DE NOVO CLASSIFICATION REQUEST FOR ACUMEN™ ASSISTED FLUID MANAGEMENT SOFTWARE FEATURE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Adjunctive open loop fluid therapy recommender.** The adjunctive open loop fluid therapy recommender is a prescription device that uses software algorithms to analyze cardiovascular vital signs and predict a patient's estimated response to fluid therapy. The device is intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy.

NEW REGULATION NUMBER: 21 CFR 870.5600

CLASSIFICATION: Class II

PRODUCT CODE: QMS

BACKGROUND

DEVICE NAME: Acumen™ Assisted Fluid Management (AFM) Software Feature

SUBMISSION NUMBER: DEN190029

DATE OF DE NOVO: June 4, 2019

CONTACT: Edwards Lifesciences LLC
One Edwards Way Irvine, CA 92614

INDICATIONS FOR USE

The Edwards Lifesciences Acumen Assisted Fluid Management (AFM) software feature provides the clinician with physiological insight into a patient's estimated response to fluid therapy and the associated hemodynamics. The Acumen AFM software feature is intended for use in surgical patients ≥18 years of age, that require advanced hemodynamic monitoring. The Acumen AFM software feature offers suggestions regarding the patient's physiological condition and estimated response to fluid therapy. Acumen AFM fluid administration suggestions are offered to the clinician; the decision to administer a fluid bolus is made by the clinician, based upon review of the patient's hemodynamics. No therapeutic decisions should be made based solely on the Assisted Fluid Management suggestions.

LIMITATIONS

The sale, distribution, and use of the Acumen Assisted Fluid Management Software Feature are restricted to prescription use in accordance with 21 CFR § 801.109.

The Assisted Fluid Management feature should not be used exclusively to treat the patient. A review of the patient's hemodynamics is recommended throughout the monitoring session to assess fluid responsiveness.

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

DEVICE DESCRIPTION

The Acumen™ Assisted Fluid Management (AFM) Software Feature ("the device") consists of software running on the Edwards Lifesciences EV1000 Clinical Platform (K160552 cleared on June 1, 2016) coupled with an Acumen IQ sensor (which was called FloTrac IQ sensor in K152980 cleared on January 19, 2016) connected to a radial arterial catheter. The goal of AFM is to reduce the barriers slowing the utilization of perioperative goal directed therapy (PGDT) during surgical procedures by easing the implementation of PGDT, recognizing patterns of fluid responsiveness (i.e. hemodynamic data and past responses to fluid), and suggesting when fluid administration may improve the patient's hemodynamic state. The clinician is responsible for reviewing the AFM software suggestion in addition to a patient's current hemodynamic state and, if the clinician agrees, the clinician can deliver fluid in the standard-of-care fashion. Alternatively, if the clinician disagrees with the fluid suggestion, it can be rejected as the clinician chooses to not deliver any fluid.

The AFM algorithm can be used on the EV1000 Clinical Platform to help maintain patient fluid balance throughout a surgery. The AFM algorithm continuously estimates patient fluid responsiveness (percent increase in Stroke Volume, Δ SV%) using current hemodynamic parameters and past responses to fluid boluses. The Acumen AFM software feature is intended to simplify the implementation of fluid management protocols/perioperative goal directed therapy (PGDT).

When an Acumen IQ sensor is connected and the AFM algorithm is initialized, the EV1000 Clinical Platform will provide notifications to the user when fluid is recommended by the AFM algorithm. The AFM algorithm learns from the stroke volume response to each fluid bolus to determine if a patient is in a fluid responsive or pre-load dependent state. The patient's tidal volume must be $\geqq$ 8 mL/kg while using the AFM software feature. Throughout the case, the algorithm tracks and records bolus and patient response information to adapt its suggestions based off of the individual patient. In order for the algorithm to analyze each fluid bolus, the start and stop time of each infusion must be entered in the system, as well as the volume of the fluid bolus. The algorithm uses data from the current patient in order to predict their fluid responsiveness; this data is not used by the algorithm to determine fluid responsiveness in future patients.

Each bolus can be administered with the fluid, rate, and volume at the discretion of the clinician. Additionally, any fluid bolus can be declined or discarded as deemed appropriate by the clinician. The AFM algorithm will analyze fluid boluses within the following range: Volume: 100 - 500 mL; Rate: 1 - 10 L / hr.

Figure 1: The AFM dashboard before AFM is started (top, left); an example of the AFM Settings Screen (bottom, left); the fluid delivery recommendation pop up (top, center); an example of information on fluid bolus delivered by the user (bottom, center); an example of the AFM dashboard while AFM is running (top, right); an example of notification prompting the user to either change the Maximum Case Volume or End AFM Session (bottom, right).

SUMMARY OF NONCLINICAL/BENCH STUDIES

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The device is a software feature installed on the EV1000 Clinical Platform (K160552 cleared on June 1, 2016). The EV1000 Clinical Platform has undergone some modifications (K193179 cleared on December 17, 2019) related to the recent Class I recall for the EV1000 Clinical Platform, Z-1193-2019.

SOFTWARE

Complete software documentation was provided in accordance with the FDA Guidance Document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," (issued May 11, 2005) for a Moderate Level of Concern (LOC). A Moderate LOC is deemed appropriate as malfunction of the device software or a latent design flaw in the device software may lead to an erroneous diagnosis or a delay in the delivery of appropriate medical care, which would likely result in minor injury but would likely not result in serious injury or death due to the availability of other patient vital signs.

Cybersecurity information was provided in accordance with the FDA Guidance Document, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices - Guidance for Industry and Food and Drug Administration Staff" (issued October 02, 2014).

Regression testing was performed to demonstrate that the device software does not adversely impact the performance of the cleared EV1000 Clinical Platform.

Translation testing was performed to demonstrate that movement of the device software from the development environment to the EV1000 Clinical Platform does not adversely impact the intended performance of the EV1000 Clinical Platform.

Algorithm unit testing was performed to demonstrate that the device software meets its software requirements. This testing was performed using privately collected patient data. Additional details are provided in the "Summary of Clinical Information" section.

The models in the AFM algorithm (i.e., the fixed population model and the patient-specific bolus log model) were fully described. This included full description of the input and output parameters of the models, and how the model outputs are combined using techniques that are designed to mitigate user error or failure of subsystem components. The transfer functions for the models of the AFM algorithm were fully described; in particular, the relationship between the inputs (i.e., stroke volume variation, pulse rate, …) and outputs (i.e., estimated percent increase in stroke volume) of the models, and the expected final recommendations (i.e., fluid is recommended, a test bolus is suggested, …) were also fully described.

