# PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, POST-MARKET CLINICAL STUDY EVALUATING THE PERFORMANCE OF HEMOBLAST™ BELLOWS COMPARED TO FLOSEAL HEMOSTATIC MATRIX IN CARDIOTHORACIC OPERATIONS

## PROTOCOL

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| **Protocol Number** | ETC 2018-005 |
| **Protocol Version (Date)** | Version 2.0 (15 October 2018) |

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| **Sponsor Address** | Biom'up SA<br>8, allée Irène Joliot Curie<br>69800 Saint-Priest<br>France<br><br>Biom'up Medical Expert: William Spotnitz, MD<br>Chief Medical Officer, Biom'up |
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This Protocol has been read and approved by:

| | |
|---|---|
| **Name** | Valérie Centis, PhD |
| **Title, Institution** | Chief Scientific Officer, Biom'up |
| **Signature** | |
| **Date (DD/MMM/YYYY)** | |

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| **Title, Institution** | Chief Medical Officer, Biom'up |
| **Signature** | |
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| **Title, Institution** | Vice President Clinical Operations North America, Biom'up |
| **Signature** | |
| **Date (DD/MMM/YYYY)** | |

**Coordinating Investigators – United States**

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| **Date (DD/MMM/YYYY)** | |

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| **Signature** | |
| **Date (DD/MMM/YYYY)** | |

**Protocol**

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**PROSPECTIVE, RANDOMIZED, CONTROLLED, MULTICENTER, POST-MARKET CLINICAL STUDY EVALUATING THE PERFORMANCE OF HEMOBLAST™ BELLOWS COMPARED TO FLOSEAL HEMOSTATIC MATRIX IN CARDIOTHORACIC OPERATIONS**

I, the undersigned, have read and understood the Protocol specified above, and agree on the contents. The Protocol and Clinical Trial Agreement will serve as a basis for cooperation in the clinical study.

Further, I agree to conduct the clinical study in accordance with the ethical principles that have their origin in the Declaration of Helsinki; guidelines of the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP);21 CFR Parts 50, 54, and 56; and any other applicable national requirements.

I am aware of my responsibilities as a Principal Investigator. I agree to conduct the study according to these guidelines and to appropriately direct and assist the study staff.

| | |
|---|---|
| **Principal Investigator Name** | |
| **Institution** | |

| | |
|---|---|
| **Principal Investigator Signature** | |
| **Date (DD/MMM/YYYY)** | |

**Protocol**

**Revision History**

| Version Number (Date) | Summary of Revision(s) | Justification for Revision(s) |
|---|---|---|
| Version 1.0 (04 October 2018) | None – new document | Not applicable |
| Version 2.0 (15 October 2018) | • Typographical edits<br>• Update to Table 7 to include assignment of SPOT GRADE™ score immediately prior to hemostat application<br>• Addition of coordinating investigator Abbas Ardehali | • Administrative<br>• Clarification on intraoperative procedure requirements |

# 1 SYNOPSIS

| | |
|---|---|
| **Title** | Prospective, Randomized, Controlled, Multicenter, Post-Market Clinical Study Evaluating the Performance of HEMOBLAST™ Bellows Compared to FLOSEAL Hemostatic Matrix in Cardiothoracic Operations |
| **Protocol Number** | ETC 2018-005 |
| **Purpose/Objectives** | To evaluate the performance (time to hemostasis, including device preparation time) of HEMOBLAST™ Bellows compared to FLOSEAL Hemostatic Matrix |
| **Indication** | HEMOBLAST™ Bellows is indicated for use in surgical procedures as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures. |
| **Study Design** | Prospective, randomized, controlled, post-market |
| **Number of Subjects/Sites** | A maximum of 104 subjects enrolled across a maximum of 5 study sites. |
| **Preoperative Inclusion Criteria** | A subject must meet all of the following preoperative inclusion criteria to be enrolled into the study:<br>• Subject is undergoing a non-emergent cardiothoracic surgery; and<br>• Subject or an authorized legal representative is willing and able to give prior written informed consent for study participation. |
| **Preoperative Exclusion Criteria** | A subject must not meet any of the following preoperative exclusion criteria to be enrolled into the study:<br>• Subject has a known sensitivity or allergy to bovine and/or porcine substance(s) or any other component(s) of the hemostatic agent;<br>• Subject has religious or other objections to porcine or bovine components; and<br>• Subject is not appropriate for inclusion in the clinical study, per the medical opinion of the Principal Investigator. |
| **Intraoperative Inclusion Criteria** | A subject must meet all of the following intraoperative inclusion criteria to be enrolled into the study:<br>• Subject in whom the Investigator is able to identify a Target Bleeding Site (TBS) for which any applicable conventional means for hemostasis are ineffective or impractical; and<br>• Subject has a TBS with minimal, mild, or moderate bleeding.[1] |
| **Assessment Schedule** | • Preoperative<br>  ○ Obtain consent<br>  ○ Confirm eligibility criteria<br>• Intraoperative<br>  ○ Confirm eligibility criteria<br>  ○ Randomization<br>  ○ Performance evaluations |

| | |
|---|---|
| | ○ Safety assessments |
| **Test Device** | HEMOBLAST™ Bellows (Biom'up, France), hereinafter referred to as HEMOBLAST™ |
| **Comparator Device** | FLOSEAL Hemostatic Matrix (Baxter Healthcare Corporation, Hayward, CA, USA), hereinafter referred to as FLOSEAL |
| **Primary Endpoint** | The primary endpoint of this study is the superiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 3 minutes. |
| **Secondary Endpoints** | The secondary endpoint of this study is non-inferiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 5 minutes. |

# 2 INTRODUCTION

## 2.1 Purpose

The purpose of this study is to evaluate the performance of HEMOBLAST™ compared to FLOSEAL.

## 2.2 Device Name

HEMOBLAST™ will be used in this study.

## 2.3 Indication for Use

HEMOBLAST™ is indicated for use in surgical procedures as an adjunct of hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

## 2.4 Study Overview

### 2.4.1 Duration of the Study

The estimated duration of the study is approximately 8 months from the time of first subject enrollment to the last subject enrollment. Enrollment occurs intraoperatively after confirmation of the intraoperative eligibility criteria. Subjects will undergo intraoperative performance assessments and then will be discontinued from the study after completion of the intraoperative visit.

