Study Protocol: Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System

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PerClot® Polysaccharide Hemostatic System

Protocol

Clinical Investigation Title: Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System

The C.L.O.T. Investigation

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PCT1101.011-C (02/15) Amendment 09
Revision History

Protocol Number	Effective Date	Detail of Changes
PCT1101.000	March 29, 2011	Not applicable – new document
PCT1101.001	October 31, 2011	The protocol has been revised to address the concerns posed by FDA in their disapproval letter to CryoLife, Inc. dated 31 March 2011.
PCT1101.002	March 9, 2012	The name and address of the Monitor/Sponsor Representative was revised. The statement "non-pyrogenic" is included in the investigational device description (Section 2.1 and Appendix A). Section 6.4.3 was revised to use the medical retinaculum as the bleeding evaluation site for knee arthroplasty procedures. The sample Informed Consent (Appendix B) was revised to include additional legal language as suggested by Sponsor General Counsel.
PCT1101.003	October 31, 2012	The protocol has been revised to address the concerns posed by FDA in their disapproval letter to CryoLife, Inc. dated 02 May 2012 and in the e-mail correspondence dated 08 May 2012. Other changes that are outside the scope of the concerns posed by FDA include: • Removal of blood count and coagulation status as a safety endpoint (Sections 1, 6.1.3, and 6.6.4); • Device description; • Increase of the maximum investigational sites to 12 (Sections 1 and 6.3; sample Subject Informed Consent Form); • Change in the manufacturer of the Investigational Product to CryoLife, Inc. (Section 2.2); • Clarification that PerClot results in a less severe foreign body response/inflammatory reaction when compared to gelatin sponge and bone wax (Section 3); • Clarification that specific sites will be evaluated for satisfaction of intraoperative eligibility criteria (Section 6.4.3); and • Update of company logo in the Instructions for Use.
PCT1101.004	May 10, 2013	The protocol has been revised to address the concerns posed by FDA in their disapproval letter to CryoLife, Inc. dated 14 December 2012. Other changes that are outside the scope of the concerns posed by FDA include: • Removal of the 3 minute hemostatic assessment time point (Sections 1, 5.1, 6.1.3, 6.2.3, 6.4.3.5, 6.6.3; 6.6.11; Sample Case Report Forms); • Increase of the maximum investigation sites to 15 (Sections 1 and 6.3, sample Subject Informed

Protocol Number	Effective Date	Detail of Changes
		Consent Form); • Addition of contraindication for use in patients who have known sensitivity to starch or starch-derived materials (Section 6.3.2, PerClot Instructions for Use, Sample Subject Informed Consent Form, Sample Screening and Enrollment Log, Sample Case Report Forms); • Addition of information regarding the comparator device (Section 6.2.2); • Revision of the Risk Analysis in accordance with ISO14971:2012; and • Revision of the sample Principal Investigator and Sub-Investigator Agreements to use consistent legal terms, reference the Clinical Research Agreement, and include language on the Physician Payment Sunshine Act.
PCT1101.005	September 26, 2013	The protocol has been revised to address the concerns posed by FDA in their conditional approval letter to CryoLife, Inc. dated 14 June 2013 and telephone communication on 12 July 2013. Other changes that are outside the scope of the concerns posed by FDA include: • Statement regarding destruction of opened investigational product (Section 2.3) • Additional biocompatibility testing (Section 3.1) • Addition of ROM, DVT, and Hemoglobin assessments for subjects undergoing orthopedic procedures (Sections 4.2, 6.4.2, 6.4.4, 6.4.5, Appendix B, Appendix E, Appendix F) • Appendix G has been revised as in vivo training is no longer necessary due to the removal of the bleeding severity assessment model.
PCT1101.006	February 18, 2014	The protocol has been revised to address the concerns posed by FDA in their conditional approval letter to CryoLife, Inc. dated 30 October 2013 and telephone communication 17 January 2014. Other changes that are outside the scope of the concerns posed by FDA include: • Addition of Biocompatibility PreClinical Studies • Addition Thromboembolism Assessment • Addition Appendix L: Blood Sugar Lowering Medications • Appendix O: Operative Steps
PCT1101.007	March 31, 2014	Corrections to protocol per G11007s2a1 interactive review questions with the FDA dated 24 March 2014.

Protocol Number	Effective Date	Detail of Changes
PCT1101.008	April 15, 2014 July 28, 2014	Formatting throughout document. Changes per FDA Approval Letter dated March 27, 2014 study design considerations. The following changes have been made: • Primary and secondary endpoints have been revised to 7 minutes and 5 minutes, respectively. • Hemostasis defined. • Maximum dose increased to 10 grams. • Revisions to IFU and Operative Steps regarding product administration. • Compliance Statement change. • Revisions to assessment method for pulmonary embolism. • Allocation eCRF removed. • Protocol Deviation eCRF created. • List of Principal Investigators revised. • Statement regarding masking added to Sections 1, 2, and 6.1.2. • Statement regarding subject numbering added to Section 6.4.1. • Section 3.2.19 added (preclinical study). • Revision of 25-minute intraoperative hemostatic evaluation to 35-minute intraoperative hemostatic evaluation in Section 4.2. • Intraoperative inclusion for bleeding flux revised. • Statement regarding dislodgement of study device added to Section 6.4.3.4. • Standard gauze revised to Covidien™ Vistec™ X-ray Detectable sponges. • Study duration modification. • Removal of legally authorized representative throughout protocol, ICF, and applicable CRF page. • Appendix C revised to reflect changes to IFU. • Appendices rearranged. • Clarifying language throughout document.
PCT1101.009	December 1, 2014	Changes per FDA Approval Letter dated August 29, 2014 study design considerations and Q-Sub Call on November 11, 2014. The following changes have been made: • Removal of language regarding multiple bleeding sites throughout protocol, Informed Consent Form, and Case Report Forms. • Hemostasis maintenance assessment for an additional 5 minutes(12 minutes post-application) added to protocol, Informed Consent Form, and Case Report Forms • Addition of intraoperative inclusion criteria related to