A Monte Carlo simulation characterized the effect of the expected uncertainty in fluid delivery volume on the device's recommendations. The simulation repeatedly applied the AFM algorithm on the data from the AFM IDE study while injecting errors into the user input (i.e., fluid delivery volume) aspect of the clinical data. The statistical distribution of the injected errors was derived using a follow up usability study, which focused on (b)(of the (b)(4) participants of the original usability study; these (b)(participants were selected based on their initial bolus estimation error, and they included those participants that had the highest over-estimation and highest under-estimation of fluid delivery volume. The participants had an even distribution of Certified Registered Nurse Anesthetists (CRNAs) and Anesthesiologists. The follow up usability study was used to derive the fluid delivery volume error distributions for a (b)(4) IV bag as a function of the amount of fluid that remains in the IV bag; the (b)(4) IV bag was chosen for the follow up usability study because participants had larger errors in volume estimation with the (b)(4) IV bag compared to the 500 mL IV bag. For each iteration of the Monte Carlo simulation, the initial volume in the IV bag was chosen from a uniform distribution between 500 mL and (b)(4) and the simulation decremented this volume after each simulated bolus to simulate the delivery of fluid boluses from a (b)(4) IV bag.

The results of the Monte Carlo simulation indicated that the expected fluid volume delivery error would not result in grossly unreasonable AFM recommendations, which would result in patient harm. In particular, the expected fluid bolus volume error rarely resulted in new AFM recommendations (i.e., (b)(4) of all simulations showed (b)(new AFM recommendations). On the other hand, there was a higher likelihood that an AFM recommendation would be missed (i.e., (b)(4) and (b)(4) of all simulations showed (b)(4) and (b)(missed AFM recommendations respectively).

In addition to user input, the AFM algorithm relies on data from the Acumen IQ sensor,

whose accuracy was characterized. An animal study was used to characterize the sensor accuracy and performance. In particular, percent increases in stroke volume measurements using the Acumen IQ sensor and a reference flow probe sensor were compared in porcine model. The radial arterial pressure was used for the computation of the Acumen IQ sensor stroke volume measurement, and the flow probe was placed in the ascending aorta for the reference stroke volume measurement.

To evaluate the performance of Acumen IQ sensor to measure stroke volume changes, percent changes in stroke volume from the Acumen IQ sensor measurements (i.e., Δ SVa%) were compared with the percent change in stroke volume from the reference sensor (i.e., Δ SVr%). For Δ SVa% ≈ (b)(4)%, data points where Δ SVr% < (b)(4) % were labeled as negatives, and data points where (b)(4) % ≤ Δ SVr% ≤ (b)(4)% were labeled as positives; the sensitivity and the specificity of the Acumen IQ sensor to predict percent changes in stroke volume were reported to be (b)(4)% and (b)(4)%. The (b)(4) % threshold was chosen because it is the smallest percent change in stroke volume that the Acumen IQ sensor needs to detect during the operation of the AFM (i.e., for a 100 mL bolus with a (b)(4) fluid strategy).

Regarding sensor data quality control measures, description was provided about the different types of typical arterial line noise that may be captured in a pressure signal and how the Acumen IQ sensor / AFM algorithms have been designed to detect each type of noise.

Finally, in order to provide a safeguard for the risk of fluid overload, a software requirement was implemented for the device. This software requirement prompts the user to enter or update their current estimate for the maximum total fluid volume (i.e., the Maximum Case Volume parameter of the device), which the user intends to cumulatively administer based on all the device's recommendations for a given patient. The device does not start issuing fluid delivery recommendations unless the user enters this estimate. As soon as the total fluid volume delivered approaches (i.e., is within 500 mL of) this estimate, the user will be prompted to either update their estimate or continue with the AFM session. If the total fluid volume exceeds this estimate, the user will be prompted to either update their estimate or end the AFM session. The device does not issue fluid delivery recommendations while these prompts for updating the estimated maximum total fluid volume are being displayed on the screen. This software requirement is designed to engage the user by entering and updating the maximum total fluid volume that can be safely administered for a specific patient.

USABILITY TESTING

Usability testing was performed to assess the user's understanding of the user's manual and the user interface of the software to mitigate use related risks. Usability test reports were provided in accordance with the FDA Guidance Document, "Applying Human Factors and Usability Engineering to Medical Devices - Guidance for Industry and Food and Drug Administration Staff" (issued February 02, 2016).

Fifteen individuals belonging to a user group of Certified Registered Nurse Anesthetists (CRNAs) and fifteen individuals belonging to a second user group of Anesthesiologists participated in a usability testing. The testing was performed in a simulated use environment using a sequence of tasks, including device set up, hemodynamic monitoring, and delivering fluid boluses. The objective and subjective data collection was preceded by product training and training decay. Specifically, users were assessed for correctly reviewing the patient hemodynamics while AFM dashboard is open prior to administering a bolus.

PERFORMANCE TESTING – ANIMAL

To support the verification and validation of the algorithm calculations, the AFM performance was evaluated in (b)(4) healthy swine by creating a hypovolemic and hypervolemic animal model. After establishing either the hypovolemic or hypervolemic condition, the swine were allowed to stabilize for (b)(4) minutes prior to initiating the AFM session which lasted (b) hours. At the end of each AFM session, the swine were allowed to stabilize, and then, the next AFM session (either hypervolemic or hypovolemic condition) began using the same rules. During each AFM session the number of fluid suggestions made by the AFM algorithm were recorded. The device outputs were compared to animal status and proposed Indications for Use. In particular, the AFM made more fluid suggestions when animals were hypovolemic compared to the hypervolemic state. One swine did not appear to respond to fluid boluses for unknown reasons.

A non-GLP (Good Laboratory Practices) animal study was designed and conducted because the animal study was not performed to assess safety or novel materials. The human clinical study data was used to demonstrate safety. Without a human clinical study demonstrating safety, a GLP animal safety study will be required.

Even though the animal study did not demonstrate safety, it provided some non-clinical justification for the basic validity of the AFM algorithm; because, there were more fluid suggestions in a hypovolemic state compared to hypervolemic state. The result of the animal study provided some non-clinical scientific justification for the validity of the AFM algorithm.

