a patient's hemodynamic status. The effect on alarm fatigue should be minimal because the AHI is a visual-only indicator.

The endpoint estimates produced by the various subgroup analysis shows that the results are largely comparable between the different subgroups. The subgroup analysis based on age (see Table 3) does show a variance between the two subgroups. Statistical literature on subgroup analyses indicates such variances are to be expected because of inadequate sample size.

Table 3: Subgroup Analysis of Primary Endpoints by Age

AGE (Median = 61 Years)	Observed		Bootstrapped [1] Mean (Std Dev)	
	Below Median Age (N=110)	Above Median Age (N=112)	Below Median Age	Above Median Age
Sensitivity	97.1%	91.9%	97.1% (1.6%)	91.8% (4.9%)
Specificity	76.2%	89.0%	76.3% (3.6%)	88.7% (2.3%)

[1] Bootstrap based on 100 samples with replacement from patient data (note: not re-sampling windows within a patient).

Due to ethical concerns regarding risks associated with arterial line invasive BP and the known significant error of noninvasive BP particularly in hypotensive patients, the primary analysis was performed using invasive BP as a reference standard rather than being performed in the population most likely to receive benefit from the device. The representativeness of the study data for ECG-monitored patients without an indwelling A-line was therefore demonstrated through several additional analyses. Concern that additional motion artifact may degrade performance in the population without A-line was addressed by comparing prevalence of noisy and missing windows as shown in the table below.

Table 4: Comparison of the Distribution of AHI Noisy and AHI Missing Windows in the Study Population and Intended Use Population

Characteristic	Study Population (Eligible Patient Set)	Intended Use Population (Scored Set)
Patients, N	222	(b) (4)
Windows, n	(b) (4)	
AHI Noisy Windows (n, %)		
Median (25, 75) [1]		
AHI Missing Windows (n, %)		
Median (25, 75) [1]		

Consistency of the prevalence of OOR windows between populations was demonstrated as shown in the table below. In these tables, "Study Population" refers to patients with indwelling A-lines, "Rest of Intended Use Population" is collected subjects who were not eligible for the Study Population, and "Intended Use Population" is the combination of both populations. Differences in the subject and measurement number are due to availability of time-aligned vital signs.

Table 5: Prevalence of Normal and Out of Range Vital Signs -Based Reference Standard Between Intended Use and Study Populations

Analysis of Distribution of Normal and OOR Reference Standard Windows	Continuous Vital Signs	Intermittent Vital Signs from EHR		
	Study Population (Analysis Set)	Intended Use Population	Study Population	Rest of Intended Use Population
	(b) (4)			
% Normal Range Reference Standard Windows				
% Out-of-Range Reference Standard Windows				

Consistency of the performance of AHI across these populations was further confirmed using intermittent non-invasive BP data from the patient record.

Table 6: Primary and Secondary Endpoints - Results Comparing Intended Use and Study Population

Performance Analysis of AHI Using EHR Recorded Vital Signs	**Intermittent Vital Signs from EHR**		
	Intended Use Population	Study Population	Rest of Intended Use Population
	905 patients *73,270 Windows*	*154 patients* *12,867 Windows*	*751 patients* *60,403 Windows*
Sensitivity	(b) (4)		
Specificity			
Positive Predictive Value			
Negative Predictive Value			

The sponsor also provided a post-hoc subject-level analysis to characterize the frequency distribution of false positive and false negative windows in individual patients.

Distribution of detection delay for OOR windows was characterized and found to be mostly within the time period of a single window.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The device User Manual includes the following essential information:

(i) The type of sensor data used, including specification of compatible sensors for data acquisition, and a clear description of what the device measures and outputs to the user;

User manual describes that the AHI uses the continuous waveform produced from Lead-II of a standard application of the electrocardiogram (ECG) monitor and lists required

specifications for the monitor and use of gel-based electrodes placed according to ECG monitor manufacturer's standards.

The manual warns that AHI uses the continuous waveform produced from Lead-II of a standard application of the ECG monitor, with the specified sampling rate and AHI depends on the quality of the data captured. It recommends that the user follow the ECG monitor manufacturer's instructions when prepping the patient and placing electrodes and ensure the patient is associated with the proper ECG monitor.