Protocol Number	Effective Date	Detail of Changes
		size of study device application area to Sections 6.3.2, 6.4.3.2, and Appendix D. • Bleeding flux inclusion criteria revised in Sections 6.3.2 and 6.4.3.2. • Information regarding responsibilities of randomization designee added to Section 6.4.3.3. • Information regarding calibration of scales added to Section 6.4.3.2. • Bleeding severity score added to randomization stratification in Section 6.6.6. • Additions to Glossary. • Revisions to Appendix A. • Appendix C revised to reflect changes to IFU. • Calibration eCRF created. • Revisions to Appendix N. • Addition of clinical investigation sites on page xii. Grammatical corrections, consistent terminology, and clarifying language added throughout document.
PCT1101.010	January 7, 2015	Changes per FDA teleconference on December 23, 2014. The following changes have been made: • DVT prophylaxis methods and duration added to Sections 6.4.5 and 6.4.6. • Case Report Forms 5 and 6 revised to include DVT prophylaxis methods and duration. • Revisions to Appendix N: the wording "and multiply those two values" was added and the type of "Anatomic Site" and "Anatomic Application Site" was changed to bold.
PCT1101.011	February 17, 2015	• Removal and addition of clinical investigation sites on page xii. • Reference to envelope-based randomization methods removed in Section 6.4.3.3 and Appendix N. • Insertion of Interactive Web Response System (IWRS) in Section 6.4.3.3 and Appendix N. • Clarifying language added regarding subject numbering in Section 6.4.1. • Version number and copyright date revised in Appendix A. • Correction of typos and grammatical errors throughout the document.
PCT1101.011 (02/15) Amendment 1	April 27, 2016	• Investigator Training (Appendix G) has been removed and replaced with the Protocol Signature Page. • Principal Investigators & Investigational Sites removed. • Sections 1, 6.3, 6.4.6, 6.4.7 Table 3, and Appendix B

Protocol Number	Effective Date	Detail of Changes
		have been revised to reflect a follow up period of 6 weeks. • Unscheduled visit added to Section 6.4.6, Laboratory and Follow up Case Report Forms. • Sections 6.3.2, 6.4.3.2, and Appendices A and D have been revised to allow inclusion of Class I and II wounds. • A pre-screening log has been added to Appendix D. • Sections 6.4.4 and 6.4.6 have been revised to use consistent language for Thromboembolism Evaluation. • Section 6.4.5 and Discharge Case Report Form revised to remove clinical assessment for signs and symptoms of embolism or thrombosis. • Appendix L revised to include additional blood modifiers. • Appendix N revised to remove reference to Operative Worksheet numbers. • Reference to Case Report Form numbers removed throughout protocol. • Operative Case Report Form modified to facilitate mass calculation of test and control articles. • Figure 1 in Section 6.3 has been revised to show the bleeding severity score. • Appendix J has been revised to include the current version of the inner pouch label. • Section 6.6.5 has been revised to reflect the sample size justification. • Operative Case Report Form has been revised to capture time of application in seconds. • Section 6.3.2, Appendix A, and Appendix D have been revised to remove the word "institution" before "laboratory's normal reference range." • Sections 6.3.2 and 6.4.2 have been revised to specify which lab value, if more than one are available, to include in the database. • Window for laboratory evaluation has been revised to 1 month (30 days) in Section 6.3.2. • Section 10.4.2, Table 6 has been revised to remove the requirement for the sites to submit SAE information to the DSMB. • Section 6.4.6.1, Postoperative and Follow up Case Report Forms have been revised to allow an opt-out of CT scan of chest. • Time points for collecting blood glucose have been revised in Section 6.4.4, and Operative, Postoperative, and Laboratory Case Report Forms.

Protocol Number	Effective Date	Detail of Changes
		• Clarifying language has been added to Appendix A. • Anticipated enrollment period, maximum duration of clinical investigation, and number of sites has been revised in Sections 1 and 6.3. • Sections 9.1 and 13 have been revised to reflect the current FDA definition of SAE. • Two preoperative exclusion criteria have been changed to intraoperative exclusion criteria in Sections 6.3.2, 6.4.3, and Screening and Operative Case Report Forms. • The preoperative exclusion criterion related to hepatic dysfunction has been replaced with a criterion related to coagulopathy in Section 6.3.2 and Appendices A and D. • Sections 1, 2.3, 6.4.3.3, 6.4.3.4, and Appendix B have been revised to reflect a single-blind study. • Sections 6.3.2, 6.4.4, 6.6.10, Appendices A and B have been revised to remove C3 values as exclusion criteria and add C3 values to the list of covariates and postoperative labs. • Section 6.3.2, and Appendices A and D have been revised to clarify the exclusion criterion regarding GFR and to revise the exclusion criterion regarding glycosylated hemoglobin. • "10g" has been replaced with "the entire contents of up to two 5g bellows" in section 1 and Appendices A, B and N. • Section 6.4.4 has been revised to remove the requirement that any abnormal glucose value be reported as an adverse event. • Sections 6.3.2, 6.4.3.2, and Appendix D have been revised to remove a redundant intraoperative exclusion criterion. • Sections 1, 6.13, 6.6.4, and Appendices A and B have been revised to separate reporting the incidence of procedure complications from incidence of adverse events. • Section 9.3 and Section 10, Table 6 have been revised to clarify adverse event reporting requirements. • Language regarding videotaping and adjudication has been added to Section 6.4.3.5. • Section 6.6.6 has been revised to include the statistical method, change in alpha, and interim analysis. • Appendix B has been revised to include time points for blood glucose measurements, language regarding videotaping, changes to follow up evaluations, and to

Protocol Number	Effective Date	Detail of Changes
		remove the Principal Investigator signature and date lines. • Appendix C has been updated. • Storage requirements have been revised in Appendices A and J. • Appendix A has been revised to allow for "up to 70cc of fluid per 1 gram". • Section 6.3.2 has been revised to allow dermatologic use of corticosteroids. • Section 3.2 was revised to clarify GLP compliance status for two preclinical studies and to remove the study entitled "Preclinical Evaluation Comparing the Efficacy of Two Starch-Based (PerClot vs. Arista) Hemostatic Agents in a Porcine Liver Bleeding Model". • Additional clinical study summary added to Section 3.3. • Clarifying language throughout protocol.
PCT1101.011 (02/15) Amendment 02	May 25, 2016	Changes per FDA teleconference on May 24, 2016. • Sections 6.3.2, 6.4.3, Appendices A, C, D and E have been modified to address FDA's concerns regarding the use of PerClot in cardiac surgery.
PCT1101.011 (02/15) Amendment 03	June 16, 2016	Changes per FDA approval letter on May 27, 2016. • Section 6.4.4, Appendices B and E have been revised to change the time of glucose monitoring. • Section 6.3.2, Appendices A, B, D, and E have been revised to remove the exclusion related to renal dysfunction. • Sections 6.4.3.3, 6.4.3.5, Appendices B and E have been revised to remove acid base status and arterial blood gas testing. • Section 6.4.3 and Appendix A have been revised to include language regarding large needle holes. • Sections 6.3.2, 6.4.3.2, Appendices D and E have been revised to change the wound classification system. • Sections 6.4.4, 6.4.6.1, Appendices B and E have been revised remove the CT scan and Doppler ultrasound. • Sections 1, 6.3, 6.4.6.2, 6.4.7, Appendices B and E have been revised to add a 24 month follow up visit for oncologic subjects. • Section 6.6.6 has been revised to clarify the sample size re-estimation. • Section 6.4.3.3 has been revised to modify the randomization method from IWRS to envelope randomization.