SUMMARY OF CLINICAL INFORMATION

Edwards Lifesciences performed a clinical study to establish a reasonable assurance of safety and effectiveness of the device with the above-mentioned indications for use in the US under an IDE. The clinical study is called Assisted Fluid Management IDE study (AFM IDE study), and its ClinicalTrials.gov identifier number is NCT03469570. Data from the AFM IDE study provided the clinical basis for the De Novo granting decision. A summary of the clinical study is presented below.

STUDY DESIGN

The AFM IDE study was a prospective, multi-center, single-arm clinical study. A total of

(b)(4) Subjects were enrolled at (b)(study sites in the United States (US). No more than (b)(4 Subjects ((b)(% of total population) were enrolled per site. It was recommended that at least (b)(Subjects be enrolled at an active study site. In order to avoid a learning curve bias, up to (b) roll-in cases were permitted per site, as needed, with a maximum total of (b)(roll-ins in the study. The proposed historical control was a historical performance criterion based on the OPTIMISE study reported in "MacDonald N, Ahmad, T. Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: an observational substudy of the OPTIMISE trial. British Journal of Anaesthesia 114 (4): 598–604 (2015)."

The primary objective of the AFM IDE study was to evaluate the performance of the device in its ability to predict a patient's fluid responsiveness compared to the historical performance criterion of 30% fluid responsiveness. In particular, the primary effectiveness endpoint (i.e., percent fluid responsiveness) was evaluated as the percentage of time an AFM recommendation that was followed by a clinician-accepted and clinician-delivered bolus resulted in an increase in stroke volume that met the selected fluid strategy; for example, for a selected fluid strategy of 15%, 500 cc of fluid should increase the patient's stroke volume by at least 15% if the patient is fluid responsive. The validity of the fluid bolus recommendation was analyzed by reporting the number of recommendations followed by delivered boluses that did and did not have a stroke volume response meeting the set fluid strategy. These data were further assessed according to the various user settings (fluid strategy, bolus volume, fluid type and rate).

Clinical Inclusion and Exclusion Criteria:

Enrollment in the AFM IDE study was limited to patients who met the following inclusion criteria.

1. ≥ 18 years of age
2. Non-cardiac/Non-thoracic surgery (e.g., abdominal surgery, combined abdominal/pelvic surgery, major peripheral vascular surgery) expected to last >2 hours post anesthesia induction
3. Procedure will require Mechanical ventilation
4. American Society of Anesthesiology (ASA) Score 3 or 4
5. Expected arterial line placement for surgical procedure and general anesthesia
6. Projected to receive hemodynamic monitoring during surgical procedure
7. Participate or have authorized representative participate in the Informed Consent process and sign/date the IRB approved informed consent form.

Potential subjects were excluded from AFM IDE study participation if during the screening and enrollment process it was determined that they (have):

1. Are < 18 years of age
2. Have a body mass index ≥ 35 kg/m²
3. Known acute congestive heart failure
4. Known aortic stenosis with valve area ≤ 1.5 cm2
5. Known moderate to severe aortic regurgitation
6. Known moderate to severe mitral regurgitation

7. Known moderate to severe mitral stenosis
8. Current persistent atrial fibrillation
9. Liver resection procedure
10. Neurosurgery
11. Open chest procedures
12. Patient or surgical procedure type known as an SVV limitation16 (e.g. tidal volume <8mL/kg of theoretical ideal weight, spontaneous ventilation, persistent cardiac arrhythmia, known atrial fibrillation, open chest surgery, Heart Rate/Respiratory Rate (HR/RR) ratio <3.6)
13. Emergent or cardiovascular surgical procedure
14. Patient who is confirmed to be pregnant
15. Participation in any other drug, device, or biologic study concomitantly, or within the last 30 days (which may clinically interfere with this Clinical Study)
16. Refusal of patient or authorized representative to sign consent

Study Schedule from Screening to Follow-up:

A subject was considered enrolled in the AFM IDE study once the subject had signed the informed consent form (ICF) and had been assigned a study identification number. Subject participation included preoperative study eligibility screening and consent, planned surgical intervention, post intervention follow-up (f/u) through discharge, and 30 days post procedure (follow-up call). Discontinued subject data were analyzed under intent-to-treat (ITT) and data were used for safety and performance analyses.

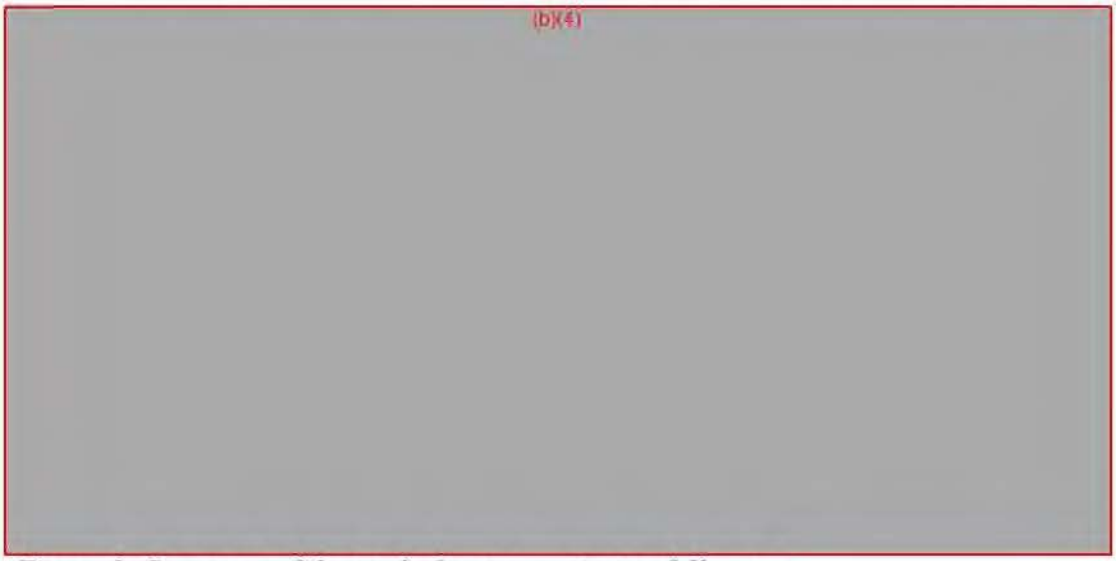


Figure 2: Summary of the study from screening to follow-up.

Clinical Endpoints:

The primary safety endpoint was the assessment of Serious Adverse Events (SAE) which may be related to the device. Safety was evaluated and reported via the collection of Adverse Events. All events were collected, analyzed and reported. The Clinical Events Committee (CEC) reviewed and adjudicated events for anticipation, severity and

relatedness to fluid management.

