# DE NOVO CLASSIFICATION REQUEST FOR EARLY BIRD BLEED MONITORING SYSTEM

## REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Intravascular bleed monitor.** An intravascular bleed monitor is a probe, catheter, or catheter introducer that measures changes in bioimpedance and uses an algorithm to detect or monitor progression of potential internal bleed complications.

**NEW REGULATION NUMBER:** 21 CFR 870.1345

**CLASSIFICATION:** II

**PRODUCT CODE:** QFJ

## BACKGROUND

**DEVICE NAME:** Early Bird Bleed Monitoring System

**SUBMISSION NUMBER:** DEN180021

**DATE DE NOVO RECEIVED:** April 23, 2018

**SPONSOR INFORMATION:**

Saranas, Inc.
2450 Holcombe Blvd. Suite X
Houston, Texas 77021

## INDICATIONS FOR USE

The Early Bird is indicated for the introduction of catheters, catheter balloons, and other diagnostic and interventional devices into the femoral artery or femoral vein while maintaining hemostasis during diagnostic and interventional endovascular procedures.

The Early Bird provides physicians with an early indication of a potential internal bleeding complication by initial detection and monitoring of extravascular fluid accumulation.

### LIMITATIONS

The sale, distribution, and use of the Early Bird are restricted to prescription use in accordance with 21 CFR 801.109.

Insertion of more than one Early Bird device in the same vessel or in the adjoining vessel is not recommended due to potential interaction between the two bioimpedance measurement signals. If more than one introducer sheath is required simultaneously to perform a procedure, use a standard introducer sheath in the secondary position.

The Early Bird may not detect an internal bleeding complication if internal bleeding has already occurred prior to insertion of the introducer sheath or prior to initial bioimpedance measurement.

Do not attempt to place a guidewire with a maximum diameter greater than 0.035" (0.89 mm) through the dilator.

Do not attempt to insert a catheter or interventional device having a diameter larger than the Early Bird introducer sheath size (Table 1). Device damage or breakage may result.

Do not attempt to insert multiple catheters or devices when the combined diameter is larger than the Early Bird introducer sheath size (Table 1). Device damage or breakage may result.

Difficulties with sheath insertion at the insertion site may result in kinking of the device. If the Early Bird is kinked, remove the device and replace with a new one.

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

## DEVICE DESCRIPTION

The device is a single use, disposable, EtO sterilized device consisting of an Introducer Sheath (IS) with integrated electrodes, Compatible Dilator, and User Interface Device (UID) with associated hardware and firmware.