### 2.4.2 Number of Subjects and Sites

A maximum of 104 subjects will be enrolled across a maximum of 5 study sites in the United States.

It is expected that approximately 20 subjects will be enrolled per site, with no more than 50% of the subjects being enrolled at any single site.

## 2.5 Sponsor Contact Information

Rachel Hoffman
Biom'up USA, Inc.
Vice President, Clinical Operations North America
412 West 15th Street

Suite 1000
New York, NY 10011

# 3 DEVICE DESCRIPTION

## 3.1 Test Device Description and Indication for Use

HEMOBLAST™ consists of a powder composed of collagen, chondroitin sulfate, and thrombin. The powder is dry, sterilized, biocompatible, and non-pyrogenic. It is resorbed within 4 weeks. No preparation, mixing or heating is required.

HEMOBLAST™ is composed predominantly of highly purified porcine collagen with smaller amounts of bovine chondroitin sulfate and human pooled plasma derived thrombin. Each device contains a maximum of 1500 IU of thrombin. Plasma donations are from US plasma centers only. All individual donations of the plasma were tested for HBsAg, anti-HIV1/-HIV2, and anti-HCV and found to be negative. The plasma pools were tested and found to be non-reactive for HCV RNA, HBV DNA, and HIV1 RNA as determined by PCR (NAT). The product complies with the specifications of the manufacturer and World Health Organization (WHO).

The manufacturing procedures for HEMOBLAST™ include processing steps designed to reduce the risk of viral transmission.

HEMOBLAST™ is approved by the United States Food and Drug Administration (FDA) for use in surgical procedures as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding[1] by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.

The Instructions for Use are included as Appendix A.

## 3.2 Test Device Manufacturer Details

The manufacturer of HEMOBLAST™ is Biom'up SA, which is located in Saint Priest, France. Biom'up is ISO 13485 certified.

## 3.3 Control Device

The control device for this study is FLOSEAL, which is distributed by Baxter Healthcare Corp. located in Hayward, California. The 5 mL Full Sterile Prep kit will be utilized for this clinical study.

# 4 BACKGROUND AND RATIONALE

## 4.1 Definition of Hemostasis

Despite advances in surgical techniques, excessive bleeding remains a major complication associated with surgery and contributes to poor clinical outcomes.[2] There is no universally accepted definition of hemostasis. The most current definition is the "cessation of bleeding."[3] The term comes from the Greek roots *heme* (blood) and *stasis* (halt). Hemostasis can be considered as control of bleeding within the finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and anti-fibrinolytic activities.[4]

Hemostasis refers to the process of causing blood to form a clot (the opposite of hemostasis is hemorrhage). Most of the time, this process includes the changing of blood from a fluid to a solid state.

Intact blood vessels are central to moderating blood's tendency to clot. The endothelial cells of intact vessels prevent blood coagulation by secretion of heparin-like molecules and thrombomodulin and prevent platelet aggregation by the secretion of nitric oxide and prostacyclin. When endothelial injury occurs, the endothelial cells cease secretion of coagulation and aggregation inhibitors and instead secret von Willebrand factor and tissue thromboplastin which initiates the maintenance of hemostasis after injury. Hemostasis has three major steps: vasoconstriction, formation of a platelet plug, and blood coagulation.

### 4.2 Current Hemostatic Therapeutic Strategies

Hemorrhage control is vital for successful clinical outcomes after surgery. It is essential to decrease postoperative morbidity and operative time, leading to potential cost savings.[5, 6, 7] During surgical operations, it is important to maintain a fine balance between bleeding and clotting so that blood continues to flow to the tissues at the surgical site without excessive blood loss. There are many tools used for hemorrhage control; these include preventive measures, transfusion of blood products, and traditional methods.[2]

Conventional techniques for obtaining hemostasis during surgery include a variety of manual, mechanical, and thermal techniques. Application of direct pressure or compression at a bleeding site is often the surgeon's first choice to assist in the control of bleeding. The placement of direct pressure over the injury site serves to compress vascular structures and promote localized clotting. Direct pressure, while widely accepted as standard of care for the control of all levels of bleeding severity, has limited discourse in the surgical literature. Other mechanical methods, including sutures, staples, and ligating clips, are useful if the source of bleeding is easily identifiable and able to be sealed.[7]

Compression and other mechanical methods may not be appropriate during all surgical procedures; this method of controlling bleeding may not be sufficient when the source of bleeding is hard to identify, as for diffuse venous bleeding.[8] Moreover, the mechanical methods are not applicable in some surgical procedures because of localization and the inaccessibility of structures.

To summarize, conventional techniques show their limits in terms of bleeding control efficacy.[7, 8, 9, 10, 11] Furthermore, they may be associated with the occurrence of complications.[10]

### 4.3 Rationale

Although the properties of the ideal local hemostatic agent may vary according to the surgical specialty, some properties are universally valued including: rapid and effective control/cessation of bleeding; ability to make effective contact with the bleeding surface; acceptable safety profile; and ease of preparation and use.

According to Spotnitz *et al.,* the ideal hemostat, sealant or adhesive must have certain performance characteristics (safety, efficacy, usability, cost, and approvability) that enable it to be used by surgeons.[12] Biom'up has developed and manufactured a hemostatic device, HEMOBLAST™, which is ready to use without any preparation required. This post-market study will be conducted to assess time to hemostasis, which includes the time of device preparation.

## 5 METHODOLOGY

### 5.1 Overall Study Design

This is a prospective, randomized, controlled, multicenter, post-market clinical study.

### 5.1.1 Objectives

The objective of this study is to evaluate the performance (time to hemostasis, including device preparation time) of HEMOBLAST™ compared to FLOSEAL.

## 5.2 Primary Efficacy Endpoint

The primary endpoint of this study is the superiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 3 minutes.

## 5.3 Secondary Efficacy Endpoints

The secondary endpoint of this study is non-inferiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 5 minutes.