The primary effectiveness endpoint was to evaluate the performance of the device in its ability to predict a patient's fluid responsiveness. The performance criterion was the percentage [(b)(4)] of time a recommendation followed by a delivered bolus resulted in an increase in stroke volume that met the fluid strategy selected by the clinician; for example, for a selected fluid strategy of [(b)(4)] of fluid should increase the patient's stroke volume by at least [(b)(4)] if the patient is fluid responsive.

The statistical hypothesis for the primary effectiveness endpoint was based on: i) a null hypothesis where the test percentage [(b)(4)] is less than or equal to the historic percentage [(b)(4)], and ii) an alternative hypothesis where the test percentage [(b)(4)] is greater than the historic percentage ([(b)(4)]. The historic percentage [(b)(4)] is [(b)(4)] responsiveness rate, as described in the sub-analyses of the OPTIMISE clinical study (see "MacDonald N, Ahmad, T. Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: an observational substudy of the OPTIMISE trial. British Journal of Anaesthesia 114 (4): 598–604 (2015)").

The primary hypothesis was evaluated with a one-sided test using [(b)(4)] and [(b)(4)] confidence intervals around the percentage estimate. The test percentage [(b)(4)] and confidence intervals were compared to the historic percentage minimum performance goal [(b)(4)] of [(b)(4)] response rate data to see if the test percentage [(b)(4)] is statistically greater than the historic percentage [(b)(4)]. If the [(b)(4)] confidence interval did not contain the historic percentage, then the test percentage [(b)(4)] was concluded to be statistically and clinically greater than the historic percentage [(b)(4)] and the primary outcome measure was met with statistical superiority.

There were no powered secondary hypotheses in this clinical study.

ACCOUNTABILITY OF DATA

A subject was considered enrolled in the study once the subject signed the informed consent and had been assigned a study identification number, an arterial line had been placed and Acumen IQ sensor had been connected. Each site was permitted to treat the first [(b)] subjects as roll-in subjects to gain facility experience with the investigational device. All enrolled subjects excluding the roll-in cohort constitute the pivotal cohort, which is the population to be analyzed for safety and effectiveness. Pivotal cohort subjects constitute the ITT population for safety assessment, since no safety subjects were excluded from the pivotal cohort. Finally, the ITT population – after excluding subjects adjudicated by the CEC to not have undergone a qualifying surgical procedure – constitute the per-protocol population for effectiveness. The following flow chart provides complete accounting of the subjects in the AFM IDE study.

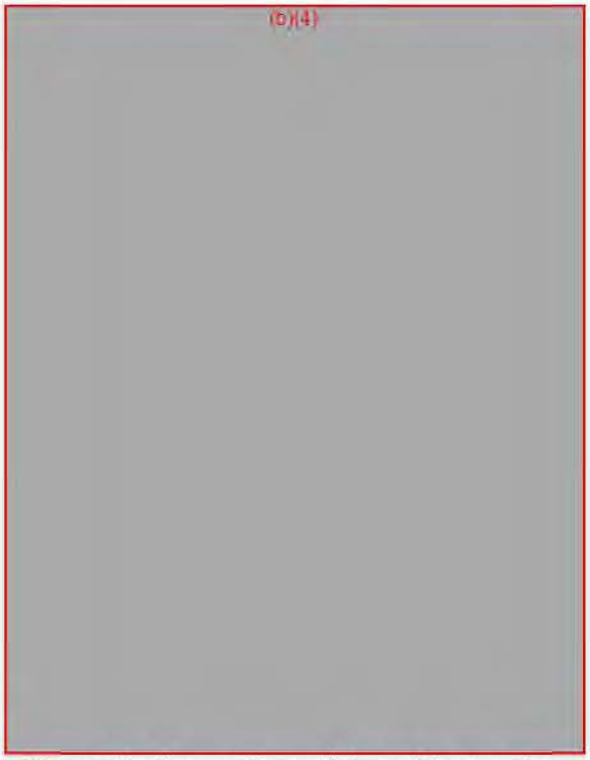


Figure 3: Accounting of the subjects; please note that this figure refers to the Acumen IQ sensor as "FloTrac."

STUDY POPULATION AND DEMOGRAPHICS

The following table provided the demographics information for the pivotal cohort (i.e., intent to treat, safety cohort).

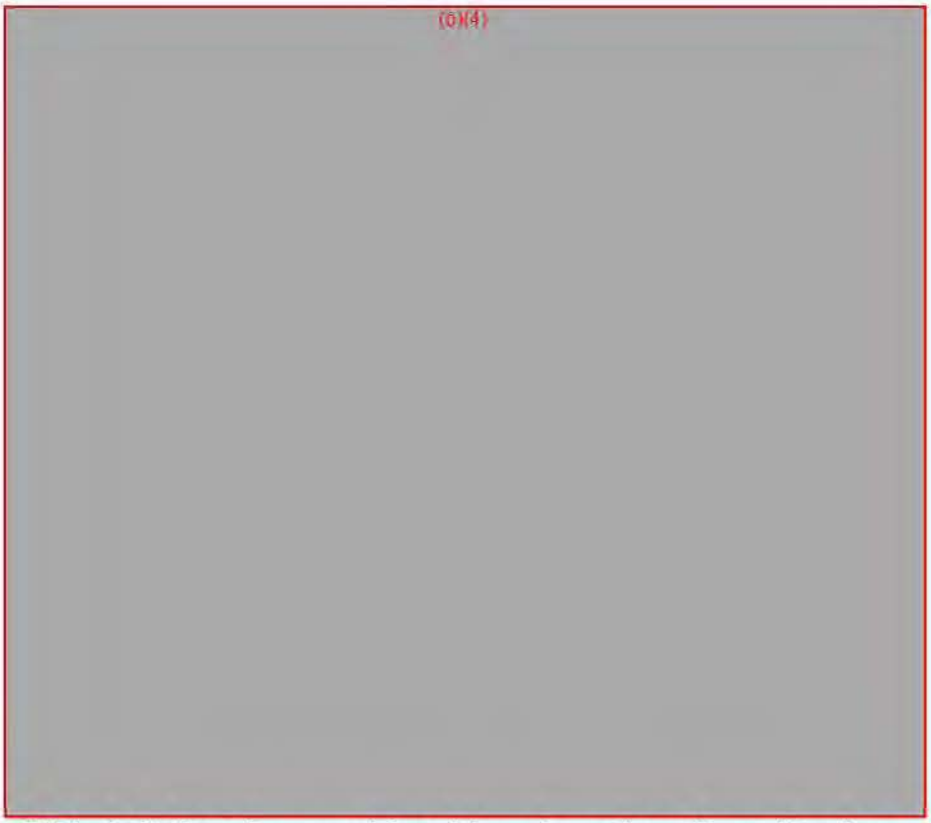


Table 1: Subject demographics of the safety cohort. Regarding the notes in the table: "note #11" denotes that there is missing race information for 1 subject; "note #12" denotes that there is missing ethnicity information for 2 subjects.