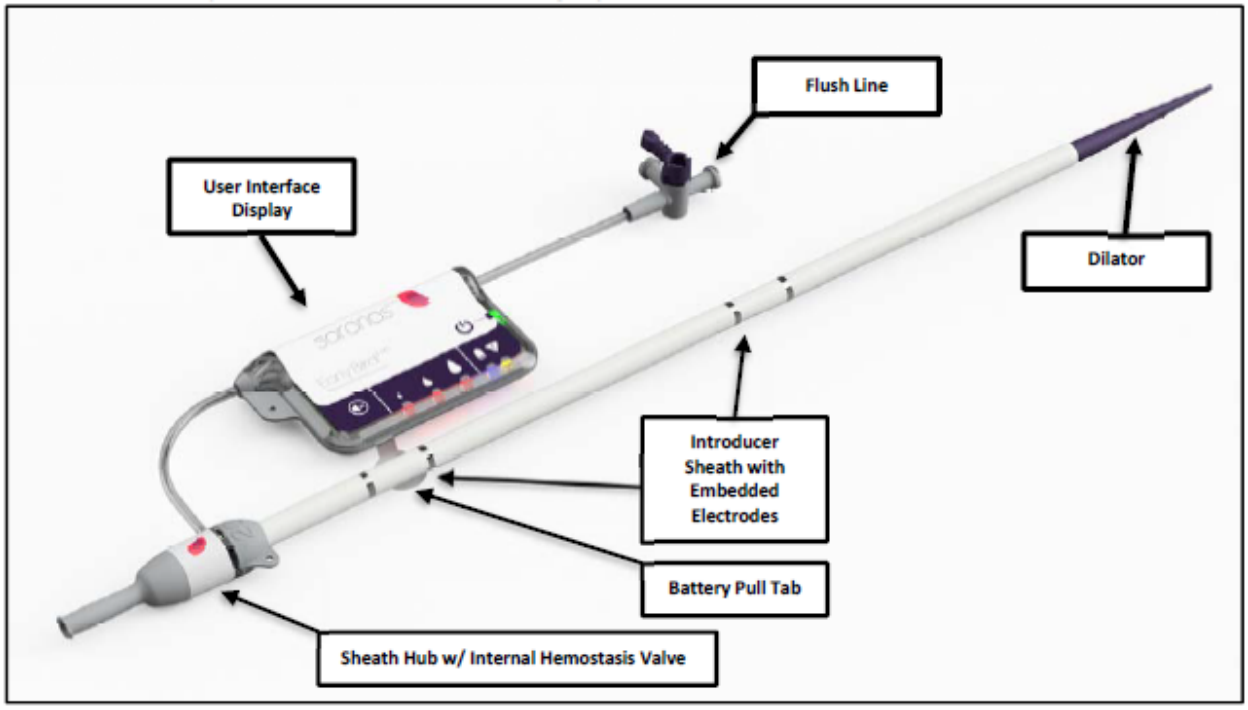


Figure 1: Early Bird Bleed Monitoring System

The Saranas Early Bird Bleed Monitoring System (Early Bird) is designed to detect extravascular fluid accumulation due to Internal Bleeding Complications (IBC) in realtime, without altering existing endovascular procedural workflows or protocols. The system allows for seamless integration by the clinician while placing the bioimpedance sensing electrodes in proximity to the site of a potential bleeding complication.

When using the Saranas sheath, the clinician will insert the sheath into the vasculature via Seldinger's technique, and power up the system per the Instructions for Use. Upon power up, the system performs a series of self-tests to ensure proper functionality, followed by initiation of the bleed monitoring algorithm.

Bleed monitoring is accomplished via a proprietary algorithm, which monitors and interrogates changes in regional bioimpedance. Bioimpedance measurements are obtained through a series of electrodes, which provide a means of electrical contact with body fluids and tissue and are located on the sheath cannula. The two outer electrodes drive a 250 µAp-p, 10k Hz, fixed frequency, alternating current to establish an electrical field, which is measured by the two inner electrodes. The limit is frequency dependent, and at 10kHz, the limit in normal condition is 100 µA RMS or 282 µAp-p. Extraneous signals are filtered out through a series of high and low pass filters integrated on the PCBA and digital filters employed in the firmware.

## SUMMARY OF NONCLINICAL/BENCH STUDIES

### BIOCOMPATIBILITY/MATERIALS

The patient contacting materials of the Early Bird Bleed Monitoring System include Pebax®, stainless steel, liquid silicone rubber, acrylonitrile butadiene styrene, ethylene propylene diene monomer rubber, polycarbonate, and cyanoacrylate. Therefore, per the FDA guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"", the device is considered an externally communicating device in contact with blood for limited contact (<24 hours). The biocompatibility tests conducted on the device are included below in Table 1 and were evaluated in accordance with the aforementioned guidance.