## 5.4 Additional Exploratory Outcomes

The additional exploratory outcomes of this study include:

- Number of operating room interruptions during preparation of the hemostatic device;
- Proportion of HEMOBLAST™ vs. FLOSEAL subjects hemostatic at 3 minutes by baseline bleeding severity (minimal, mild, or moderate); and
- Proportion of HEMOBLAST™ vs. FLOSEAL subjects hemostatic at 5 minutes by baseline bleeding severity (minimal, mild, or moderate).

## 5.5 Subject Selection Criteria

A maximum of 104 subjects undergoing non-emergent cardiothoracic surgery will be enrolled into the clinical study. Subjects will need to meet all eligibility criteria to be enrolled into the study, as detailed below.

#### *5.5.1.1 Preoperative Inclusion Criteria*

A subject must meet all of the following preoperative inclusion criteria to be enrolled into the study:

- Subject is undergoing a non-emergent cardiothoracic surgery; and
- Subject or an authorized legal representative is willing and able to give prior written informed consent for study participation.

#### *5.5.1.2 Preoperative Exclusion Criteria*

A subject must not meet any of the following preoperative exclusion criteria to be enrolled into the study:

- Subject has a known sensitivity or allergy to bovine and/or porcine substance(s) or any other component(s) of the hemostatic agent;
- Subject has religious or other objections to porcine or bovine components; and
- Subject is not appropriate for inclusion in the clinical study, per the medical opinion of the Investigator.

#### 5.5.1.3 Intraoperative Inclusion Criteria

A subject must meet all of the following intraoperative inclusion criteria to be enrolled into the study:

- Subject does not have an active or suspected infection at the surgical site;
- Subject in whom the Investigator is able to identify a Target Bleeding Site (TBS) for which any applicable conventional means for hemostasis are ineffective or impractical; and
- Subject has a TBS with minimal, mild, or moderate bleeding.[1]

**Table 1. Enrollment Based on Surface Bleeding Severity Scale (SBSS) / SPOT GRADE™ Score[1]**

| SBSS Score | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Verbal Descriptor** | None | Minimal | Mild | Moderate | Severe; not immediately life-threatening | Extreme; immediately life-threatening |
| **Visual Descriptor** | Dry | Oozing | Pooling | Flowing | Streaming | Gushing |
| **Expected Intervention(s)** | None | Manual pressure, cautery, adjuvant hemostat(s) | Manual pressure, cautery, suture, adjuvant hemostat(s) | Manual pressure, cautery, suture, adjuvant hemostat(s) | Manual pressure, cautery, suture, staples, tissue repair | Manual pressure, cautery, suture, staples, tissue repair |
| **Maximum Expected ACS-ATLS Shock Risk Class** | 1 | 1 | 1 | 2 | 3 | 4 |
| **Eligible for Enrollment** | **No** | **Yes** | **Yes** | **Yes** | **No** | **No** |

### 5.6 Point of Enrollment

All patients presenting to the Investigator for a non-emergent cardiothoracic operation are potential study subjects and should be screened for eligibility. Subjects will need to meet all eligibility to be enrolled into the study.

A subject is enrolled when he/she meets all preoperative inclusion/exclusion criteria, signs the informed consent form, and meets the intraoperative inclusion criteria. The point of enrollment into the clinical study will occur intraoperatively.

### 5.7 Withdrawal Criteria

Subjects may withdraw from the study at any time without providing a reason. Subjects will not be penalized nor lose any benefits to which they are otherwise entitled if they should choose to withdraw. The Investigator may also choose to withdraw the subject if he or she feels that this is in the subject's best interest.

Subjects who withdraw from the study before receiving the test or control hemostatic device will receive routine care. No study-specific assessments will be conducted.

### 5.8 Subject Compliance

Subject loss to follow-up is not expected, as the endpoints are collected intraoperatively and there are no follow-up visits after the surgical procedure.

## 6 STUDY PROCEDURES

### 6.1 Schedule Overview

Table 2 details the study visits, corresponding timing, and evaluations to be performed at the visit. Table 3 lists the Case Report Forms (CRFs) that need to be completed at each visit.

**Table 2. Study Evaluation Schedule**

| Visit | Timing | Evaluations |
|---|---|---|
| Preoperative | Prior to surgery | Informed consent, preoperative eligibility criteria confirmation |
| Intraoperative | Day of surgery | Intraoperative inclusion criteria confirmation, enrollment and randomization, performance evaluation, and safety assessments |

**Table 3. CRF Completion Schedule**

| CRF | Preoperative | Intraoperative | Subject Study Completion |
|---|---|---|---|
| Preoperative CRF | **X** | | |
| Intraoperative CRF | | **X** | |
| Discontinuation CRF | | | **X** |
| Adverse Event CRF | | **O** | |
| Device Deficiency CRF | | **O** | |

| | |
|---|---|
| **X** | Mandatory |
| **O** | As applicable |

## 6.2 Preoperative Evaluations

### *6.2.1 Informed Consent*

Prior to performing any study specific procedures, a detailed explanation of the study procedures, potential discomforts, risks and benefits of participation, and alternatives will be reviewed with potential study subjects by a qualified member of the study team. The informed consent process will follow applicable institutional and regulatory guidelines. Subjects will be provided adequate time to review the informed consent document and all questions will be answered to the satisfaction of the subject prior to signing the informed consent.

If the subject is willing to participate in the clinical study, he/she or an authorized legal representative must sign the informed consent form indicating that they have read and understand the information provided. Each site will follow their local Institutional Review Board (IRB) and applicable regulatory guidelines for obtaining informed consent. Documentation of the informed consent process for each subject and the original signed informed consent will be retained at the site and as required by applicable regulations. A copy of the signed informed consent will be provided to the subject.

### *6.2.2 Preoperative Eligibility*

Once written informed consent has been obtained, the Preoperative CRF will be completed to document adherence to the preoperative inclusion and exclusion criteria.

Where a subject fails to fulfill any element of the preoperative eligibility criteria, this will be documented and any signed consent form and completed preoperative inclusion/exclusion criteria retained. This information will be tracked on the Screening and Enrollment Log. The subject will not be advanced any further into the clinical study.