Warning:

(ii) Warnings identifying factors that may impact output results;

The user manual warnings include the following:

- The device being intended for adjunctive use with other physical vital sign parameters and patient information and not being intended to independently direct therapy.
- AHI providing additional information regarding the patient's physiological condition for reference only and that no diagnostic or therapeutic decisions should be made based solely on AHI's output.
- AHI is an adjunct to and is not intended to replace ECG monitoring and is not intended for arrhythmia alarm notification. Since AHI is not indicated for use under conditions of sustained atrial or ventricular arrhythmia, clinicians should consider any arrhythmia alarms provided directly by their ECG monitoring system when interpreting AHI outputs.
- AHI depends on the quality of the data captured. Follow the ECG monitor manufacturer's instructions when prepping the patient and placing electrodesand to be sure the patient is associated with the proper ECG monitor.
- Warnings note that AHI is designed to detect if a patient is showing signs of hemodynamic instability as represented by the hemodynamic variables of heart rate and blood pressure, and that the AHI display does not address all potential physiologic conditions and no diagnostic or therapeutic decisions should be made based solely on AHI's output.

(iii) Guidance for interpretation of the outputs, including warning(s) specifying adjunctive use of the measurements;

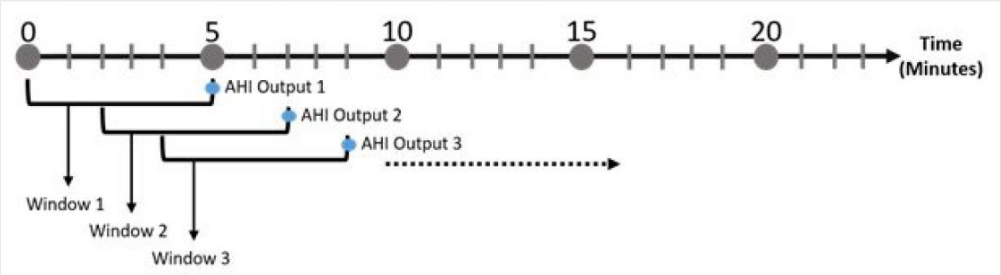
The user manual describes the AHI output as reflecting a patient's hemodynamic status and indicating if a patient is showing signs of hemodynamic stability or instability by identifying subtle ECG-II patterns and providing an indicator that can be viewed both as the most recent window (colored bar) as well as displaying the time trend of bars to show the pattern of AHI classifications for an individual patient over time. The AHI device is not intended to provide a definitive diagnosis of hemodynamic instability but is intended to provide additional information about hemodynamic status that can be used to support clinical decision-making.

For each window with sufficient ECG data quality, the extracted ECG features are classified by AHI to produce a classification output of either "AHI Stable" or "AHI Unstable".

The user manual states that for purposes of validating AHI and its Indications for Use, signs of hemodynamic instability are defined as hypotension (systolic blood pressure <90 mmHg or mean arterial pressure (MAP) < 70 mmHg) combined with tachycardia (heart rate ≥ 100 bpm).

There is no universally accepted definition of hemodynamic instability. For AHI, the definition is based on medial literature references in which hemodynamic instability can be defined as one or more out-of-range vital sign measurements represented by clinical features of circulatory shock and advanced heart failure. Hemodynamic instability is associated with the development of potentially life-threatening shock. It has been clinically recognized that a combination of hypotension and tachycardia can ensue in any type of shock.

- The user manual describes that the AHI provides a binary output every 2 minutes from a rolling 5-minute window of ECG data showing either AHI Unstable (red bar) or AHI Stable (green bar). If AHI is not able to produce an analytic output, a user may obtain further information based upon the following scenarios: Noisy (gray bar)
- Missing data (black bar)
- Prior to initialization of patient (no bar)



The manual describes the interpretation of each of the outputs as follows:

AHI Stable (green bar) - The AHI output is indicating to the healthcare professional that the patient is showing signs of hemodynamic stability, specifically no combination of hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure (MAP) < 70 mm Hg) and tachycardia (heart rate ≥ 100 bpm), in their 5-minute ECG-II signal, hence maintain the normal course of care.