Protocol Number	Effective Date	Detail of Changes
PCT1101.011 (02/15) Amendment 04	July 15, 2016	Changes per FDA email on July 13, 2016. • Section 4.2 has been revised to note that the CT scan of chest and Doppler Ultrasound will only be performed if clinically indicated. • Section 6.6.11 has been revised to include aspirin as a covariate. • Appendices E and F have been revised to add a data field regarding aspirin use.
PCT1101.011 (02/15) Amendment 05	November 09, 2016	• IMARC added as Monitor/Sponsor Representative on cover page and Section 6.5.4. • Clarifying language regarding endpoint determination added to Sections 1 and 6.4.3.5. • Clarifying language regarding removal/replacement of subjects added to Section 6.6.9. • Clarifying language regarding power of the study added to Section 6.6.5. • Clarifying language regarding bleeding site added to Section 6.4.3.4. • Definition of embolism added to glossary. • Clarifying language regarding block randomization process added to Section 6.6.8. • Appendices E and F were revised to update the protocol amendment number.
PCT1101.011 (02/15) Amendment 06	February 03, 2017	• Monitor/Sponsor Representative address updated on cover page and Appendix B. • "Urine" removed before "pregnancy test" in Section 4.2, 6.3.2, and Appendices A, B, and D. • Note regarding total hysterectomy added to Section 6.3.2. • Definition of total hysterectomy added to glossary. • Cell saver language clarified in Section 6.4.3.1 and Appendix A. • Appendices E and F revised to update the protocol amendment number. • Appendix C updated.
PCT1101.011 (02/15) Amendment 07 DRAFT	September 06, 2017	• Follow up assessments at 24 month visit revised in Sections1, 6.3, 6.4.6.2, Appendix B, and Appendix E. • Definition of overall survival added to glossary.
PCT1101.011 (02/15) Amendment 07	October 24, 2017	Changes per FDA approval of PCT1101.011 (02/15) Amendment 07 DRAFT • The word "DRAFT" has been removed from protocol number throughout the document. • Date of protocol updated.

Protocol Number	Effective Date	Detail of Changes
PCT1101.011 (02/15) Amendment 08	July 06, 2018	• Language regarding video imaging and Clinical Adjudication Committee has been removed from Sections 1, 6.4.3.5 and Appendix B. • Clarification regarding pre-screening log added to Section 6.3.1. • Revision of window for 6 week follow up visit in Sections 6.3, 6.4.6, and 6.4.7. • Revision to phone and fax number in Section 6.5.4. • Appendices E and F revised to reflect protocol changes and amendment number.
PCT1101.011 (02/15) Amendment 09 DRAFT	August 02, 2018	• Maximum and minimum enrollment numbers revised in Section 6.6.2. • Appendices E and F revised to reflect protocol changes and amendment number
PCT1101.011 (02/15) Amendment 09	October 01, 2018	Changes per FDA approval of PCT1101.011 (02/15) Amendment 09 DRAFT • The word “DRAFT” has been removed from protocol number throughout the document. • Date of protocol updated.

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Table of Contents

1 Synopsis

The device under investigation is PerClot® Polysaccharide Hemostatic System (hereinafter referred to as PerClot). This is a prospective, multicenter, multidisciplinary, controlled clinical investigation evaluating the safety and efficacy of PerClot compared to a similar marketed hemostatic device.

The overall objective of this clinical investigation is to collect clinical data concerning the safety and efficacy of PerClot versus a similar marketed hemostatic device (the control) in multiple surgical disciplines when used as an adjunct to conventional means of achieving hemostasis such as pressure or ligature. Hemostasis is defined as complete cessation of bleeding.

This will be a single-blinded trial. The subjects will be blinded as to the hemostatic treatment received. Unblinding will be permitted after a subject has completed his or her 6 week follow-up visit evaluation.

The primary objective of this investigation is to demonstrate non-inferiority in the achievement of hemostasis of the treated bleeding site at 7 minutes in subjects receiving PerClot compared to subjects receiving a control hemostatic device. The secondary objective of this investigation is to compare the achievement of hemostasis of the treated bleeding site at 5 minutes in subjects receiving PerClot compared to subjects receiving a control hemostatic device.

The primary endpoint is hemostasis of the treated bleeding site at 7 minutes. The secondary efficacy endpoint for this investigation is hemostasis of the treated bleeding site at 5 minutes. After the 7 minute assessment, the treated bleeding site will be observed for 5 additional minutes (12 minutes post-application) and just prior to closure to assess hemostasis maintenance.

The safety endpoints will consist of:

- Total operative time;
- Hemostasis at 5 and 7 minutes;
- Hemostasis maintenance;
- Total intraoperative estimated blood loss;
- Alternative means required to achieve hemostasis (where applicable);
- Units of blood transfused intraoperatively and postoperatively (where applicable);
- Incidence of reoperation;
- Total hospitalization time;
- The incidence of procedure complications; and
- The incidence of adverse events through final follow-up, including, but not limited to:
  - Adhesions or fibrosis;
  - Anaphylaxis;
  - Blockage of the bladder or ureteral lumen;
  - Blockage of the bypass system;
  - Cancer recurrence and/or progression;
  - Compromised attachment of prosthetic devices to bone or tissue;
  - Death;
  - Embolism;
  - Failure of deep or superficial wound healing;

- Failure to obtain hemostasis;
- Fever;
- Hemorrhage;
- Infection;
- Peri-operative hyperglycemia;
- Exacerbation of surgical procedure-associated adverse events;
- Swelling and compression of pressure-sensitive tissues and structures;
- Thromboembolism;
- Thrombosis; and
- Toxicity.