### *6.2.3 Subject Identification*

After a subject has signed informed consent and met the preoperative inclusion and exclusion criteria, the subject will be allocated to the next available study number (subject ID number), which will be assigned.

The subject ID number will consist of the site number and the subject number. The subject number will be 01 for the first subject, 02 for the second subject and so on. This subject ID number will be the unique identifier of the subject and included on each CRF page and all other study-specific documentation relating to that subject.

### 6.3 Preoperative Procedures and Evaluations

The following data will be collected and recorded at the preoperative visit on the Preoperative CRF:

- Demographic data
  - Age
  - Gender
  - Race and ethnicity
- Physical exam
  - Height
  - Weight
- Medical history
  - Disease process(es) / indication(s) for surgery
  - Concomitant illnesses
  - Preoperative anticoagulation and antiplatelet regimen, if applicable

### 6.4 Intraoperative Procedures and Evaluations

All subjects will undergo the same intraoperative study evaluations. Intraoperative is defined as the time interval from when the subject enters the surgical suite until the subject exits the surgical suite.

Subjects undergoing the non-emergent cardiothoracic surgeries are eligible for enrollment into the clinical study. The Investigator will perform the surgery per his or her standard procedures, including conventional methods of hemostasis where practical (pressure, ligature, cautery, etc.).

Both test and control devices (not opened or prepared) should be available at the start of each procedure.

#### 6.4.1 Intraoperative Inclusion Criteria

A subject must then meet all of the following intraoperative inclusion criteria:

- Subject does not have an active or suspected infection at the surgical site;
- Subject in whom the Investigator is able to identify a TBS for which any applicable conventional means for hemostasis are ineffective or impractical; and
- Subject has a TBS with minimal, mild, or moderate bleeding.[1]

If all of these intraoperative eligibility criteria are met, then the subject is formally enrolled into the clinical study and randomized. Each subject will have one TBS assessed and documented for the purposes of this study.

The bleeding severity of the TBS will be assessed via the SBSS/SPOT GRADE™ for intraoperative inclusion, which is immediately prior to enrollment. The bleeding severity of the TBS will also be assessed and confirmed immediately prior to hemostat application, as bleeding severity may change between the time of enrollment and when the hemostat is ready to be applied. Both bleeding severities will be recorded on the Intraoperative CRF. Both bleeding severities will be presented in the analysis of the study data.

If the bleeding severity at the time when the hemostat is ready to be applied is not minimal, mild, or moderate bleeding, then the TBS will not be treated. If another suitable TBS is identified, the subject may undergo intraoperative evaluations for that TBS. If another suitable TBS is not identified, the subject will be withdrawn from the clinical study.

### 6.4.2 Randomization and Hemostat Application

Subjects will be randomized to receive HEMOBLAST™ or FLOSEAL in a 1:1 ratio:

- 52 subjects will be randomized to receive HEMOBLAST™; and
- 52 subjects will be randomized to receive FLOSEAL.

To ensure balance through time, blocked randomization will be performed. Random block sizes of 2, 4, or 6 will be implemented to conceal treatment allocation. After enrollment and randomization, the assigned hemostat will be used in the subject.

A study-specific stopwatch will be used in the performance evaluations.

After randomization, the assigned hemostat will be opened and prepared. The study-specific stopwatch will be started at the time of hemostat outer packaging opening (time 00:00).

The assigned hemostat will be prepared and applied to the TBS per its respective Instructions for Use (IFU).

At time 03:00 (3 minutes after hemostat packaging opening), hemostasis will be assessed using the SPOT GRADE™. If the TBS is hemostatic (SPOT GRADE™ score = 0), the performance evaluations are complete. If the TBS is not hemostatic (SPOT GRADE™ score > 0), a re-application of the assigned hemostat will be performed per the respective IFU.

At time 05:00 (5 minutes after hemostat packaging opening), hemostasis will be assessed using the SPOT GRADE™. If the TBS is not hemostatic (SPOT GRADE™ score > 0), the Investigator may use any means necessary to obtain hemostasis.

The study-specific stopwatch will run continuously until the 5 minute evaluation time point, except in cases where preparation of the hemostat is interrupted by other activities and obligations of the surgical staff. The study-specific stopwatch will be run by a trained and delegated study staff member. In cases where the individual(s) involved in preparing the hemostat are required to perform other activities, the stopwatch will be paused and restarted when preparation resumes. The number of interruptions will be recorded for each case.

### 6.4.3 Bleeding Severity and Hemostasis Evaluations

Bleeding severity and hemostasis will be assessed using the SBSS / SPOT GRADE™ at each time point.

A SPOT GRADE™ score of 0 is equivalent to hemostasis. All other SPOT GRADE™ scores are considered failure of hemostasis. See below in Table 6.

**Table 6. Bleeding Severity and Hemostasis**

| SBSS Score | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **Verbal Descriptor** | None | Minimal | Mild | Moderate | Severe; not immediately life-threatening | Extreme; immediately life-threatening |
| **Visual Descriptor** | Dry | Oozing | Pooling | Flowing | Streaming | Gushing |
| **Expected Intervention(s)** | None | Manual pressure, cautery, adjuvant hemostat(s) | Manual pressure, cautery, suture, adjuvant hemostat(s) | Manual pressure, cautery, suture, adjuvant hemostat(s) | Manual pressure, cautery, suture, staples, tissue repair | Manual pressure, cautery, suture, staples, tissue repair |
| **Maximum Expected ACS-ATLS Shock Risk Class** | 1 | 1 | 1 | 2 | 3 | 4 |
| **Hemostasis** | **Yes** | **No** | **No** | **No** | **No** | **No** |

In any case where hemostasis is initially achieved but bleeding recurs prior to subject closure, the event will be documented.

### 6.4.4 Other Bleeding Sites

For bleeding sites other than the TBS, the Investigator may use any means necessary to control bleeding, including either the test or control hemostat. No study data will be collected for other bleeding sites.