AHI Unstable (red bar) - The AHI output is indicating that the patient is showing signs of hemodynamic instability, specifically hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure (MAP) < 70 mm Hg) combined with tachycardia (heart rate ≥ 100 bpm), in their 5-minute ECG-II signal. The interpretation of a red AHI output is to increase clinical vigilance on that patient and review patient hemodynamics in the context of other available clinical information to identify any potential causes for hemodynamic instability and intervene if appropriate. AHI is intended for use by healthcare professionals as additional information regarding the patient's physiological condition for reference only and no diagnostic or therapeutic decisions should be made based solely on AHI's output.

Missing (black bar) - A black bar indicates that an AHI output could not be generated for patients on ECG monitoring due to missing data in the 5-minute window. Potential causes include a patient being removed from ECG monitoring for transport or discharge, patient with poor electrode contact, patient associated with more than one ECG monitor, or problem with the ECG monitor or network.

Noisy (gray bar) - In order to increase the accuracy of AHI, each 5-minute window of patient ECG data is pre-qualified. If the pre-qualification of the ECG window detects heart rate, heart rate variability, or waveform morphology outside of the validated analytic inputs, the window is described as noisy and is represented with a gray bar. Noisy windows (gray bars) do not indicate patient status. Patient deterioration should be detected via the normal course of care using the full clinical context information available to the healthcare professional. Every 2 minutes, each rolling 5-minute window of ECG data is pre-qualified independently.

Prior to initialization of patient (no bar) - AHI will not display an output bar in the following conditions:

- AHI is Initializing upon the start of a new patient. The first output will be displayed when the first AHI output is calculated, typically within 5 to 7 minutes
- Time period to the left of the first AHI output
- Duplicate MRN, a patient is registered in two ECG monitors

Further description is provided in the user manual of how trends of outputs should be interpreted:

How many red AHI outputs indicate that I should intervene?

> Each AHI output is based on analysis of a specific 5-minute window of ECG data. AHI outputs are based on a "point-in-time" pattern analysis and are not cumulative, so while more red AHI outputs indicate that AHI is repeatedly identifying concerning patterns, there is no specific number of red bars that indicate required intervention. The interpretation of a red AHI bar is to increase clinical vigilance on that patient and review patient hemodynamics in the context of other available clinical information to identify any potential causes for the identified signs of hemodynamic instability (hypotension and tachycardia) and intervene if appropriate. AHI is intended for use by healthcare professionals as additional information regarding the patient's physiological condition for reference only and no diagnostic or therapeutic decisions should be made based solely on AHI's output.

If the patient's AHI output was GREEN and goes to RED, do I need to increase vigilance?

> The most recent red AHI output is indicating to the healthcare professional that the patient is showing signs of hemodynamic instability (hypotension and tachycardia) in their 5-minute ECG-II signal. The interpretation of a red AHI bar is to increase clinical vigilance on that patient and review patient hemodynamics in the context of other

available clinical information to identify any potential causes for the signs of hemodynamic instability (hypotension and tachycardia) and intervene if appropriate. AHI is intended for use by healthcare professionals as additional information regarding the patient's physiological condition for reference only and no diagnostic or therapeutic decisions should be made based solely on AHI's output.

If the patient's AHI output was RED and goes to GREEN, should I decrease vigilance?

The most recent green AHI output is indicating to the healthcare professional that the patient is showing signs of stable hemodynamic status (no combination of hypotension and tachycardia) in their 5-minute ECG-II signal, indicating that they should maintain the normal course of care in treating the patient. AHI is an adjunct to and is not intended to replace other sources of clinical information. Healthcare professionals should rely on other clinical measures to make decisions about care.

Should I order a medical intervention based solely on an AHI Unstable (red) output?

AHI is intended for use by healthcare professionals as additional information regarding the patient's physiological condition for reference only and no diagnostic or therapeutic decisions should be made based solely on AHI's output. The interpretation of a red AHI bar is to increase clinical vigilance on that patient and review patient hemodynamics in the context of other available clinical information to identify any potential causes for signs of hemodynamic instability (hypotension and tachycardia) and intervene if appropriate.

How will patients deteriorating for non-hemodynamic reasons be detected by AHI?