Table 1: Biocompatibility Testing/Assessment Completed on the Early Bird Bleed Monitoring System

| Biocompatibility Endpoint | Method | Result |
|---|---|---|
| Cytotoxicity | ISO 10993-5:2009 Biological Evaluation of Medical Devices- Part 5: Tests for in vitro cytotoxicity | Non-cytotoxic |
| Sensitization | ISO 10993-10:2010 Biological Evaluation of Medical Devices- Part 10: Tests for irritation and skin sensitization | Non-sensitizer |
| Irritation | ISO 10993-10:2010 Biological Evaluation of Medical Devices- Part 10: Tests for irritation and skin sensitization | Non-irritant |
| Pyrogen Study – Material Mediated | ISO 10993-11:2017 Biological Evaluation of Medical Devices- Part 11: Tests for acute systemic toxicity and pyrogenicity | Non-pyrogenic |
| ASTM Hemolysis | ASTM F756, Standard Practice for Assessment of Hemolytic Properties of Materials | Non-hemolytic |
| Acute Systemic Toxicity | ISO 10993-11:2017 Biological Evaluation of Medical Devices- Part 11: Tests for acute systemic toxicity and pyrogenicity | No acute systemic toxicity |
| SC5b-9 Complement Activation | ISO 10993-4: 2017 Biological Evaluation of Medical Devices- Part 4: Selection of tests for interactions with blood. | No complement activation |
| In Vivo Thromboresistance Study | ISO 10993-4: 2017 Biological Evaluation of Medical Devices- Part 4: Selection of tests for interactions with blood. | Thrombogenic. Data leveraged from non-clinical animal study for acceptable result. |

### SHELF LIFE/STERILITY

Sterilization validation, packaging validation, and shelf-life testing completed for the device can be found below in Table 2.

Table 2: Sterilization, Packaging and Shelf-life Validation Overview

| Test | Result |
|---|---|
| **Sterilization Validation**<br>ISO 11135-1:2007 | Passed |
| **Sterilization Residuals**<br>ISO 10993-7:2008/(R)2012, Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide sterilization residuals. | Passed |
| **Bioburden**<br>ANSI/AAMI/ISO 11737-1:2006/(R) 2011 Sterilization of healthcare products – Microbiological Methods – Part 1: Determination of the population of microorganisms on product | Passed |
| **Bacteriostasis/Fungistasis**<br>- AAMI 11737-1-2006 (R2011)<br>- USP<71> Sterility Tests | Passed |
| **Packaging and Shelf Life Validation**<br>- ISO 11607-1:2016 Packaging for Terminally Sterilized Medical Devices – Part 1: Requirements for Material, Sterile Barrier Systems and Packaging.<br>- ASTM D4332-14, Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing<br>- ASTM D4169-14, Standard Practice for Performance Testing of Shipping Containers and Systems<br>- ASTM F2096-11, standard test method for detecting gross leaks in packaging by internal pressurization<br>- ASTM F1980-16, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices<br>- Functional Testing | Passed |

## ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The Early Bird Bleed Monitoring System conforms with FDA-recognized standards for basic safety and essential performance of Medical Electrical Equipment. Acceptable justifications and rationale were provided when not conforming to specific clauses.

- ANSI AAMI ES60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012 (Consolidated Text) Medical electrical equipment - Part 1: General requirements for basic safety and essential performance (IEC 60601 1:2005, MOD)60601-1-2
- IEC 60601-1-2 Edition 4.0 2014-02
  Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests
- IEC 60601-1-6 Edition 3.1 2013-10
  Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability
- IEC 60601-1-8 Edition 2.1 2012-11
  Medical electrical equipment - Part 1-8: General requirements for basic safety and

essential performance - Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems

- IEC 62366-1 Edition 1.0 2015-02
  Medical devices - Part 1: Application of usability engineering to medical devices [Including CORRIGENDUM 1 (2016)]

**MAGNETIC RESONANCE (MR) COMPATIBILITY**

The Early Bird Bleed Monitoring System has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration, or image artifact in the MR environment. Therefore, the device is MR Unsafe.

**SOFTWARE**

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 erroneous information 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 current practice of medicine.

**USABILITY TESTING**

Usability testing was necessary to mitigate risks associated with delayed or incorrect treatment due to user misinterpretation or overreliance on the indicator. 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). A total of 15 end-users participated in the study. Testing was performed in a simulated environment using a sequence of tasks that targeted the critical tasks identified by the sponsor. The results of the testing met the predetermined, quantitative and qualitative acceptance criteria.