In addition, the relevant demographics information for the users in the AFM IDE study was provided.

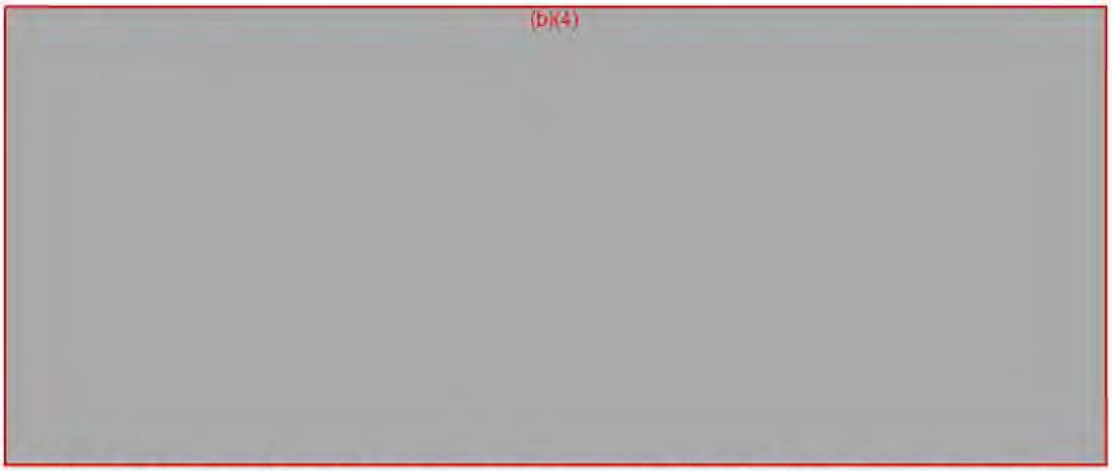


Table 2: Relevant clinician demographics associated with the safety cohort subjects. Regarding the notes in the table: "notes #10 & #13" denote that denominators are based on the total number of available data captured for each parameter.

SAFETY AND EFFECTIVENESS RESULTS

Safety Results:

The analysis of safety was based on the pivotal (ITT, safety) cohort of (b)(4) subjects. There were no adverse device effects (ADEs) or serious adverse device effects (SADEs) adjudicated by the independent CEC as definitely related to the device. A small proportion of subjects were adjudicated to have one or more possibly related SADEs ((b)(4) of the (b)(4) safety cohort subjects). The SADEs are summarized in the table below. These possibly related SADEs were consistent with and had clear potential antecedents related to the associated major surgery; however, the CEC could not exclude the use of the investigational device as possibly related to the event. There were no unanticipated ADEs related to the device. One death occurred which was adjudicated to be unrelated to the device.

CEC Adjudicated Serious Adverse Device Events (SADE)
Occurring Day 0 - Day 30
AFM: ITT - Pivotal

(b)(4)

'n' is the number of subjects with the event.
'm' is the number of events.
Since a subject can have multiple types of events within the same category, the number of unique subjects with an event in the main category may not add up to the number of subjects with an event in the individual sub-categories.
Denominators for AEs are based on the total number of subjects enrolled.
Categories and event names are based on SOC and preferred terms from Medra coding if it exists, Site AE form otherwise.

Table 3: SADEs adjudicated by the CEC.

Effectiveness Results:

Out of the 330 subjects enrolled in the study, 307 subjects were assigned to the per-protocol pivotal cohort and included in the effectiveness evaluation for the primary endpoint. In the per-protocol pivotal cohort, 94% (289/307) and 54% (165/307) of the subjects received AFM Test suggestions and AFM Recommended suggestions, respectively, and 6% of the subjects (18/307) did not receive any AFM suggestions. Therefore, it should be noted that the primary effectiveness endpoint is based on the 54% that received AFM Recommended boluses.

The primary objective of the AFM IDE study was to evaluate the performance of the device in its ability to predict a patient's fluid responsiveness. The primary objective is based upon the performance of the device and the clinical decision making that occurred during the AFM IDE study. The validity of the fluid responsiveness was measured by reporting the number of recommendations followed by delivered boluses that did and did not have a stroke volume response meeting the set fluid strategy (for example, for a selected fluid strategy of 15%, 500 cc of fluid should increase the patient's stroke volume by at least 15% if the patient is fluid responsive).

The device showed that 66.1% [62.1%, 69.7%] of the time a bolus was administered after an AFM Recommendation (based primarily on the subject's previous stroke volume response), there was an increase in stroke volume per set fluid strategy. Additionally, the AFM software feature showed that 60.5% [57.8, 63.2] of the time a bolus was administered after a test bolus suggestion (based primarily on stroke volume variation) there was an increase in stroke volume per set fluid strategy. These are summarized in the table below.

Type of Bolus Event	Mean Response Rate (%) [Confidence Interval]
AFM Recommendation	66.1% [62.1, 69.7]
AFM Test	60.5% [57.8, 63.2]

Table 4: The mean response rate for boluses delivered based on AFM prompts.

An analysis of the response rate at the subject level demonstrates that the mean response rate was 65.62% and the median [interquartile range] per-subject response is 75% [50%, 100%] with a range from 0% to 100%.

The primary effectiveness endpoint involved comparison with the historical control, which was the performance criterion of 30%. In the AFM IDE study, 66% of the AFM Recommended boluses produced the desired change in stroke volume that met the fluid strategy as reported in Table 4 above. However, a study limitation was that fluid was not delivered when the user declined an AFM Recommendation and, as such, the stroke volume responses of the declined AFM suggestions are unknown. If each declined AFM Recommendation was categorized as a negative response, the response rate could be as low as 37%. Reasons for these declines included normotension, fluid contraindicated by

the procedure at the present time, and clinician preference to use a vasopressor.

User boluses during the study were recorded whenever fluid was given outside of an AFM test or recommendation while the device was in use. When the clinician administered a user bolus, there was an increase in stroke volume 40.9% [37.4, 44.1] of the time. However, the user boluses were not given exclusively as part of a manually administered fluid management protocol, but rather were administered while the device was being used. The AFM IDE study was not designed to compare against manually administered fluid management protocols; therefore, it is not appropriate to compare AFM boluses against user boluses, which would be considered an internal control group. Please see the benefit risk determination section for more information.