Patient deterioration for causes that do not lead to signs of hemodynamic instability hypotension and tachycardia) will not be detected by AHI. Such patient deterioration should be detected via the normal course of care using the full clinical context information available to the healthcare professional. This is outside of the intended use of AHI . AHI is an adjunct to and is not intended to replace other sources of clinical information.

How often does AHI indicate "AHI Unstable" when the patient is actually stable?

Based on the windows-level analysis in the clinical validation study, this question represents the False Positive Rate of AHI. It will be captured in the Specificity value within the Clinical Validation portion of the Instructions for Use.

How often does AHI indicate "AHI Stable" when the patient is actually unstable?

Based on the windows-level analysis in the clinical validation study, this question represents the False Negative Rate of AHI. It will be captured in the Sensitivity value within the Clinical Validation portion of the Instructions for Use.

(iv) Key assumptions made in the calculation and determination of measurements.

There is no universally accepted definition of hemodynamic instability. For AHI, the definition is based on medical literature references in which hemodynamic instability can be defined as one or more out-or-range vital sign measurements represented by clinical features of circulatory shock and advanced heart failure.

AHI is an adjunct to and is not intended to replace ECG monitoring and is not intended for arrhythmia alarm notification. Since AHI is not indicated for use under conditions of sustained atrial or ventricular arrhythmia, clinicians should consider any arrhythmia alarms provided directly by their ECG monitoring system when interpreting AHI outputs.

AHI uses the continuous waveform produced from Lead-II of a standard application of the electrocardiogram (ECG) monitor. AHI depends on the quality of the data captured. Follow the ECG monitor manufacturer's instructions when prepping the patient and placing electrodes. Be sure the patient is associated with the proper ECG monitor.

Designed to detect if a patient is showing signs of hemodynamic stability or instability as represented by the hemodynamic variables of heart rate and blood pressure, the AHI display does not address all potential physiologic conditions and no diagnostic or therapeutic decisions should be made based solely on AHI's output. See Indications for Use.

Follow ECG monitor manufacturer's standards for electrode placement.

Before a new patient's outputs are displayed in the AHI user interface, the user must affirm that the patient does not meet any of the contraindicated criteria by clicking on the "Start AHI Monitoring" button to begin display of AHI outputs for that patient. If one of the contraindicated criteria applies, the user should click the "Contraindicate" button which will prevent the display of AHI outputs for that patient.

Each AHI output is based on analysis of a specific 5-minute window of ECG data. AHI outputs are based on a "point-in-time" pattern analysis and are not cumulative, so while more red AHI outputs indicate that AHI is repeatedly identifying concerning patterns, there is no specific number of red bars that indicate required intervention.

Patient deterioration for causes that do not lead to signs of hemodynamic instability (hypotension and tachycardia) will not be detected by AHI. Such patient deterioration should be detected via the normal course of care using the full clinical context information available to the healthcare professional. This is outside of the intended use of AHI. AHI is an adjunct to and is not intended to replace other sources of clinical information.

(v) The performance of the device for all presented parameters, for all intended use populations, with appropriate confidence intervals, and the supporting evidence for this performance; and

Table 2 Primary Analysis of Windows-Based Primary Endpoints. Primary Analysis Set.

Windows-Based Performance Measure	Observed	95% one-sided confidence interval [1]	Acceptable Threshold [2]
Sensitivity	95.6%	2.5% LCB: 88.9%	>85%
1-Specificity	15.1%	97.5% UCB: 19.7%	<25%
Specificity	84.9%	n/a	>75%

[1] Bootstrap confidence interval based on 100 samples with replacement from Primary Analysis Set patient data (note: not re-sampling windows within a patient). LCB = lower confidence bound; UCB = upper confidence bound; 1-specificity = false positive fraction.

[2] The null hypothesis is rejected and we conclude that sensitivity > 85% and 1-specificity < 25% (equivalently, specificity > 75%) if 2.5% LCB is > 85% and 97.5% UCB is < 25%.

The endpoint estimates produced by the various subgroup analysis shows that the results are largely comparable between the different subgroups. The subgroup analysis based on age (see Table 3) does show a variance between the two subgroups. Statistical literature on subgroup analyses indicates such variances are to be expected because of inadequate sample size.