### 6.4.5 Intraoperative Data Collection

The following data will be recorded on the Intraoperative CRF:

- Surgical procedure(s)
- Description of TBS
  - Location
  - Conventional means for hemostasis (pressure, suture, cautery, etc.)
- Confirmation of intraoperative eligibility criteria
- Approximate dimensions of target bleeding site
- SPOT GRADE™ scores at baseline
  - Assessment of intraoperative eligibility
  - Immediately prior to hemostatic device application
- SPOT GRADE™ score at 3 minutes
- SPOT GRADE™ score at 5 minutes (if hemostasis is not achieved within 3 minutes)
- Randomization
  - Time of randomization
  - Treatment arm
  - Device lot/batch number data
- Number of incidence(s) of interruption of hemostatic device preparation

- Satisfaction on time and ease of hemostatic device preparation
- Incidence of TBS re-bleeding prior to subject closure
- Incidence of any device deficiencies
- Incidence of any device-related adverse events

Table 7 below shows a timeline of intraoperative procedures.

**Table 7. Timeline for Intraoperative Procedures***

| Time Point (MM:SS) | Study Procedures or Assessments |
|---|---|
| Prior to 00:00 | • Identify Target Bleeding Site (TBS)<br>• Assign SPOT GRADE™ score<br>• Perform randomization |
| 00:00 (start stopwatch) | • Open HEMOBLAST™ or FLOSEAL packaging and start preparation |
| 0X:XX | • Assign SPOT GRADE™ score immediately prior to hemostat application |
| 03:00 | • Assign SPOT GRADE™ score<br><br>***If SPOT GRADE™ score = 0***<br>• Intraoperative efficacy evaluation completed<br><br>***If SPOT GRADE™ score is NOT 0***<br>• Re-apply HEMOBLAST™ or FLOSEAL |
| 05:00 | • Assign SPOT GRADE™ score<br><br>***If SPOT GRADE™ score = 0***<br>• Intraoperative efficacy evaluation completed<br><br>***If SPOT GRADE™ score is NOT 0***<br>• Rescue treatment |

* Assuming subject meets all intraoperative eligibility criteria

### 6.5 Discontinuation Procedures and Documentation

Subjects will be discontinued after completion of the intraoperative visit.

The Discontinuation CRF should be completed to document the reason for discontinuation:

- Subject has completed the study;
- Subject withdrawal and reason for withdrawal; or
- Subject death (prior to completion of study evaluations).

The date of discontinuation will also be noted on the Discontinuation CRF.

## 7 ADVERSE EVENTS

### 7.1 General

An adverse event (AE) is ‘any untoward medical occurrence in a subject’.

A device deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labeling.

Only Adverse Events (AEs) possibly, probably, or definitely related to the hemostatic device (using the definitions below) will be recorded as part of this clinical study. Anticipated adverse device effects are included in Section 12.

### 7.2 Adverse Event Documentation

Only Adverse Events (AEs) possibly, probably, or definitely related to the hemostatic device (using the definitions below) will be recorded as part of this clinical study. AEs not related to the hemostatic device (the AE is due to the underlying disease state or is due to concomitant medications or therapy not related to the use of the hemostatic device) will not be recorded as part of this clinical study.

AEs will be documented by the Investigator on the appropriate source document(s) at the study site and also on the Adverse Event CRF. Adverse events are to be recorded and dated according to when they are first observed. The subsequent treatment(s) should also be documented. The following will be recorded on the Adverse Event CRF:

- Accepted medical term for the AE;
- Description of the event;
- Date of onset;
- Date of resolution, if applicable;
- Outcome;
- Treatment(s)/action(s) taken;
- Severity;
- Relationship to the hemostatic device; and
- Determination of reportability (see Reporting Section below).

The severity of the event will be determined by the Investigator using the following definitions:

- Mild: the symptoms are transient, barely perceptible by the subject and do not hinder normal activity; no treatment is usually prescribed to reduce these symptoms;
- Moderate: the symptoms are sufficiently severe to provoke discomfort in the subject and sufficiently uncomfortable to prevent normal activity; a treatment may be required; or
- Severe: the symptoms considerably modify the normal course of the subject's activities or are disabling or are life-threatening; the treatment studied should be suspended; a treatment for the symptoms is prescribed.

The relationship to the hemostatic device will be determined by the Investigator using the following definitions:

- Possibly related: the AE has a reasonable temporal relationship to the use of the hemostatic device but alternative etiology is equally or more likely compared to the potential relationship to the use of the hemostatic device;
- Probably related: the AE has a strong temporal relationship to the use of the hemostatic device and alternative etiology is less likely compared to the potential relationship to the use of the hemostatic device; or

- Definitely related: the AE has a strong temporal relationship to the use of the hemostatic device, follows a known response pattern and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies.

The expectedness of the AE will be determined by the Investigator as:

- Anticipated; or
- Unanticipated.

Anticipated AEs are those that are identified as potential risks in the device labeling (e.g., IFU). Unanticipated AEs are those that are, by their nature, incidence, severity, or outcome, not identified in the device labeling.

### 7.3 Reporting

A serious adverse event (SAE) is defined as an adverse event that:

- Led to death;
- Led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A serious adverse device effect (SADE) is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

An unanticipated [serious] adverse device effect (UADE/USADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

All SADEs and UADEs must be reported to the Sponsor representative within 24 hours of the Investigator becoming aware of it.

There are two methods of reporting. The first is to complete and save the Adverse Event CRF within 24 hours of the Investigator becoming aware of the SADE or UADE.

The second method of reporting is to contact the Sponsor representative for event reporting:

Telephone Number: +1 404 702 9253
E-Mail: medical@biomup.com

The Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and record them in the subject's source documentation and on the Adverse Event CRF. It

is the responsibility of the Principal Investigator to inform the appropriate personnel as required by IRB policy.

For SADEs and UADEs that are unresolved at the time of subject discontinuation, the Investigator will continue to follow the event to resolution or stabilization per standard medical care.

### 7.4 Regulatory Authority Reporting

The study site will provide Sponsor-requested [redacted] details regarding the SADE or UADE and the Sponsor Regulatory Affairs Department will be notified to determine reportability per applicable regulations and guidelines. Sponsor reporting to FDA will be performed per 21 CFR Part 803.