Three hundred and twenty four subjects across a maximum of 25 investigational sites undergoing open elective cardiac, general, or urological surgical procedures who meet the eligibility criteria will be intraoperatively randomized to receive no more than the entire contents of up to two 5 gram bellows of either the investigational device or a control hemostatic agent on a bleeding site, whose anatomic site is smaller than or equal to 25cm² and whose anatomic application site is smaller than or equal to 47cm^2, when bleeding is within the pre-defined bleeding severity range after any applicable conventional means for hemostasis are attempted as specified in the intraoperative procedures (Section 6.4.3). Please refer to Section 13 (Glossary) for term definitions. Each investigational site is expected to enroll approximately 13-40 subjects. All investigational sites will be located in the U.S. Follow-up will occur at hospital discharge and 6 weeks post-device application. For oncologic subjects, overall survival data will be collected at 24 months post device application.

2 Investigational Device

2.1 Description and Intended Use

PerClot is a medical device composed of absorbable polysaccharide granules and delivery applicators. The granules are biocompatible, non-pyrogenic, and derived from purified plant starch. The granules do not contain any human or animal components. PerClot granules have a molecular structure that rapidly absorbs water, forming a gelled adhesive matrix that provides a mechanical barrier to further bleeding and results in the accumulation of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.) at the site of application. One gram of PerClot absorbs at least 19 mL of water. The gelled adhesive matrix thus promotes the normal physiological clotting cascade. PerClot granules are enzymatically degraded by alpha-amylase and glucoamylase and by macrophages. Based on preclinical studies, absorption normally requires several days and is dependent on the amount of material applied on the wound and the site of use.

The intended use for PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.

2.2 Manufacturer

The manufacturer of the PerClot investigational device is CryoLife, Inc., which is located in Kennesaw, Georgia, The United States of America.

2.3 Investigational Product

Following the execution of all applicable contracts, receipt of the critical documents from the investigational site, and approval by the United States Food and Drug Administration (FDA) and applicable Institutional Review Boards (IRBs), investigational product will be shipped to the investigational site by the Sponsor. The Sponsor is responsible for the traceability and accountability for the investigational product being used in this study.

Investigational product will be traced using an identifier number (lot number or unique device identification number). The Sponsor or Sponsor representative will verify that the investigational product is being properly stored and accounted for during investigational site visits. The use of the device, specifically labeled for this investigation as "Investigational Product," outside of this protocol is prohibited. The investigational site will be expected to retain all unused investigational product supplied until the completion of the investigation and/or until the Sponsor or a Sponsor representative has inventoried and made arrangements for the return of the unused investigational product to the Sponsor or for proper investigational product destruction. Any opened investigational product will be destroyed per individual hospital policy for destruction of medical devices.

The intended use of PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical. The therapeutic areas in which PerClot will be used consist of open elective cardiac, general, and urological surgical procedures.

Investigators will be trained on the use of PerClot, the control product and intraoperative evaluation procedures prior to the enrollment of subjects. The PerClot Instructions For Use (IFU) is included in Appendix A.

3 Justification for the Design of the Clinical Investigation

Operative blood loss is one of the main causes for postoperative morbidity and mortality.[1] Excessive intraoperative bleeding may necessitate blood product administration, resulting in an increase in cost and the occurrence of potential associated adverse effects. Potential adverse effects associated with blood product administration can include, but are not limited to, anaphylactic transfusion reactions, transfusion-related lung injuries, and the transmission of infectious agents.[2] Benzoni E, *et. al.* published on their multivariate analysis of postoperative outcomes and complications after liver resection surgery.[3, 4] Blood transfusion of more than 600mL was significantly associated with in-hospital mortality (p=0.02), overall complications (p=0.04), biliary leakage (p=0.001), abscess formation (p<0.001), and hemoperitoneum (p=0.009).

Figueras J, *et. al.* published similar findings.[5] The authors conducted a univariate analysis of predictive factors for experiencing postoperative complications. Intraoperative transfusion and blood loss were found to be significant predictors for experiencing postoperative complications (p=0.037 and p=0.009, respectively). Another group of authors found that the amount of intraoperative transfusion was significantly related to postoperative infection.[6]

One method for improving operative outcomes is the use of hemostatic agents.[7] Hemostatic agents have proven to be useful in reducing perioperative and postoperative bleeding and associated adverse outcomes.[2] According to one clinical review, an ideal hemostatic agent would be safe, efficacious, easy to use, cost-effective, and approved for use by regulatory authorities.[7] Another

review claims that the ideal hemostat "would be one that was deployable even against brisk hemorrhage, which was independent of native clotting mechanisms and would not pass through salvage filtration systems, and which was not sourced from a bovine or human origin."[2]

PerClot possesses many of the above-mentioned characteristics of an ideal hemostatic agent. Relevant available preclinical and clinical data, summarized below in Sections 3.1-3.3, demonstrate the safety and efficacy of PerClot. It is derived from plant starch and absorbed within several days of application. Further, there is no risk of infectious disease transmission since none of the components are sourced from animals or humans. Additionally, animal studies have shown that the use of PerClot results in a less severe foreign body response/inflammatory reaction when compared to other hemostatic agents, such as gelatin sponge and bone wax (see Section 3.2). The product is easy to use, with no preparation steps required. PerClot does not work completely independent of native clotting mechanisms, but it forms a gelled, adhesive matrix, which provides a mechanical barrier to further bleeding. The gelled adhesive matrix promotes the normal physiological clotting cascade, resulting from the accumulation of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.) at the site of application. A randomized, controlled trial is justified in order to evaluate the safety and efficacy of PerClot compared to another currently approved hemostatic agent in a clinical setting.

3.1 Biocompatibility Studies

Nonclinical biocompatibility studies were conducted in accordance with the FDA Code of Federal Regulations (CFR) Title 21 Part 58 – Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies. Table 1 details the tests performed and corresponding results. Testing was performed on PerClot manufactured by Starch Medical Incorporated (SMI) in China and PerClot manufactured by CryoLife Inc.