Table 3: Subgroup Analysis of Primary Endpoints by Age

AGE (Median = 61 Years)	Observed		Bootstrapped [1] Mean (Std Dev)	
	Below Median Age (N=110)	Above Median Age (N=112)	Below Median Age	Above Median Age
Sensitivity	97.1%	91.9%	97.1% (1.6%)	91.8% (4.9%)
Specificity	76.2%	89.0%	76.3% (3.6%)	88.7% (2.3%)

[1] Bootstrap based on 100 samples with replacement from patient data (note: not re-sampling windows within a patient).

(vi) A detailed description of the patients studied in the clinical validation (e.g., age, gender, race/ethnicity) as well as procedural details of the clinical study.

AHI Clinical Validation

Clinical validation of the AHI software device used privately collected data. Data utilized was IRB approved and prospectively collected from a large single-center quaternary health care system. The database contains AHI outputs and continuous hemodynamic vital signs from 222 critical care patients monitored with ECG and an arterial line. Each patient contributed at most 150 5-min windows for the analysis, which compared AHI to out-of-range invasive blood pressure (systolic blood pressure < 90 mmHg or mean arterial pressure (MAP) < 70 mm Hg) and heart rate (≥ 100 bpm). The sensitivity and specificity of the clinical validation on a per-window basis were 95.6% and 84.9% respectively.

Relevant characteristics of the patients studied in the clinical validation and a summary of validation results are presented in Table 1 and Table 2.

Table 1: Patient Demographics Summary for Primary Analysis Set.

Characteristic Statistic	Primary Analysis Set N=222
Gender	
Male, n (%)	125 (56.3%)
Female, n (%)	97 (43.7%)
Age (Years)	
Mean (SD)	58.8 (15.3)
Median (Q1, Q3)	61 (47, 70)
Minimum, Maximum	19, 92
Race, n (%)	
American Indian or Alaska Native	0 (0%)
Asian	9 (4.1%)
Black or African American	24 (10.8%)
Native Hawaiian and Other Pacific Islander	0 (0%)
White	175 (78.8%)
Other	9 (4.1%)
Unknown or not reported	5 (2.3%)
Ethnicity	
Hispanic	10 (4.5%)
Non-Hispanic	203 (91.4%)
Unknown or not reported	9 (4.1%)

(vii) Recommended user practices for maintaining cybersecurity of the software.

Recommended practices described in the user manual include:

- Only use approved browser versions as specified in the AHI labeling.
- Use Virtual Private Network (VPN) to remotely access the AHI system when connecting outside the firewall.
- Users should regularly install operating system (OS) updates per manufacturer's recommendations to ensure that the latest security patches have been applied.
- Regularly run anti-virus software to detect and remove for viruses and malware as recommended by the OS manufacturer.
- AHI user passwords should use strong passwords and rotate them according to the customer site's security policy; Two-factor authentication is recommended.
- Do not share passwords with others.
- Users should log off when the AHI system is not in use

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the adjunctive hemodynamic indicator with decision point and the measures necessary to mitigate these risks.

Identified Risks to Health and Mitigation Measures

Identified Risks to Health	**Mitigation Measures**
Delayed or incorrect treatment due to erroneous output as a result of software malfunction or algorithm error	Software verification, validation, and hazard analysis Non-clinical performance testing Clinical data Labeling
Delayed or incorrect treatment due to user misinterpretation	Usability assessment Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the adjunctive hemodynamic indicator with decision point is subject to the following special controls:

(1) Software description, verification, and validation based on comprehensive hazard analysis and risk assessment must be provided, including:
    (i) Full characterization of technical parameters of the software, including algorithm(s);
    (ii) Description of the expected impact of all applicable sensor acquisition hardware characteristics on performance and any associated hardware specifications;
    (iii) Specification of acceptable incoming sensor data quality control measures;
    (iv) Mitigation of impact of user error or failure of any subsystem components (signal detection and analysis, data display, and storage) on output accuracy; and
    (v) The sensitivity, specificity, positive predictive value, and negative predictive value in both percentage and number form for clinically meaningful pre-specified time windows consistent with the device output.
(2) Scientific justification for the validity of the hemodynamic indicator algorithm(s) must be provided. Verification of algorithm calculations and validation testing of the algorithm must use an independent data set.
(3) Usability assessment must be provided to demonstrate that risk of misinterpretation of the status indicator is appropriately mitigated.
(4) Clinical data must support the intended use and include the following:
    (i) The assessment must include a summary of the clinical data used, including source, patient demographics, and any techniques used for annotating and separating the data;
    (ii) Output measure(s) must be compared to an acceptable reference method to demonstrate that the output represents the measure(s) that the device provides in an accurate and reproducible manner;
    (iii) The data set must be representative of the intended use population for the device. Any selection criteria or limitations of the samples must be fully described and justified;
    (iv) Where continuous measurement variables are displayed, agreement of the output with the reference measure(s) must be assessed across the full measurement range;
    (v) Data must be provided within the clinical validation study or using equivalent datasets to demonstrate the consistency of the output and be representative of the range of data sources and data quality likely to be encountered in the intended use population and relevant use conditions in the intended use environment; and
(5) Labeling must include the following:
    (i) The type of sensor data used, including specification of compatible sensors for data acquisition, and a clear description of what the device measures and outputs to the user;
    (ii) Warnings identifying factors that may impact output results;

(iii) Guidance for interpretation of the outputs, including warning(s) specifying adjunctive use of the measurements;
(iv) Key assumptions made in the calculation and determination of measurements; and
(v) A summary of the clinical validation data, including details of the patient population studied (e.g., age, gender, race/ethnicity), clinical study protocols, and device performance with confidence intervals for all intended use populations.

BENEFIT-RISK DETERMINATION

The risks of the device are based on nonclinical software verification/validation and usability testing as well as data collected in the clinical study described above.

The consequences of a false negative reading would be a delay in the provision of care or false reassurance. This would be a serious consequence in that a patient could suffer harm from the delay in providing care. However, there currently are no noninvasive alternatives to provide the same functionality. A false positive reading will likely prompt a confirmatory noninvasive BP measurement by the HCP. While it increases resource utilization, there may not be serious harm to the patient when used as labeled. Additional subject level analysis has further shown that the false positive readings were more likely to occur in patients who also had at least several and often many true positive readings, further limiting the clinical impact of the false positive results. Based on the protocol-specified (per window) analysis, the probability of a false positive was estimated to be (b) (4) The magnitude of false results is not excessive, and the severity is quite low.

Additional per-subject analyses of the validation data show that (b) (4) of patients will receive significant false positive results. These have potential to place undue burden on healthcare professionals. Since no intervention should be given without confirmatory assessment/BP check, false positive results are unlikely to lead to serious patient harm. It is recognized that any diagnostic device without perfect specificity, such as the subject device, may increase burden on the healthcare professionals. Based on the reported specificity and the proposed conditions of use, however, the risk for undue burden to the health care is not expected to be excessive.

The risk of misinterpreting the user output was addressed in the software validation and usability study. Critical tasks assessed included correctly interpreting patient AHI outputs in the user interface as an indication of OOR vital sign measurements and that the outputs are updated every 2 minutes. The software user interface also prominently displays the vital sign definition of hemodynamic instability as implemented on the device software to avoid any misinterpretation.

The probable benefits of the device are also based on data collected in a clinical study as described above.

The clinical validation study results support that the device is reasonably effective at detecting a combination of hypotension and tachycardia. Continuous monitoring for early detection of

hypotension/tachycardia events are likely to translate into timing intervention that may lead to better patient outcomes. The device has demonstrated a high negative predictive value and would be beneficial for patients under telemetry monitoring. Currently, there isn't a cleared non-invasive continuous BP/HR monitoring device. Other alternatives include frequent cuff BP readings or invasive arterial line which are associated with patient discomfort or risks for serious complications. Since the device technology offers significant advantages over existing cleared alternatives, device availability would be in the best interest of patients.

This device allows continuous monitoring of patients for hemodynamic instability (defined as low BP and high heart rate) without requiring arterial catheterization. This circumvents the limitations of non-invasive blood pressure monitoring while avoiding the risks associated with invasive arterial instrumentation. With frequent updates, the device may identify asymptomatic patients who can benefit from higher levels of care earlier than with currently marketed noninvasive alternatives. The availability of the device has the potential to expand the use of telemetry for monitoring patients at risk of hemodynamic deterioration. The device is indicated to be an adjunct to the existing standard of care and not intended to replace current accepted vital sign monitoring.