Subgroup Analyses:

A secondary analysis provided the device performance stratified by delivered bolus volume as shown in the table below. The results demonstrate that the device performance can depend on the bolus volume used.

Bolus Volume (mL)	Mean Response (%)	(2.5% LCL, 97.5% UCL)	Number of Boluses	Number of Subjects
≤100	77.26%	(72.60, 81.81)	147	76
>100-200	59.92%	(54.61, 65.13	152	76
>200-250	57.73%	(50.63, 64.94)	79	49
>250-300	65.27%	(59.18, 69.39)	49	39
All Boluses	66.04%	(61.56, 71.13)	424	207

Table 5: The device performance stratified by delivered bolus volume (in mL).

As a clinical decision support system, AFM suggestions can be declined or discarded by the user. The following table provides complete accounting of the fluid boluses (e.g., declined, discarded, …) for the 307 subjects in the per protocol cohort (effectiveness cohort). Although post-hoc analysis revealed no difference in performance based on compliance to AFM suggestions, the AFM IDE study was not designed to directly address this question. Therefore, the device performance may be affected by the compliance to AFM suggestions.

Bolus Originator	Prompted	Declined	Accepted	Discarded	Completed	Analyzed
AFM	2550	1209	1341	168	1173	1165
Recommended	803	324	479	52	427	424
Test	1747	885	862	116	746	741
User	606	14	592	81	511	508
Total	3156	1223	1933	249	1684	1673

Table 6: Complete accounting of the fluid boluses in the AFM IDE study.

To summarize, the AFM IDE study was a clinical validation using an independent data set, which provided scientific justification for the validity of the device's algorithms. The AFM IDE study subjects were representative of the intended use population for the device. One of

the limitations of the study was that about half of the recommendations were declined or discarded. The performance of the device during the AFM IDE study was reported using statistical metrics and confidence intervals for the primary endpoint. In addition, subgroup analyses were provided as discussed above.

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 labeling includes the following key items below.

a. The device labeling describes what the device measures. In particular, the inputs to the device include hemodynamic data from an arterial pressure-based analysis (e.g., pulse rate, mean arterial pressure, stroke volume, stroke volume variation, systemic vascular resistance, and the rate of stroke volume change over the past two minutes) and user inputs (e.g., fluid strategy, surgery mode, fluid delivery data). The device labeling describes how the device uses a rule-based algorithm to issue fluid management recommendations, while accounting for the patient's hemodynamic data, the surgery mode, and the user's fluid strategy. Finally, the device labeling provides the following summary of the expected range of frequency of recommendations, and the device labeling provides a statement indicating the possibility of a recommendation immediately after an incorrect recommendation.

Table 17-7 Frequency of AFM Recommendations Per Hour**

AFM Recommendations Per Hour	Frequency of Occurrence*
0	73.8% (784/1062)
1	10.9% (116/1062)
2	6.7% (71/1062)
3	5.3% (56/1062)
4	2.4% (26/1062)
5	0.6% (6/1062)
6	0.3% (3/1062)

*The frequency of occurrence is based upon the number of hours with a given number of AFM recommendations divided by the total number of hours.
**The frequency of AFM recommendations per hour is presented as general guidance and may not be representative of individual experience.

"It is also possible for an AFM suggestion to immediately follow the completion of a nonresponsive fluid bolus if current hemodynamic state has changed since the prior non-responsive bolus"

b. The device labeling provides the following detailed information regarding limitations of the device's algorithm, and key assumptions made when the device issues a recommendation.

"The fluid suggestions generated by the AFM software feature are focused on SV and CO and independent of MAP. Therefore, AFM may suggest fluid when a patient is normotensive."

"It is also possible for an AFM suggestion to immediately follow the completion of a nonresponsive fluid bolus if current hemodynamic state has changed since the prior non-responsive bolus"

c. The device labeling contains the following cautions identifying sensor acquisition factors that may impact measurement results.

CAUTION

Inaccurate FT-CO measurements can be caused by factors such as:

- Improperly zeroed and / or leveled sensor / transducer
- Over- or under-damped pressure lines
- Excessive variations in blood pressure. Some conditions that cause BP variations include, but are not limited to:
  - Intra-aortic balloon pumps
- Any clinical situation where the arterial pressure is deemed inaccurate or not representative of aortic pressure, including but not limited to:
  - Extreme peripheral vasoconstriction which results in a compromised radial arterial pressure waveform
  - Hyperdynamic conditions as seen in post liver transplant
- Excessive patient movement
- Electrocautery or electrosurgical unit interference

Aortic valve regurgitation may cause an over estimation of Stroke Volume / Cardiac Output calculated depending on the amount of valvular disease and the volume lost back into the left ventricle.
(Chapter 7)

CAUTION

Fluid management suggestions provided by the AFM feature can be compromised by factors such as:

- Inaccurate FT-CO measurements
- Acute changes in FT-CO measurements secondary to vasoactive medication administration, patient repositioning or surgical interventions
- Bleeding at rates similar to, or greater than, the rate of fluid delivery
- Arterial line interference

Always review patient hemodynamic status before complying with AFM suggestions.

d. The device labeling contains the following statements to identify user errors which affect the device's recommendations.

CAUTION

The presence of confounding factors during bolus delivery may lead to an incorrect fluid recommendation by AFM. Therefore, boluses delivered in the presence of confounding factors should be discarded. Potential confounding factors include but are not limited to:

- Vasoactive agent was administered during bolus administration
- Additional fluid given after primary bolus administered
- Subject repositioning
- Ventilatory changes
- Surgical manipulation
- Arterial line interference
  - External compression (i.e., leaning on A-line)
  - ABG Draw, Fast Flush
  - Overdamping of Line
- Vascular clamping
- Additional line of fluid simultaneously opened during bolus administration
- Known acute hemorrhage during fluid administration

"Precaution. When estimating the amount of fluid delivered and entering the information into the system for analysis, it is important to ensure that the fluid bolus volume entered into the system is as accurate as possible."

e. The device labeling describes the consequences of user input errors, which may include: selecting the wrong Surgery Mode, selecting Fluid Strategy that is not aligned with the clinician's fluid management strategy, underestimating or overestimating the bolus volume that was given.

f. The device labeling provides the following guidance for interpretation of the device's recommendations.