**PERFORMANCE TESTING - BENCH**

A summary of the performance bench testing completed on the Early Bird Bleed Monitoring System can be found below in Table 3.

Table 3: Performance Bench Testing Overview of the Early Bird Bleed Monitoring System

| Test | Purpose | Result |
|---|---|---|
| Dimensional | Demonstrate conformance of various device diameters and lengths. | Passed |
| Guidewire Compatibility | Demonstrate that a 0.035" guidewire can pass through the dilator. | Passed |

| | | |
|---|---|---|
| Flush Test | Demonstrate that the dilator and sheath can allow fluid to pass through. | Passed |
| Leak Test | Demonstrate no formation of a falling drop. | Passed |
| Dilator Insertion Force | Demonstrate insertion force and that the hemostasis valve does not dislodge. | Passed |
| Dilator Latch/Unlatch Force | Demonstrate a 7.0 lbf max latch force and 3.0 – 8.0 lbf unlatch force. | Passed |
| Device and Component Tensile | Demonstrate tensile strength of the overall device and individual components. | Passed. |
| Sheath and Dilator Kink/Bend | Demonstrate device ability to withstand kinking/bending. | Observations reported. Data leveraged from non-clinical animal testing and warning added to labeling regarding risk of kinking/bending for acceptable result. |
| Sheath and Dilator 3-Point Bending | Demonstrate ability to bend within specifications. | Passed. |
| Sheath Torsional Stiffness | Demonstrate torsional stiffness conforms to specification. | Passed. |
| Device Torque | Demonstrate device ability to withstand torqueing. | Passed. |
| Device and Component Friction | Demonstrate device ability to operate within frictional requirements. | Passed. |

**PERFORMANCE TESTING - ANIMAL AND/OR CADAVER**

A prospective, self-controlled acute animal investigation was conducted to evaluate the safety and efficacy of the Early Bird in detecting extravascular fluid accumulation via simulated IBC. The primary endpoint was sensitivity of Level 1 bleed detection, and the secondary endpoint was bleed progression performance. Twenty (20) female Yorkshire Cross swine underwent femoral vessel cannulation with the Early Bird. After preparation of the access site, the Early Bird was introduced into the target vessel. To simulate a bleed, 500 ml of blood solution was infused at 10 ml/min in the subcutaneous tissue near the access site. Blood volumes and fluoroscopic images were collected upon triggering of the Early Bird bleed indicators. Systemic gross necropsy was performed to study the end-organ effects of the Early Bird. Level 1 bleed detection resulted in 100% sensitivity and 100% specificity.

Table 4: Sensitivity and Specificity at Level 1 Detection

| Early Bird Level 1 Bleed Detection | Bleed Status | |
|---|---|---|
| | Bleed Simulations or Access Site Bleeds | No Bleed Simulations or No Access Site Bleeds |
| Detection | 40 = True Positive* | 0 = False Positive |

| | | |
|---|---|---|
| Non-Detection | 0 = False Negative | 30 = True Negative |
| Sensitivity/Specificity | Sensitivity = 100% | Specificity = 100% |
| * 10 true bleeds that occurred prior to bleed simulation and 30 bleeds that were detected during bleed simulation (40 total). | | |

The Early Bird successfully identified bleed progression with a statistically significant increase in volume detected at each bleed indicator level (as described in Table 5, Wilcoxon Signed Rank Test P<0.001). No vessel trauma related to the Early Bird was detected by histopathology.