## 8 DATA COLLECTION

### 8.1 Completion of Case Report Forms

Prior to enrollment of subjects at each study site, the Sponsor representative will provide the Principal Investigator and designated study site staff with training on electronic CRF completion procedures. The Principal Investigator will be responsible for the timing, accuracy, and completeness of CRFs for each individual subject. The personal data recorded on all paper and electronic documents will be regarded as confidential.

### 8.2 Source Documentation

Source documents are where clinical study information for subjects are first recorded. Data collected for the clinical study must be supported by source documents, and may include, but is not limited to, subject medical records, hospital charts, operative reports, laboratory and diagnostic test reports, and study worksheets. Study worksheets should be used when other source documents do not capture study-specific data as part of standard of care.

### 8.3 Retention of Clinical Study Documentation

Clinical study records will be stored in a confidential manner so as to protect the confidentiality of subject information. All records related to this clinical study will be retained in appropriate study files.

The Principal Investigator is responsible for retaining all copies of the records for a period of no less than 5 years from the date on which the clinical study is completed/terminated. In all cases, the Principal Investigator must contact the Sponsor prior to disposing of any records related to the clinical study.

The Sponsor must approve the destruction of any study records.

In addition, if the Principal Investigator moves/retires, etc., he/she should provide the Sponsor with the name and address of the person who will look after and be responsible for the clinical study related records.

### 8.4 Training

Principal Investigators and study site staff will be trained on the clinical study and the specific tasks to which they are delegated. Study site staff will also have documented training on Good Clinical Practice.

Further, Investigators (Principal Investigators and sub-investigators responsible for enrolling study subjects and applying the hemostatic devices) will have training on use of the test device, control device, and the SPOT GRADE™.

# 9 TERMINATION OF THE CLINICAL STUDY

## 9.1 Subject Withdrawals and Discontinuation

During the course of this clinical study, subjects may elect to withdraw from study participation for any reason. In addition, subjects will be withdrawn from the study for any of the following reasons:

- TBS bleeding severity not appropriate for treatment immediately prior to hemostat application, but after enrollment and randomization; or
- Subject death (prior to completion of study evaluations).

Subjects who are withdrawn prior to receiving test or control device will be replaced.

## 9.2 Early Termination of the Clinical Study

Both the Sponsor and Principal Investigator reserve the right to terminate the clinical study at any time. Should this be necessary, the procedures will be arranged on an individual site basis after review and consultation by both parties. In terminating the clinical study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests. In case the study is terminated for safety reasons, this will be communicated to all participating Principal Investigators, who will be responsible for notifying their reviewing IRBs per IRB policy.

# 10 DATA MANAGEMENT

All data will be housed in a validated database program.

Once all the subject data has been collected, the analysis and reporting will be conducted. Any data existing for subjects who have not received treatment will not be used in the analysis.

Any data existing for subjects who have received the test or control device, who withdraw voluntarily or who are withdrawn from the clinical study, will be used in the final analysis. The inclusion of partial data will be documented in the final report. The final report will be the responsibility of Biom'up.

# 11 STATISTICS

## 11.1 Overview

### 11.1.1 Primary Endpoint

The primary endpoint of this study is the superiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 3 minutes.

### 11.1.2 Secondary Efficacy Endpoints

The secondary endpoint of this study is non-inferiority of HEMOBLAST™ relative to FLOSEAL for the proportion of subjects reaching hemostasis within 5 minutes. A margin of 10% (absolute difference) will be used for determining non-inferiority of HEMOBLAST™ relative to FLOSEAL.

### 11.1.3 Safety Outcomes

The rate of occurrence of device malfunctions, device-related AEs, SADEs, and UADEs will be summarized for each treatment group. Events will be summarized by severity.

### 11.1.4 Study Success

Study success will be defined as superiority of HEMOBLAST™ relative to FLOSEAL in the proportion of subjects achieving hemostasis at the 3 minute assessment time point.

## 11.2 General Analysis Considerations

All statistical analyses will be performed using Power BI, SAS®, and/or R. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

### 11.2.1 Analysis Populations

Safety analyses will be performed on the Full Analysis Population, defined as all subjects who were randomized into the study and received study intervention. Efficacy analyses will be conducted on the time to hemostasis (TTH) Analysis Population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored (defined as the use of an additional hemostatic product or surgical rescue prior to the end of observation time, or failing to achieve and maintain complete hemostasis prior to the end of observation time). Data summaries will be based on the intervention received, regardless of which intervention was randomly assigned.

### 11.2.2 Handling of Missing Data

In primary analyses, missing TTH values will not be imputed. All values censored prior to 3 minutes will be considered treatment failures for the purpose of the primary analysis. For the key secondary analysis, all values censored prior to 5 minutes will be considered treatment failures for the purpose of the primary analysis. A sensitivity analysis for the primary endpoint will consider a worst-case scenario in which all values censored prior to 3 minutes in the HEMOBLAST™ arm will be considered treatment failures while hemostasis at 3 minutes will be imputed for all values censored prior to 3 minutes on the FLOSEAL arm.

### 11.2.3 Subgroup Analyses

Analyses of performance (primary and secondary endpoints) will be presented by baseline bleeding severity. Additionally, the primary and secondary endpoints will be presented stratified by preoperative anticoagulation regimen.

### 11.2.4 Data Transformations

No transformations of data are planned.

### 11.2.5 Subject Disposition and Characteristics

The number of subjects randomized to each treatment arm will be tabulated. Demographic variables will include age, sex, race, ethnicity, height, weight, and Body Mass Index (BMI). Baseline disease characteristics will include indication(s) for surgery and related co-morbidities/concomitant illnesses. All continuous endpoints will be summarized using descriptive statistics, that will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

### 11.2.6 Subject Compliance

Because the study device will be applied by the investigator during a single surgery, subject compliance with completing the study evaluations is not an issue and will not be reported.

### 11.2.7 Protocol Deviations

Eligibility criteria that were not met will be listed along with whether or not an exception was granted. Important protocol deviations will be summarized by treatment group. Important protocol deviations are defined as:

- Any unauthorized protocol deviations that result in a significant added risk to the study subject;
- Performing study-specific activities without subject written informed consent;
- Non-adherence to eligibility criteria without prior Sponsor approval; and
- Non-adherence to Good Clinical Practice and/or applicable regulations;
- Protocol deviations will be summarized in tables produced by the Medical Monitor or Clinical Research Associate.