Table 17-2 AFM Fluid Status Icons

AFM Fluid Status Icon in Navigation Bar Display	AFM Fluid Status Icon in AFM Dashboard	Meaning
		Fluid is recommended. The estimated % change in Stroke Volume exceeds the threshold defined by the **Fluid Strategy** setting (10%, 15%, 20%). When AFM recommends fluid, the final prediction is based on input from both the population model and the individual patient bolus history.

AFM Fluid Status Icon in Navigation Bar Display	AFM Fluid Status Icon in AFM Dashboard	Meaning
		A test bolus is suggested. To learn about the patient's fluid responsiveness, a test bolus is suggested. When AFM suggests a test bolus, the final prediction contains little to no input from the individual patient bolus history and relies primarily on the patient population model and will trigger a test bolus suggestion if SVV > 9% in Open Surgery Mode or SVV > 12% in Laparoscopic / Prone Surgery Mode.
		Fluid is not recommended The AFM software feature will not suggest fluid (neither AFM recommendation nor test bolus) when specific physiology indicates that fluid is not recommended. This status display will appear when the AFM software feature has learned that the patient has not responded to fluid in this hemodynamic state in the past through the individual patient bolus history. If it does not have information in the individual patient bolus history, it relies on SVV and will not suggest fluid if SVV ≤ 9% in Open Surgery Mode or SVV ≤ 12% in Laparoscopic / Prone Surgery Mode.
		AFM Mode is paused / suspended The AFM software feature will not suggest fluid in this state.

"A full review of the patient's hemodynamic status is recommended prior to accepting an AFM recommendation or AFM test suggestion."

"The Assisted Fluid Management feature should not be used exclusively to treat the patient. A review of the patient's hemodynamics is recommended throughout the monitoring session to assess fluid responsiveness."

g. The device labeling shows that the performance and limitations of the Acumen IQ sensor will affect the device's fluid recommendation performance. Because: i) the Acumen IQ sensor measures stroke volume changes; ii) stroke volume changes are used to derive fluid responsiveness; iii) fluid responsiveness is used to compute predicted increase in stroke volume; and iv) predicted increase in stroke volume is used to derive the device's fluid recommendations.

h. The device labeling shows the response rates reported in the AFM IDE study as follows.

Table 17-4 AFM Response Rates by Bolus Type

Type of Bolus Event	Mean Response Rate (%) [Confidence Interval]
AFM Recommendation	66.1% [62.1, 69.7]
AFM Test	60.5% [57.8, 63.2]

"An analysis of the response rate at the subject level demonstrates that the mean response rate was 65.62% and the median [interquartile range] per-subject response is 75% [50%, 100%] with a range from 0% to 100%."

In addition, the labeling describes the following limitations of the AFM IDE study so that users have adequate information to understand the expected performance of the device, despite the reported results of the AFM IDE study.

"The primary objective is based upon the performance of the AFM feature and the clinical decision making that occurred during the clinical study."

"Out of the 330 subjects enrolled in the study, 307 subjects were assigned to the per-protocol pivotal cohort and included in the effectiveness evaluation for the primary endpoint. In the per-protocol pivotal cohort, 94% (289/307) and 54% (165/307) of the subjects received AFM Test suggestions and AFM Recommended suggestions, respectively, and 6% of the subjects (18/307) did not receive any AFM suggestions. Therefore, it should be noted that the primary effectiveness endpoint is based on the 54% that received AFM Recommended boluses."

"User boluses during the study were recorded whenever fluid was given outside of an AFM test or recommendation while the AFM feature was in use. When the clinician administered a user bolus, there was an increase in stroke volume 40.9% [37.4, 44.1] of the time. The user boluses were not given exclusively as part of a manually administered fluid management protocol."

"In the clinical validation study, 66% of the AFM Recommended boluses produced the desired change in SV that met the Fluid Strategy as reported in Table 17-4. However, a study limitation was that fluid was not delivered when the user declined an AFM Recommendation and, as such, the SV responses of the declined AFM suggestions are unknown. If each declined AFM Recommendation was categorized as a negative response, the response rate could be as low as 37%. Reasons for these declines included normotension, fluid contraindicated by the procedure at the present time, and clinician preference to use a vasopressor."

i. The device labeling provides following relevant characteristics of the subjects in the AFM IDE study along with a summary of the validation results.

Table 17-3 Subject Demographics

Type	AFM IDE Study
# of Patients	330
Age	64.2 ± 12.9
BMI	26.3 ± 4.5
ASA 3	91.8%
ASA 4	8.2%

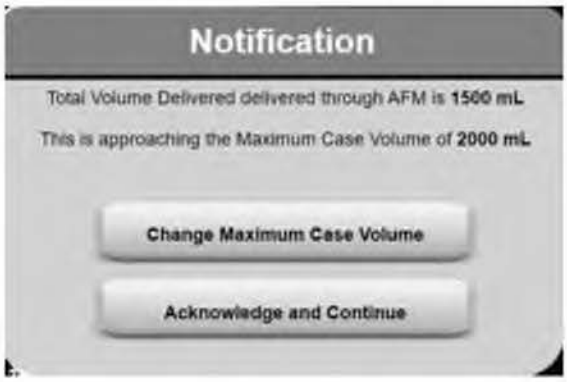
Table 17-4 AFM Response Rates by Bolus Type

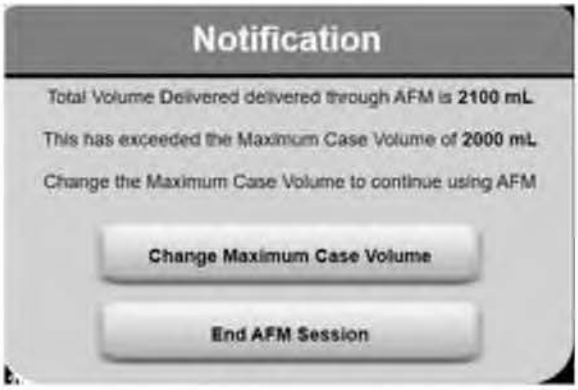
Type of Bolus Event	Mean Response Rate (%) [Confidence Interval]
AFM Recommendation	66.1% [62.1, 69.7]
AFM Test	60.5% [57.8, 63.2]

j. The Maximum Case Volume, which is a safeguard to prevent fluid overload, is described as follows in the device labeling.