Table 1. GLP Biocompatibility Study Overview—SMI Manufactured PerClot

Test Performed	Extract(s)	Extract Conditions	Test and Control(s) Used	Results / Comments
Cytotoxicity	1X Minimal Essential Media (1XMEM)	37°C / 24 hours	• Test: PerClot • Negative controls: high density polyethylene (HDPE), 1XMEM • Positive control: plasticized vinyl	Pass
ISO[i] Maximization Sensitization	0.9% sodium chloride (NaCl), sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil	Pass
ISO Intracutaneous	0.9% NaCl, sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil	Pass
ISO Systemic Toxicity	0.9% NaCl, sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil	Pass
4 Week Systemic Toxicity	Not applicable	Not applicable	• Test: PerClot • Negative control: HDPE	Pass
Genotoxicity – Bacterial Reverse Mutation	0.9% NaCl, ethanol (EtOH)	50°C / 72 hours	• Test: PerClot • Negative controls: 95% EtOH, 0.9% NaCl • Positive controls: sodium azide, methyl methanesulfonate (MMS), 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, ICR-191	Pass
Genotoxicity – Mouse Lymphoma Assay	Serum free media (RPMI), EtOH	50°C / 72 hours	• Test: PerClot • Negative control: HDPE	Pass for EtOH, mutagenic for RPMI[ii]
Genotoxicity – Mouse Peripheral Blood Micronucleus	0.9% NaCl, sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil • Positive control: MMS	Pass
Genotoxicity – Chromosome Aberration Study	McCoy's 5A Media, Dimethyl Sulfoxide (DMSO)	50°C / 72 hours	• Test: PerClot • Negative controls: McCoy's 5A Media, DMSO • Positive control: Mitomycin C, cyclophosphamide	Pass
ISO 2 Week Muscle Implantation	Not applicable	Not applicable	• Test: PerClot • Negative control: HDPE	Pass
ASTM[iii] Hemolysis	Calcium and magnesium free phosphate buffered saline (CMF-PBS)	50°C / 72 hours	• Test: PerClot • Negative control: HDPE • Positive control: sterile water for injection • Blank control: CMF-PBS	Pass
C3a Complement Activation Assay	Normal human serum (NHS)	37°C / 60 minutes	• Test: PerClot • Positive biomaterial reference: latex examination glove • Negative control: low density polyethylene (LDPE) • Positive control: 10U cobra venom factor • Low control: reconstituted human plasma with C3a content < 200ng/mL • Activated NHS: NHS incubated at 37°C for 60 minutes • Inactivated NHS: NHS incubated on ice for 60 minutes	Potential Activator[iv]
Pyrogen	0.9% NaCl	50°C / 72 hours	• Test: PerClot	Pass

[i] International Organization for Standardization 10993 – Biological Evaluation of Medical Devices.
[ii] The explanation for these results is included in the study summary, provided in Section 3.1.7.
[iii] American Society for Testing and Materials F756 – 08 – Standard Practice for Assessment of Hemolytic Properties of Materials.
[iv] This result was not unexpected, as activation of complement could be caused by the hydrophilicity of the PerClot granules as well as the high relative surface area.

Table 2. GLP Biocompatibility Study Overview—CryoLife Manufactured PerClot

Test Performed	Extract(s)	Extract Conditions	Test and Control(s) Used	Results / Comments
Cytotoxicity	1X Minimal Essential Media (1XMEM)	37°C / 24 hours	• Test: PerClot • Negative controls: high density polyethylene (HDPE) • Positive control: latex	Pass
ISO Skin Irritation	0.9%sodium chloride (NaCl), sesame oil	50°C / 72hours	• Test: PerClot • Negative controls: 0.9%sodium chloride (NaCl), sesame oil	Pass
ISO[v] Maximization Sensitization	0.9% sodium chloride (NaCl), sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil	Pass
ISO 1Week Muscle Implantation Rabbit	Not applicable	Not applicable	• Test: PerClot • Negative control: HDPE	Pass
ISO 2 Week Muscle Implantation Rabbit	Not applicable	Not applicable	• Test: PerClot • Negative control: HDPE	Pass
USP Pyrogen Rabbit	0.9% NaCl	50°C / 72 hours	• Test: PerClot	Pass
ISO Systemic Toxicity Mice	0.9% NaCl, sesame oil	50°C / 72 hours	• Test: PerClot • Negative controls: 0.9% NaCl, sesame oil	Pass

3.1.1 Cytotoxicity

This *in vitro* study was conducted to evaluate PerClot for potential cytotoxic effects following the guidelines of ISO 10993-5: Biological Evaluation of Medical Devices, Part 5: Tests for *In Vitro* Cytotoxicity. A single preparation of PerClot was extracted in 1X MEM at 37°C for 24 hours. The negative control (HDPE), reagent control (media alone), and positive control (plasticized vinyl containing 10,10'-oxybisphenoxarsine) were similarly prepared. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% CO_2 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

PerClot showed no evidence of causing cell lysis or toxicity. PerClot met the requirements of the test since the grade was 0 (no reactivity).

3.1.2 ISO Maximization Sensitization

PerClot was evaluated for the potential to cause delayed contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization. PerClot was extracted in 0.9% NaCl and sesame oil. Each extract was intradermally injected and occlusively patched to ten test guinea pigs per extract. The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs per vehicle. Following a recovery period, the test and control animals received a challenge patch of the appropriate PerClot extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

[v] International Organization for Standardization 10993 – Biological Evaluation of Medical Devices.

PerClot showed no evidence of causing delayed dermal contact sensitization in the guinea pig. PerClot was not considered a sensitizer in the guinea pig maximization test.

3.1.3 ISO Intracutaneous

The potential for PerClot to cause irritation following intracutaneous injection in rabbits was evaluated based on ISO10993-10: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization. PerClot was extracted in 0.9% NaCl and sesame oil. A 0.2mL dose of the appropriate test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (control) was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24, 48, and 72 hours after injection.

There was very slight erythema and no edema from the NaCl test extract injected intracutaneously into rabbits. There was very slight erythema and very slight edema from the sesame oil test extract injected intracutaneously into rabbits. Each PerClot extract met the requirements of the test since the difference between the test extract overall mean score and corresponding control overall mean score was 0.4 and 0.7 for the NaCl and sesame oil test article extracts, respectively.

3.1.4 ISO Systemic Toxicity

PerClot was evaluated for acute systemic toxicity in mice based on ISO 10993-11: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity. PerClot was extracted in 0.9% NaCl and sesame oil. A single dose of the appropriate test article extract was injected into a group of five animals. Similarly, a separate group of five animals was dosed with each corresponding extraction vehicle alone (control). The animals were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48, and 72 hours after injection. Body weights were recorded prior to dosing and on days 1, 2, and 3.