Table 5: Volume of Blood Infused and Detected at Each Level

| | Level 1 | Level 2 | Level 3 |
|---|---|---|---|
| Median, ml [IQR] | 28.5 [26.0, 35.8] | 64.0 [52.8, 79.8] | 111.0 [85.3, 154.0] |
| Mean, ml (SD) | 31.5 (±12.7) | 77.80 (±53.5) | 145.50 (±100.5)_ |
| Range, ml | 5.0 – 74.0 | 17.0 – 315.0 | 44.0 – 488.0 |
| IQR = interquartile range; SD = standard deviation | | | |

The activation of level 1, 2 and 3 bleed indicators resulted in clinically significant hematoma development as bleed simulation progressed (as shown in Figure 2).

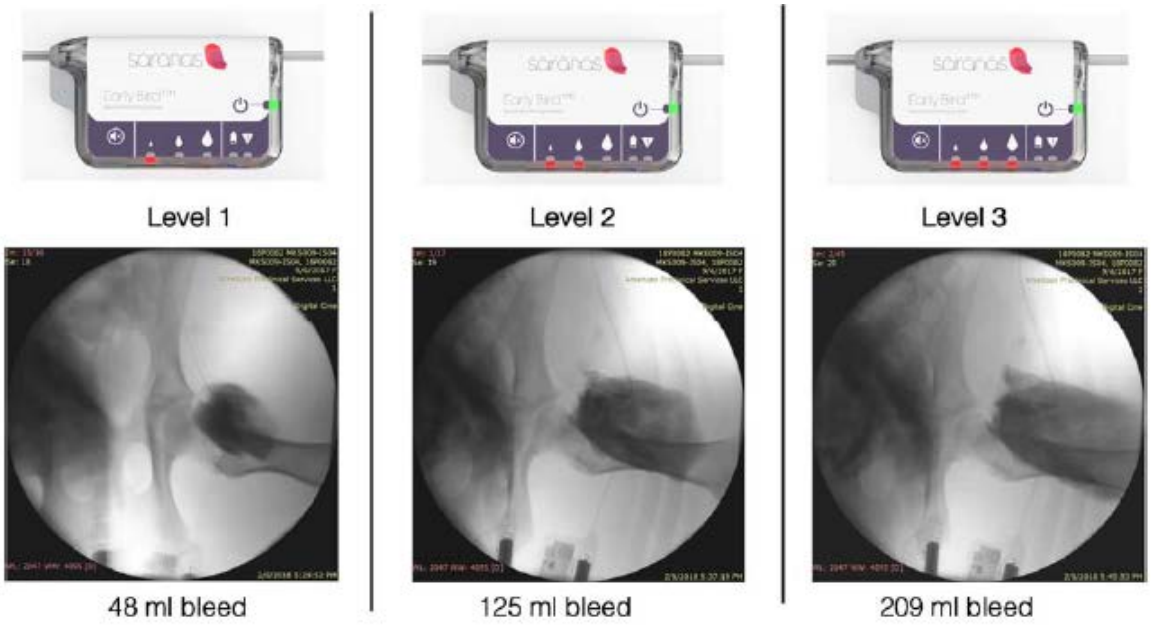


Figure 2: Bleed Progression with Early Bird Indicator Levels

## SUMMARY OF CLINICAL INFORMATION

A clinical study was not completed to support this De Novo classification request.

## LABELING

The labeling includes the following elements;

a. A sizing table for choosing the correct size device:

Table 6: Sizing Table for Choosing Early Bird Introducer Sheath

| Size (French) | Minimum Sheath Internal Diameter, inches (mm) | Working Length (cm) | Working Length w/ Dilator (cm) |
|---|---|---|---|
| 6 | 0.085 (2.16) | 20 | 23 |
| 8 | 0.110 (2.79) | 20 | 23 |

b. Warnings and Precautions to address potential risks to patient health;

"Insertion of more than one Early Bird device in the same vessel or in the adjoining vessel is not recommended due to potential interaction between the two bioimpedance measurement signals. If more than one introducer sheath is required simultaneously to perform a procedure, use a standard introducer sheath in the secondary position."

"The Early Bird may not detect an internal bleeding complication if internal bleeding has already occurred prior to insertion of the introducer sheath or prior to initial bioimpedance measurement."