Protocol deviations will be either self-reported by the study site or identified by the Sponsor/Sponsor representative during site visits. Protocol deviations will be recorded and retained in the study files.

## 11.3 Analytic Methods

### 11.3.1 Analysis of Primary and Secondary Efficacy Endpoints

#### 11.3.1.1 Analysis Population

Efficacy analyses will be conducted on the TTH Population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored.

#### 11.3.1.2 Methods of Analysis

The primary efficacy endpoint is the difference in the probability of TTH at 3 minutes comparing HEMOBLAST™ to FLOSEAL. Letting $\theta$ denote the true difference in the probability of hemostasis at 3 minutes between HEMOBLAST™ to FLOSEAL, the trial will test the null hypothesis $H_0$: $\theta \leq 0$ vs. the alternative hypothesis $H_A$: $\theta > 0$ using a one-sided level 0.025 Wald test. The resulting p-value based upon the asymptotic normal distribution and a corresponding (2-sided) 95% confidence interval for the difference in binomial proportions (HEMOBLAST™ minus FLOSEAL) will also be computed and reported.

### 11.3.2 Analysis of Safety Outcomes

#### 11.3.2.1 Analysis Population

Safety analyses will be conducted on the Safety Analysis Population, defined as all subjects who were randomized into the study and received study intervention.

11.3.2.2 Methods of Analysis

Summaries of the number and percent of subjects with at least one device-related AE will be provided. Comparisons of the proportion of subjects experiencing SADEs and UADEs will be made between treatment arms.

### 11.3.3 Sample Size Justification

The sample size for the proposed study is based on:

- Type I error $\alpha = 0.025$ (one-sided);
- Type II error $\beta = 0.10$;
- $\delta = 0.30$;
- $\theta_{\text{HEMOBLAST™}} = 0.40$ at 3 minutes; and
- $\theta_{\text{FLOSEAL}} = 0.10$ at 3 minutes.

Based upon the above model specification, the proposed study will require approximately N=98 patients (49 patients per arm). While early discontinuation is expected to be rare, to account for potential loss of patients due to early discontinuation, a total of N=104 subjects (52 patients per arm) will be enrolled in order to ensure at least 90% power under the design assumptions while allowing for up to 5% attrition.

## 12 RISK/BENEFIT ANALYSIS

### 12.1 Anticipated Clinical Benefits

It is anticipated that application of a hemostatic device to a bleeding site will result in a reduced time to hemostasis compared to conventional methods of hemostasis (pressure, suture, or cautery). Individual subjects may not directly benefit from participation in this study. However, conducting this research could contribute to the overall advancement of medical and scientific knowledge and may benefit future patients.

### 12.2 Risks Associated with Participation in the Clinical Study

There are possible risks, complications, and discomforts associated with undergoing a cardiothoracic surgical procedure. The Investigator will be responsible for discussing these risks, complications and discomforts with subjects along with the risks associated with anesthesia.

Potential risks related to the use of hemostats similar to HEMOBLAST™ include:

- Adhesion formation;
- Allergy or anaphylaxis;
- Blockage of cardiopulmonary bypass system and cell saver devices;
- Compromised attachment of orthopedic implants;
- Creutzfeldt-Jakob disease (CJD) agent;
- Increased infection;
- Nerve compression;
- Thrombosis or thromboembolism;

- Transmissible Spongiform Encephalopathies (TSE); and
- Viral disease transmission.

Hypersensitivity of allergic/anaphylactoid reactions may occur with HEMOBLAST™. Symptoms associated with allergic anaphylactic reactions include: flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension, and anaphylactic shock.

These reactions may occur in patients receiving HEMOBLAST™ for the first time or may increase with repetitive applications of HEMOBLAST™. In the event of hypersensitivity reactions, discontinue administration of HEMOBLAST™. Mild reactions can be managed with antihistamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

Subjects randomized to receive the control are exposed to risks associated with FLOSEAL, as described in the current device labeling.

Participation in this clinical study also presents additional risks or inconveniences. These may include, but are not limited to:

- Additional intraoperative assessments of bleeding severity at 3 and 5 minutes.

There may also be other unforeseen risks.

### 12.3 Risk/Benefit Analysis

Individual patients may experience no direct benefit from participation in the study. However, a potential benefit of HEMOBLAST™ to be investigated in the study includes a higher probability of hemostasis within 3 minutes of device package opening, as will be tested for potential superiority.

Risk mitigation steps have been taken through test device specifications; further, the test device has been approved by the United States Food and Drug Administration for the indication under which it will be used in this clinical study. Risk mitigation steps are also implemented in the manufacture and shipment of the test device.

The Sponsor, Medical Expert, and coordinating Investigator have determined that this clinical study is justified because the potential benefits outweigh the potential risks.

### 12.4 Conduct of Clinical Study to Reduce Risk

Further efforts to minimize risk in this clinical study will involve selecting investigators who are experienced and skilled in cardiothoracic surgery, have clinical study experience, and who are adequately trained on the use of the hemostatic devices and study procedures.

Risks and benefits of this clinical study are included in the sample Subject Informed Consent Form, included as Appendix B. Potential risks and benefits will be discussed with potential subjects during the informed consent process.

## 13 REPORTS AND PUBLICATIONS

### 13.1 Interim Reports

Interim reports will not be issued during the conduct of this clinical study.

### 13.2 Final Report

The final report will be compiled by the Sponsor or designated Sponsor representative and reviewed, approved and signed off by the Sponsor and coordinating investigator.

### 13.3 Publications

The conduct and results of this clinical study will be documented in the final report, as mentioned above. Because this is a multicenter study, it is intended that the combined clinical data from all participating sites will be presented and/or published. Individual investigators will not publish or present results prior to publication of the combined multicenter results without prior written consent from the Sponsor. All publications must include the name of the Sponsor (Biom'up, France).