There was no mortality or evidence of systemic toxicity from the extracts. The PerClot extracts met the requirements of the study.

3.1.5 4 Week Systemic Toxicity in Rats Following Subcutaneous Implant

PerClot was surgically implanted in the subcutaneous tissue of the rat to evaluate potential systemic toxicity and local tissue response at the implantation site. This study was conducted based in part on ISO 10993-11: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity and the OECD (Organization for Economic Cooperation and Development) Guidelines for Testing of Chemicals, Test Number 407, Repeated Dose 28-Day Oral Toxicity Study in Rodents. A separate group of animals was similarly implanted to serve as the control group.

Six male and six female animals were randomly assigned to either the test or control group. Animals were observed daily for overt signs of toxicity. Detailed clinical examinations were conducted weekly. Animals were weighed prior to implantation and at weekly intervals. At 4 weeks, the animals were euthanized and blood samples were collected for hematology and clinical chemistry analysis. A necropsy was conducted, selected organs

were collected and weighed, and implantation sites were excised and examined macroscopically. A microscopic evaluation of the implantation sites and collected organs was conducted.

There was no evidence of systemic toxicity from PerClot following subcutaneous implantation in the rat, although non-adverse, minimal vacuolation of macrophages was observed at test sites and within lymphoid organs. Local macroscopic tissue reaction at the PerClot implantation sites was not significant compared to the control article. Microscopically, PerClot was classified as a non-irritant compared to the control article.

3.1.6 Genotoxicity – Bacterial Reverse Mutation

A bacterial reverse mutation assay was conducted to evaluate whether a 95% EtOH extract and a saline extract of PerClot would induce reverse mutations at the histidine locus of the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 or at the tryptophan locus of *Escherichia coli* tester strain WP2*uvrA*. This study was based on OECD Guidelines for Testing of Chemicals, Test Number 471, Bacterial Reverse Mutation Test and ISO 10993-3: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity. The assay was conducted in the presence or absence of metabolic activation.

Tubes containing molten top agar were inoculated with culture from one of the five tester strains, along with the 95% EtOH and NaCl extract. An aliquot of sterile water for injection or rat liver S9 homogenate, providing metabolic activation, was added. The mixture was poured across triplicate plates. Parallel testing was conducted with a negative control (extraction vehicle alone) and positive controls. The mean number of revertants for the test extract plates was compared to the mean number of revertants of the negative control plates for each of the five tester strains.

The 95% EtOH and saline test article extract was considered to be nonmutagenic to *S. typhimurium* tester strains TA98, TA100, TA1535, and TA1537, and to *E. coli* tester strain WP2*uvrA*.

3.1.7 Genotoxicity – Mouse Lymphoma Assay

The purpose of this study was to evaluate the mutagenic potential of PerClot using the mouse lymphoma forward gene mutation assay procedure. The study was based on the OECD Guidelines for Testing of Chemicals, Test Number 476, *In Vitro* Mammalian Cell Gene Mutation test; ISO 10993-3: Biological Evaluation of Medical Devices, Part 3: Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity; and ASTM guideline E1280-97: Standard guide for performing the mouse lymphoma assay for mammalian cell mutagenicity.

The test article, PerClot, was extracted in RPMI culture medium at 37°C for 72 hours and 95% ethanol at 50°C for 72 hours. The ethanol test article extract was diluted to 1.0% with RPMI medium supplemented with 3% horse serum prior to dosing. The 1.0% ethanol test article extract was tested in the absence and presence of S9 metabolic activation for a 4 hour treatment period and for a 24 hour treatment period in the absence of S9 metabolic activation. The 1% ethanol test article extract did not cause any positive increase in the mean mutant frequency in the L5178Y/TK$^{+/-}$ cell line either in the presence of absence of metabolic activation.

The RPMI culture medium test article extract, supplemented with 3% horse serum prior to dosing, was tested undiluted in the absence and presence of S9 for a 4 hour treatment and for a 24 hour treatment in the absence of S9. The undiluted RPMI test article extract was toxic and could not be evaluated for genotoxicity. As a result, a toxicity screening assay was conducted with multiple dilutions of the RPMI test extract. Based on the results of the screening assay, the definitive genotoxicity assay was conducted with a 50% dilution of the RPMI extract in the absence of S9 for a 4 hour and 24 hour treatment. A 75% dilution of the RPMI test extract was tested in the presence of S9 for a 4 hour treatment. The 50% and 75% RPMI test extract 4 hour treatments did not cause any positive increase in the mean mutant frequency in the L5178Y/$TK^{+/-}$ cell line either in the presence or absence of metabolic activation. The 50% RPMI test extract 24 hour treatment showed a 2-fold increase in the mean mutant frequency in the L5178Y/$TK^{+/-}$ cell line in the absence of metabolic activation. This is considered an indication of genotoxicity.

A confirmatory dose-response study was then performed with 50%, 25%, 12.5%, and 6.25% dilutions of the RPMI test extract 24 hour treatment. The 50%, 25%, 12.5%, and 6.25% RPMI test extract 24 hour treatment showed a 2.9-fold, 2.4-fold, 1.2-fold, and 1.0-fold increase in the mean mutant frequency in the L5178Y/$TK^{+/-}$ cell line in the absence of metabolic activation. This demonstrates a dose-dependent mutagenic response.

PerClot was evaluated for its potential to elicit a mutagenic response using three different testing methods (one non-mammalian and two mammalian), which include the bacterial reverse mutation assay (Section 3.1.6) and the mouse peripheral blood micronucleus assay (Section 3.1.8) in addition to the mouse lymphoma assay.

PerClot was determined to be non-mutagenic in the *in vivo* model (mouse peripheral blood micronucleus assay), which is the more clinically relevant method of evaluation.

The overall genotoxicity of PerClot passes per the requirements of FDA Recognized Consensus Standard 2-117: AAMI / ANSI/ISO 10993-3:2003/(R)2009. No additional testing is warranted.

3.1.8 Genotoxicity – Mouse Peripheral Blood Micronucleus

The purpose of this *in vivo* study is to evaluate the potential of PerClot to cause damage to chromosomes or the mitotic apparatus of murine erythroblasts by measuring the frequency of micronucleated reticulocytes of treated mice. This study is based on the requirements of OECD Guidelines for Testing of Chemicals, Test Number 474: Mammalian Erythrocyte Micronucleus Test. PerClot was extracted in 0.9% NaCl and sesame oil. The extracts were evaluated for the potential to produce cytogenetic damage, resulting in micronuclei formation in the mouse peripheral blood micronucleus model.