"Do not attempt to place a guidewire with a maximum diameter greater than 0.035" (0.89 mm) through the dilator."

"Do not attempt to insert a catheter or interventional device having a diameter larger than the Early Bird introducer sheath size (Table 1). Device damage or breakage may result."

"Do not attempt to insert multiple catheters or devices when the combined diameter is larger than the Early Bird introducer sheath size (Table 1). Device damage or breakage may result."

"Do not attempt sheath advancement or withdrawal without guidewire and dilator in place. Major bleeding, vessel damage or serious injury to the patient, including death, may result."

"Difficulties with sheath insertion at the insertion site may result in kinking of the device. If the Early Bird is kinked, remove the device and replace with a new one."

"To prevent or reduce the risk of clot formation, consider using systemic anticoagulation and keeping the introducer sheath filled with an appropriate heparinized flushing solution when it is in the vessel."

"Electronic equipment, including portable and mobile Radio Frequency (RF) communications equipment, and RF emitters such as diathermy, electrocautery, RFID, and security systems, can affect the operation of the Early Bird. Operating non-essential equipment in the vicinity of the Early Bird should be avoided. If interference is suspected, the responsible equipment and associated cables should be moved away from the Early Bird."

c. Required accessories;

“0.035” (0.89mm) Guidewire”

“Heparinized Saline”

d. A description of the device display/indicators;

| LED/Indicator | Description |
|---|---|
| Bleed Monitoring (Red)  | The red Bleed Monitoring indicators are a series of three (3) LEDs that sequentially illuminate as bioimpedance continues to change over the course of a procedure, indicating a possible internal bleeding complication.<br>• Level 1 indicator (1st LED) is triggered by the early onset of a bleed. An audible alert is momentarily activated once this level is triggered.<br>• Level 2 indicator (2nd LED) is triggered as the bleed progresses when a bioimpedance threshold is reached. An audible alert, longer in duration than the 1st LED, is momentarily activated once this level is triggered.<br>• Level 3 indicator (3rd LED) is triggered as the bleed continues to progress further when a higher bioimpedance threshold is reached. An audible alert is activated once this level is triggered and requires the attending physician to silence the device by pressing the silence button. |

| | |
|---|---|
| Low Battery (Blue)  | The blue Low Battery indicator will blink when the battery is near end of life. The audible indicator will momentarily beep.<br><br>If the system shuts down due to a low battery, the device has reserved enough power so that the system can be powered on to observe the last state of bleed monitoring indicators. |
| Device Error (Yellow)  | The yellow Device Error indicator will illuminate when an internal system error has been detected. The audible indicator will momentarily beep.<br><br>If the yellow Device Error is illuminated, press and hold the Power button to turn off the device and turn the device back on for one additional attempted use of bleed detection and monitoring. If the yellow Device Error illuminates again, the device cannot be used. Once the procedure is completed, report the event to Saranas. |
| Power (Green)  | The green Power indicator will blink after the device is first turned on and until it detects a bioimpedance signal which is in an acceptable range. Then, the indicator will stop blinking and remain illuminated throughout the procedure. |
| **Button** | **Function** |
| Silence  | This button is used to silence the audible indicator. |
| Power  | After the battery pull tab is pulled, the system will run through a series of self-tests which will illuminate all indicators. The audible indicator will momentarily beep.<br><br>If required, press and hold the button to turn off the device. Note that the device can be turned off only within the first five (5) minutes after powering on the device. |

e. A summary of supporting non-clinical animal data, as described above in this document.

## RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of intravascular bleed monitors and the measures necessary to mitigate these risks:

Table 7: Identified Risks to Health and Mitigation Measures

| **Identified Risks to Health** | **Mitigation Measures** |
|---|---|
| Adverse tissue reaction | Biocompatibility evaluation |
| Infection | Sterilization validation<br>Pyrogenicity testing<br>Shelf-life testing<br>Labeling |
| Blood loss, bleeding, hematoma | Human factors testing<br>Labeling<br>Animal performance testing<br>Non-clinical performance testing |
| Embolization (micro or macro) with transient or permanent ischemia | Human factors testing<br>Labeling<br>Animal performance testing<br>Non-clinical performance testing |
| Vascular trauma (i.e., dissection, rupture, perforation, tear, etc.) | Human factors testing<br>Labeling<br>Animal performance testing<br>Non-clinical performance testing |
| Electrical shock | Electrical safety testing |
| Device failure due to interference with other devices | Electromagnetic compatibility (EMC) testing<br>Electrical safety testing |
| Device failure due to software malfunction | Software verification, validation, and hazard analysis |

## SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the intravascular bleed monitor is subject to the following special controls:

(1) *In vivo* animal performance testing must demonstrate that the device performs as intended under anticipated conditions of use and evaluate the following:
   (i) Device performance characteristics;
   (ii) Adverse effects, including gross necropsy and histopathology; and
   (iii) Device usability, including device preparation, device handling, and user interface.

(2) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    (i) Tensile testing of joints and materials;
    (ii) Mechanical integrity testing;
    (iii) Friction testing;
    (iv) Flush testing;
    (v) Air leakage and liquid leakage testing;
    (vi) Latching and unlatching testing;
    (vii) Kink and bend testing;
    (viii) Insertion force testing;
    (ix) Torque testing;
    (x) Corrosion testing; and
    (xi) Dimensional tolerance testing.

(3) Performance data must support the sterility and pyrogenicity of the device components intended to be provided sterile.

(4) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(5) The patient contacting components of the device must be demonstrated to be biocompatible.

(6) Software verification, validation, and hazard analysis must be performed.

(7) Performance data must demonstrate electromagnetic compatibility (EMC), electrical safety, thermal safety, and mechanical safety.

(8) Human factors performance evaluation must demonstrate that the user can correctly use the device, based solely on reading the directions for use.

(9) Labeling must include:
    (i) Instructions for use;
    (ii) A shelf life and storage conditions;
    (iii) Compatible procedures;
    (iv) A sizing table; and
    (v) Quantification of blood detected.

## BENEFIT-RISK DETERMINATION

The risks of the device are based on the nonclinical laboratory and animal studies described above.

The risks for catheter introducers are well known. The risks associated with the bleed monitoring feature are additional observation of the patient or unnecessary radiological imaging due to false

positive results and undetected bleeding (current standard of care) for false negative results. The anticipated overall risks in clinical use are low based on the performance data from the animal study (100% Sensitivity/100% Specificity). Uncertainty is low as the animal model is felt to well represent human use.

The probable benefits of the device are also based on nonclinical laboratory and animal studies described above.

Benefits include enhanced peri-procedural safety monitoring of bleed complications, avoidance of morbidity from bleed complication during and after vascular access procedures, and reduced mortality risk during and after vascular access procedures. The magnitude of the benefit is substantial for patients that experience a retroperitoneal bleed event since this is currently not easily detected early. The benefit of this device for patients with superficial bleed events, that can be observed directly, is lower. All patients undergoing procedures with the device can benefit from improved peri-procedural bleed monitoring.

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 Early Bird is indicated for the introduction of catheters, catheter balloons, and other diagnostic and interventional devices into the femoral artery or femoral vein while maintaining hemostasis during diagnostic and interventional endovascular procedures.
>
> The Early Bird provides physicians with an early indication of a potential internal bleeding complication by initial detection and monitoring of extravascular fluid accumulation.

The probable benefits outweigh the probable risks for the Early Bird Bleed Monitoring System. 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 Early Bird Bleed Monitoring System is granted, and the device is classified as follows:

> Product Code: QFJ
> Device Type: Intravascular bleed monitor
> Regulation Number: 21 CFR 870.1345
> Class: II