## 14 ETHICAL CONSIDERATIONS

### 14.1 Institutional Review Board Approval

Prior to the initiation of this clinical study, the Principal Investigator must submit the Protocol, informed consent form, and any other documents as may be required to the appropriate IRB for review and approval. The Principal Investigator, and any other member of the study team, must not participate in the decision-making. A signed and dated letter granting IRB approval must be provided to the Sponsor prior to the initiation of the clinical study. A list of the members of the IRB reviewing this Protocol will be requested.

### 14.2 Informed Consent and Patient Information

The Principal Investigator or designee must explain to each subject the nature of the clinical study, including any risks and benefits, its purpose and procedures, and expected duration of involvement in the clinical study. Each subject must be informed that participation in the clinical study is voluntary and non-participation will not affect his/her right to the most appropriate surgical treatment or affect the doctor/clinician-patient relationship. Subjects have the full right to withdraw from the clinical study at any time, irrespective of their initial consent.

Each subject must also give their permission for representatives of the Sponsor, auditor and regulatory authorities to review their hospital records for purposes of source data verification.

### 14.3 Subject Confidentiality

Confidentiality of subject data will be maintained at all times. Subject anonymity will be maintained and all documentation relating to a subject will be kept in a secure location. The Sponsor, authorized Sponsor representatives, and regulatory bodies may have access to subject records, but identifying information will not be retained in the study files.

### 14.4 Indemnity

Indemnity will be documented in the Clinical Trial Agreement for each study site.

### 14.5 Insurance

The Sponsor is responsible for obtaining and maintaining clinical study insurance.

# 15 COMPLIANCE

## 15.1 Overview

This clinical study will be conducted in accordance with Good Clinical Practice (GCP, ICH E6) and 21 CFR Parts 50, 54, and 56.

## 15.2 Clinical Study Personnel Responsibilities

Prior to the initiation of this clinical study, each Principal Investigator will approve this Protocol by signing the signature page. This signature confirms that the clinical study will be performed in compliance with the Protocol.

The Sponsor shall also provide accurate, complete, and current information about any aspect of the clinical study as requested by reviewing IRB(s) or regulatory authorities. Current applicable national regulations shall be followed.

The Sponsor is also responsible for the retention of clinical study documentation per applicable regulations.

## 15.3 Monitoring

The monitor will be responsible for securing the compliance of the Principal Investigators to the signed agreement, the Protocol, GCP, applicable laws and regulations, and conditions of approval imposed by the reviewing IRBs or regulatory authorities, as specified in the study-specific Clinical Monitoring Plan.

The Principal Investigator will permit the Sponsor or designated representative of the Sponsor to inspect all CRFs and corresponding portions of the subject's clinic records and/or original hospital medical records, at regular intervals throughout the clinical study. These inspections are for the purpose of verifying adherence to the Protocol and the completeness and accuracy of the data being entered on the CRFs.

The planned extent of source data verification is detailed within the study-specific Clinical Monitoring Plan.

## 15.4 Audits

During the conduct of the clinical study, the Sponsor may appoint Quality Assurance (QA) personnel to provide audit of the administration and conduct of the clinical study, at the study site(s), Sponsor, and/or Sponsor representative(s).

The relevant Regulatory Authority also has the right to conduct an audit of the clinical study. It is the joint responsibility of the Sponsor and the Principal Investigator to ensure that the clinical study has been conducted in accordance with all government regulations.

In the event that the regulatory authority desires to inspect this clinical study, the Principal Investigator will permit authorized inspectors to inspect all facilities and records relating to the clinical study and aid the Inspector to perform the audit in a timely fashion.

## 15.5 Modifications to the Protocol

Except in emergency situations, prior approval by the Sponsor is required for changes in or deviations from this Protocol. This provision does not apply to those changes made to reduce discomfort or overt risks to

the subject. In the event of an emergency situation, the Principal Investigator must institute any and all medical procedures he/she deems to be medically sound.

## 16 ABBREVIATIONS AND DEFINITIONS

| Abbreviation / Term | Definition |
|---|---|
| ACS-ATLS | American College of Investigators – Advanced Trauma Life Support® Shock Risk Class: 1 – involves up to 15% of blood volume; typically no change in vital signs and fluid resuscitation is not usually necessary. Class 2 – involves 15-30% of total blood volume; patient is often tachycardic with a narrowing of the difference between the systolic and diastolic blood pressures; the body attempts to compensate with peripheral vasoconstriction; skin may start to look pale and be cool to the touch; volume resuscitation with crystalloids is all that is typically required; blood transfusion is not typically required. Class 3 – involved loss of 30-40% of circulating blood volume; patient's blood pressure drops; heart rate increases, peripheral hypoperfusion worsens; fluid resuscitation with crystalloid and blood transfusion are usually necessary. Class 4 – involves loss of > 40% of circulating blood volume; the limit of the body's compensation is reached and aggressive resuscitation is required to prevent death. |
| ADE | Adverse Device Effect - any untoward and unintended response to an investigational medical device |
| AE | Adverse Event - any untoward medical occurrence in a subject |
| ASA Classification | American Society of Anesthesiologists Classification: 1 – normal health patient; 2 – patient with mild systemic disease; 3 – patient with severe systemic disease; 4 – patient with severe systemic disease that is constant threat to life; 5 – moribund patient who is not expected to survive with the operation; 6 – a declared brain-dead patient whose organs are being removed for donor purposes |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| Device deficiency | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance, which may include device malfunctions, use errors and inadequate labelling |
| Enrollment | For this study, the point of enrollment is intraoperatively, when the subject meets all intraoperative inclusion criteria |
| FDA | Food and Drug Administration |
| ICF | Informed Consent Form |
| Intraoperative Time | Time from skin open to skin closure |
| IRB | Institutional Review Board |
| QA | Quality Assurance |
| SADE | Serious Adverse Device Effect – an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune |
| SAE | Serious Adverse Event – an adverse event that:<br>• Led to death |

| | |
|---|---|
| | Led to a serious deterioration in the health of the subject, that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. |
| SBSS | Surface Bleeding Severity Scale, also known as SPOT GRADE™ |
| TBS | Target Bleeding Site |
| TTH | Time To Hemostasis |
| UADE (also USADE) | Unanticipated [Serious] Adverse Device Effect – any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects |
| WHO | World Health Organization |

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