For three consecutive days, twelve mice (six per set) were injected intraperitoneally with the PerClot extracts. Similarly, six animals per sex were dosed with either the appropriate vehicle as the negative control or MMS as a positive control. All animals were observed immediately following dosing and daily for assessment of general health. On day 4, blood was collected from the tail veins and reticulocytes were evaluated for the presence of micronuclei by flow cytometry.

PerClot extracts did not induce micronuclei in mice.

3.1.9 Genotoxicity – Chromosome Aberration Study

PerClot was extracted in DMSO and serum free McCoy's 5A Media. A chromosomal aberration study was conducted to determine whether the extract would cause genotoxicity in Chinese Hamster Ovary (CHO-WBL) cells in the presence and absence of S9 metabolic activation.

A monolayer of CHO-WBL cells was exposed to the test article extracts in duplicate and in the presence and absence of S9 metabolic activation. Parallel testing was also conducted with corresponding negative controls and positive controls. Cells were exposed for 4 hours with and without metabolic activation, and for 20 hours without metabolic activation.

The DMSO and serum free McCoy's medium test article extracts did not produce a statistically significant increase in chromosome aberrations as compared to the negative control in the presence or absence of S9 metabolic activation.

3.1.10 ISO 2 Week Muscle Implantation

PerClot was implanted in the muscle tissue of the rabbit to evaluate the local tissue response in accordance with ISO 10993-6: Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects After Implantation.

PerClot and negative control articles were intramuscularly implanted and animals were euthanized 2 weeks later. Muscle tissues were excised and the implant sites were examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.

The macroscopic reaction was not significant as compared to the negative control article. Microscopically, PerClot was classified as a nonirritant as compared to the negative control article.

3.1.11 ASTM Hemolysis

PerClot was evaluated for the potential to cause red blood cell hemolysis according to procedures based on ASTM F756, Standard Practice for Assessment of Hemolytic Properties of Materials and ISO 10993-4: Biological Evaluation of Medical Devices, Part 4: Selection of Tests for Interactions with Blood. Anticoagulated whole rabbit blood from 3 rabbits was pooled, diluted, and added to glassware with the test article in CMF-PBS or in tubes with a CMF-PBS PerClot extract. Negative and positive controls and blanks were prepared in the same manner. Following incubation for at least 3 hours at 37°C, the samples were centrifuged, and the supernatant was collected and mixed with a reagent to measure hemoglobin with a spectrophotometer at 540 nm.

The hemolytic index for PerClot in direct contact with blood was 0.5%, and the hemolytic index for the PerClot extract was 1.3%. The PerClot in direct contact with blood was non-hemolytic and the PerClot extract was non-hemolytic.

3.1.12 C3a Complement Activation Assay

PerClot was evaluated for the potential to activate the complement system. This study was conducted based on ISO 10993-4: Biological Evaluation of Medical Devices, Part 4: Selection of Tests for Interactions with Blood. The test article was incubated in NHS and C3a was measured in the serum using an enzyme immunoassay. The C3a concentration from the test article sample was compared to activated NHS and a negative control (LDPE).

The C3a concentration of the PerClot sample was 41,415 ± 4,762 ng/mL (mean ± standard deviation) and was statistically higher than the activated NHS control and negative control, and was 200.15% of a positive biomaterial reference control (latex). The C3a concentration of the test sample was greater than the historical ranges of the activated NHS and negative controls. As a result, PerClot was considered to be a potential activator of the complement system. This was not an unexpected result, as activation of complement could be caused by the hydrophilicity of the PerClot granules as well as the high relative surface area.

3.1.13 Pyrogen

PerClot was extracted in sterile, non-pyrogenic 0.9% NaCl. The test extract was evaluated in the rabbit for material mediated pyrogenicity. The test was conducted based on United States Pharmacopeia (USP), General Chapter <151>, Pyrogen Test. The procedure is recommended in ISO 10993-11: Biological Evaluation of Medical Devices, Part 11: Tests for Systemic Toxicity.

A single dose of extract (10mL/kg) was intravenously injected via the marginal ear vein into each of three animals. Rectal temperatures were measured and recorded prior to injection and at 30 minute intervals between 1 and 3 hours after injection.

The total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. PerClot was judged as nonpyrogenic.

3.1.14 Cytotoxicity

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife Inc., was evaluated to determine the potential for cytotoxicity based on the requirements of ISO 10993-5, Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity. A 1.0 gram portion of the test article was hydrated with 30 mL of Single Strength Minimum Essential Medium supplemented with 5% fetal bovine serum, 2% antibiotics and 1% L-glutamine (IX MEM) and placed into an incubator at 37°C for 24 hours and 25 minutes. Triplicate wells were covered with enough hydrated test article to cover an approximate 1 cm x 1 cm area. Triplicate wells were dosed with a 1 cm length portion of high density polyethylene as a negative control. Triplicate wells were dosed with a 1 cm x 1 cm portion of latex as a positive control. Each was placed on an agarose surface directly overlaying a subconfluent monolayer of L-929 mouse fibroblast cells. After incubating at 37°C in the presence of 5% C02 for 24 - 26 hours, the cultures were examined macroscopically and microscopically for any abnormal cell morphology and cell lysis.

The test article showed no evidence of causing any cell lysis or toxicity. The test article met the requirements of the test since the grade was less than a grade 2 (mild reactivity).

3.1.15 ISO Maximization Sensitization

PerClot, manufactured by CryoLife Inc., was evaluated for the potential to cause delayed contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10: Biological Evaluation of Medical Devices, Part 10: Tests for Irritation and Skin Sensitization. PerClot was extracted in 0.9% NaCl and sesame oil. Each extract was intradermally injected and occlusively patched to ten test guinea pigs per extract. The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs per vehicle. Following a recovery period, the test and control animals received a challenge patch of the appropriate PerClot extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

PerClot showed no evidence of causing delayed dermal contact sensitization in the guinea pig. PerClot was not considered a sensitizer in the guinea pig maximization test.