In the pivotal study, the device achieved sensitivity and specificity of (b) (4) and (b) (4) respectively, based on the pre-specified analysis. The results met the predetermined acceptance criteria. The sensitivity and specificity were very high for the majority of the subjects (on a per subject analysis, the median sensitivity and specificity estimates were (b) (4) and (b) (4) respectively). About 1/4 of patients received not infrequent false positive results. However, additional analysis showed that these patients were also likely to have a high prevalence of out-of-range vital signs. The false positive episodes might have reflected a delay in autonomic recovery after normalization of patient's blood pressure in some cases. A signal for heightened vigilance on these patients is expected to be beneficial.

The major concern for the benefit observed in the pivotal study is how well it can be generalized to the full spectrum of the target population. Due to ethical considerations, the study enrolled only patients who received an arterial line for blood pressure monitoring. As a result, the study population is generally sicker than the intended use population. Given the invasive hemodynamic monitoring, these patients were cared for in the ER or ICU units. The differences between the populations introduce uncertainties to the generalizability of the study results to telemetry patients. Additional analyses showed that the device's performance was consistent across gender and race and in the less sick subgroup based on pressor/inotrope use. Comparative performance was shown to be consistent in patients without A-line based on available intermittent BP measurements. The results of the post-hoc analysis provide some assurance that the device is effective across the spectrum of the intended population.

The validation study results support that the device is reasonably effective for the detection of a combination of hypotension and tachycardia. Continuous monitoring for early detection of hypotension/tachycardia events are expected to translate into timing intervention that may lead to better patient outcomes. The device has demonstrated a high negative predictive value and would be beneficial for patients under telemetry monitoring. Currently, there isn't a cleared non-invasive continuous BP/HR monitoring device. Other alternatives include frequent cuff BP

readings or continuous arterial BP monitoring via an arterial line. Invasive hemodynamic monitoring is associated with patient discomfort and risks for serious complications. Since the device technology offers significant advantages over existing cleared alternatives, device availability would be in the best interest of patients.

The analyses of the validation data show that the device performed with high sensitivity and specificity in a large proportion of patients. Patients who receive multiple false positive results also were more likely to have true hypotensive and tachycardia events. Since no intervention should be given without confirmatory assessment/BP check, false positive results are unlikely to lead to serious patient harm. It is recognized that any diagnostic device without perfect specificity, such as the subject device, may increase burden on the healthcare professionals. Based on the reported specificity and the proposed condition of use, however, the risk for undue burden to the health care is not expected to be excessive.

A combination of hypotension and tachycardia is a well-recognized sign for significant physiologic distress and signals a potential serious condition. A device that can provide continuous non-invasive monitoring for these vital signs for at-risk patients is clinically valuable. Based on the observed device performance, it is reasonable to conclude that the benefit of the device for identifying patients who need escalated care outweighs the theoretical risk of medical resource over-utilization. There is a reasonable assurance of safety and effectiveness for the device when used as intended.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The AHI software is intended for use by healthcare professionals managing in-hospital patients 18 years or older who are receiving continuous physiological monitoring with electrocardiography (ECG).
>
> AHI provides a frequently updated binary output over time based on pattern analysis of a lead-II ECG waveform intended to describe a patient's hemodynamic status and indicate if a patient is showing signs of hemodynamic stability or instability. Signs of hemodynamic instability are defined as hypotension (systolic blood pressure <90 mmHg or mean arterial pressure (MAP) <70 mmHg) combined with tachycardia (heart rate ≥ 100 bpm).
>
> The goal of this adjunctive monitoring method is to enable identification of patients who are showing signs of hemodynamic instability and to allow clinicians an opportunity to increase vigilance. This device is intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy.

The probable benefits outweigh the probable risks for the Analytic for Hemodynamic Instability (AHI). The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Analytic for Hemodynamic Instability (AHI) is granted and the device is classified as follows:

Product Code: QNV
Device Type: Adjunctive hemodynamic indicator with decision point
Class: II
Regulation Number: 21 CFR 870.2220