> "The Maximum Case Volume provides the user with a target fluid volume delivery and is set by the clinician at the start of the case based upon available clinical data at that point. A patient's fluid needs may change over the course of the case and therefore this value should be considered as a guide and not the absolute threshold between optimal and excessive fluid delivery. During an active AFM session a visual notification pop-up is provided when the total fluid delivered through the AFM feature approaches (within 500 mL) or exceeds the pre-set Maximum Case Volume to guard against potential fluid overload."

In addition, the device labeling illustrates the following examples of user prompts associated with the Maximum Case Volume parameter. The second prompt below illustrates that the total volume delivered through the device could slightly exceed the pre-set Maximum Case Volume.





RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the adjunctive open loop fluid therapy recommender and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Delay in monitoring or treatment.	Software verification, validation, and hazard analysis; Usability assessment; and Labeling
Inappropriate or missed treatment due to over-reliance on software recommendation which is affected by: algorithm or software error, or inaccurate input from sensors or users.	Software verification, validation, and hazard analysis; Non-clinical performance testing; Usability assessment; Clinical performance testing; and Labeling
Fluid overload due to over-reliance on software recommendations which are affected by: algorithm or software error, or inaccurate input from sensors or users.	Software verification, validation, and hazard analysis; Non-clinical performance testing; Usability assessment; Clinical performance testing; and Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the adjunctive open loop fluid therapy recommender is subject to the following special controls:

1. Clinical performance testing under anticipated conditions of use must fulfill the following:
    a. A summary of the clinical performance testing must include the relevant patient demographics, and any statistical techniques used for analyzing the data;
    b. Subjects must be representative of the intended use population for the device. Any selection criteria or sample limitations must be fully described and justified;
    c. Testing must demonstrate the recommendation consistency using the expected range of data sources and data quality encountered in the intended patients, users, and environments; and
    d. Testing must evaluate the relationship between algorithm recommendations, therapeutic actions, and predicted physiological event or status.

2. A software description and the results of verification and validation testing based on a comprehensive hazard analysis and risk assessment must be provided, including:
    a. A full characterization of the software technical parameters, including algorithms;
    b. A description of the expected recommendation, accounting for differences in patient condition and environment;
    c. A description of all mitigations for user error or failure of any subsystem components (including signal detection, signal analysis, data display, and storage) that affect the device's recommendations;
    d. A characterization of algorithm sensitivity to variations in user inputs;
    e. A characterization of sensor accuracy and performance;

f. A description of sensor data quality control measures; and
g. Safeguards to reduce the possibility of fluid overload.

3. A scientific justification for the validity of the algorithm(s) must be provided. This justification must include non-clinical verification and validation of the algorithm calculations and clinical validation using an independent data set.

4. A human factors and usability engineering assessment must be provided.

5. Labeling must include:
   a. A description of what the device measures, how the device decides to issue recommendations, and the expected range of frequency of recommendations, while accounting for differences in patient condition and environment;
   b. Detailed information regarding limitations of the device's algorithm, and key assumptions made when the device issues a recommendation;
   c. Warnings identifying sensor acquisition factors that may impact measurement results;
   d. Warnings identifying user errors that affect the device's recommendations;
   e. Detailed information regarding the expected impact of user input errors on the device recommendations;
   f. Guidance for interpretation of the device's recommendations, including a description that the recommendation is adjunctive to other physical vital sign parameters and patient information;
   g. Description of the impact of the compatible sensor(s) on the device's performance;
   h. The expected performance of the device for all intended patients, users, and environments;
   i. Relevant characteristics of the patients studied in the clinical validation (such as age, gender, race or ethnicity, and patient condition) and a summary of validation results; and
   j. Description of the software safeguards that are in place to prevent fluid overload, and description of any limitation of the software safeguards.

BENEFIT/RISK DETERMINATION

The probable benefits of the device are based on the AFM IDE study. The certainly demonstrated benefit of the device is automating a tedious and time-consuming process of manually recording hemodynamic values, fluid boluses and the associated fluid responses to allow for easier and more standardized performance of goal-directed fluid therapy. The device provides benefit by electronically recording entered boluses, along with the associated hemodynamics. On the other hand, the main proposed benefit of the device is to determine fluid responsiveness in the gray zone. The AFM IDE study results cause a high extent of uncertainty related to this benefit. An inappropriate historical control group followed by an equally inappropriate internal control group limits conclusions made from the AFM IDE study. Due to the high extent of uncertainty of this proposed benefit, it is impossible to conclude that the device provides this benefit regarding prediction of fluid responsiveness as compared to manual management.

The probable risks of the device are based on the AFM IDE study summarized above, as well as a clinical study result from the closed-loop version of the AFM algorithm (Joosten et al., Anesthesiology. 2018 Jan;128(1):55-66). The primary risk associated with the device is fluid overload caused by acceptance of all fluid bolus recommendations by the user. Although no patients in the AFM IDE study were determined to have fluid overload, more than 50% of 2655 AFM boluses were declined or discarded, making it impossible to determine the risk of fluid overload if the user followed all bolus recommendations. Additionally, a clinical study using a closed-loop version of the AFM algorithm demonstrated that 20% of patients reached the maximum allowable fluid dose during automated bolusing (Joosten et al., Anesthesiology. 2018 Jan;128(1):55-66). Therefore, there is a moderate degree of uncertainty related to this risk of fluid overload.

To summarize, the probable benefit of improved prediction of fluid responsiveness has a high extent of uncertainty due to limitation of the AFM IDE study (e.g., due to inappropriate historical control group and inappropriate comparison with manual fluid management). Although the probable risk of fluid overload has a moderate degree of uncertainty (e.g., because about half of the recommended boluses were not accepted during the AFM IDE study), the probable risk of fluid overload in the event that the users accept all recommended fluid boluses can be mitigated by: i) requiring user entry of a Maximum Case Volume to be entered before AFM recommendations will appear, and requiring issuing of notifications for nearing and exceeding pre-set Maximum Case Volume, ii) labeling the device to thoroughly explain the limitations of the clinical study in assessing benefit and risk of the device, iii) labeling the device to thoroughly explain the conditions leading to bolus recommendations and the potential frequency of bolus recommendations.

Patient Perspectives

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

Benefit/Risk Conclusion

In conclusion, given the available clinical and pre-clinical information summarized above, the data support that for the indications for use specified above, the probable benefits outweigh the probable risks for the Acumen Assisted Fluid Management Software Feature. 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 Acumen Assisted Fluid Management Software Feature is granted and the device is classified under the following:

Product Code: QMS
Device Type: Adjunctive open loop fluid therapy recommender
Class: II
Regulation: 21 CFR 870.5600