3.1.16 ISO Skin Irritation Study in Rabbits – Extracts

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife, Inc., was evaluated for primary skin irritation in accordance with the guidelines of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP (SC) and sesame oil, NF (SO). A 0.5 mL portion of the test article extract, along with the corresponding control extract, was topically applied to the skin of each of three rabbits and left in place for a minimum of 23 hours to a maximum of 24 hours. The sites were graded for erythema and edema at 1, 24, 48 and 72 hours after removal of the single sample application.

There was no erythema to very slight erythema and no edema observed on the skin of the animals treated with the SC test article extract. The Primary Irritation Index for the SC test article extract was calculated to be 0.1. The irritation response of the SC test article extract was categorized as negligible. There was no erythema and no edema observed on the skin of the animals treated with the SO test article extract. The Primary Irritation Index for the SO test article extract was calculated to be 0.0. The irritation response of the SO test article extract was categorized as negligible.

3.1.17 ISO Muscle Implantation Study in Rabbits of PerClot Polysaccharide 1 Week

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife, Inc., was implanted in muscle tissue of the rabbit to evaluate the local tissue response in accordance with ISO 10993-6, Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects After Implantation.

PerClot and negative control articles were intramuscularly implanted and animals were euthanized 1 week later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.

The macroscopic reaction was not significant as compared to the negative control article. Microscopically, PerClot was classified as a nonirritant as compared to the negative control article.

3.1.18 ISO Muscle Implantation Study in Rabbits of PerClot Polysaccharide 2 Weeks

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife, Inc., was implanted in muscle tissue of the rabbit to evaluate the local tissue response in accordance with ISO 10993-6, Biological Evaluation of Medical Devices, Part 6: Tests for Local Effects After Implantation.

PerClot and negative control articles were intramuscularly implanted and animals were euthanized 2 weeks later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.

The macroscopic reaction was not significant as compared to the negative control article. Microscopically, PerClot was classified as a nonirritant as compared to the negative control article.

3.1.19 USP Rabbit Pyrogen Study - Material Mediated with Continuation

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife Inc., was extracted in sterile, nonpyrogenic 0.9% sodium chloride solution. The test extract was evaluated in the rabbit for material mediated pyrogenicity. The test was conducted based on USP, General Chapter <151>, Pyrogen Test. The procedure is recommended in ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity.

A single dose of 10 mL/kg was intravenously injected via the marginal ear vein into each of eight animals. Rectal temperatures were measured and recorded prior to injection and at 30 minute intervals between 1 and 3 hours after injection.

The total rise of rabbit temperatures during the 3 hour observation period was within acceptable USP limits. The test article was judged as nonpyrogenic.

3.1.20 ISO Systemic Toxicity Study in Mice

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife Inc., was evaluated for acute systemic toxicity in mice based on ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity. The test article was extracted in 0.9% sodium chloride (SC). A single dose of the test article extract was injected into a group of five animals. Similarly, a separate group of five animals was dosed with the extraction vehicle alone (control). The animals were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48 and 72 hours after injection. Body weights were recorded prior to dosing and on days 1, 2 and 3.

There was no mortality or evidence of systemic toxicity from the extract injected into mice. The test article extract met the requirements of the study.

3.1.21 ISO Systemic Toxicity Study in Mice

The test article, PerClot Polysaccharide Hemostat manufactured by CryoLife, Inc., was evaluated for acute systemic toxicity in mice based on ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity. The test article was extracted in 0.9% sodium chloride USP solution (SC) and sesame oil, NF (SO). A single

dose of the SO test article extract was injected into a group of five animals and only two animals received the SC test article extract. Similarly, a separate group of five animals were dosed with each corresponding extraction vehicle alone (control). All SO animals and SC control animals were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48 and 72 hours after injection. Body weights were recorded prior to dosing and on days 1, 2 and 3.

There was no mortality or evidence of systemic toxicity from the SO extract injected into mice. The SO test article extract met the requirements of the study. The SC testing was cancelled following the 4 hour observation period and no conclusions were drawn from the SC test article extract.

3.2 Preclinical Studies

This section includes summaries of the relevant preclinical studies that have been performed by both Starch Medical, Inc. and the Sponsor. The studies in Sections 3.2.1-3.2.10 were completed by the Starch Medical, Inc. and were not performed in accordance with GLP regulations. The studies in Section 3.2.11-3.2.19 were completed by the Sponsor. Compliance or non-compliance with GLP regulations is included in each of these sections.

3.2.1 Degradation of PerClot Implanted Intramuscularly in Rats (non GLP)

Forty rats were divided into 4 equal groups to receive intramuscular implants:

- 200mg PerClot;
- 200mg SuperClot[vi];
- 200mg Arista®[vii]; or
- 200mg native starch.

The wounds were examined using iodine staining at 24 hours. Iodine staining was performed to detect the presence of intact starch molecules at 24 hours after the intramuscular implant.

No starch material was detected at 24 hours in the PerClot, SuperClot, and Arista animals. However, starch material was detected at 24 hours in the native starch animals. The study showed that PerClot remained in the intramuscular implant site for less than 24 hours.

3.2.2 Degradation of PerClot Implanted Subcutaneously in Mice (non GLP)

Forty-eight mice were randomly divided into 8 equal groups. Four 1.5cm incisions were made on each side of the midline on the back of each animal. Two different materials at 2 different doses were subcutaneously implanted in the wounds:

- 50mg PerClot;
- 200mg PerClot;
- 50mg SuperClot;
- 200mg SuperClot;

[vi] A starch-derived hemostatic agent manufactured by Starch Medical, Inc. (San Jose, CA).
[vii] A starch-derived hemostatic agent manufactured by Medafor, Inc. (Minneapolis, MN).

- 50mg Arista;
- 200mg Arista;
- 50mg native starch; and
- 200mg native starch.

The wounds were examined using iodine staining at 30 minutes and 1, 6, 24, 48, and 72 hours. Iodine staining was performed to assess the presence of intact starch molecule at different time points after subcutaneous implantation.

Starch material was detected at the site of implantation in the PerClot, SuperClot, and Arista groups (50mg and 200mg) at 30 minutes, 1 hour, and 6 hours, but not at 24, 48, and 72 hours. In the native starch group, starch material was detected at the site of implantation at all-time points. The results indicate that subcutaneously implanted PerClot, SuperClot, and Arista were completely absorbed or degraded within 24 hours.

3.2.3 Eye Irritation of New Zealand Rabbits (non GLP)

One gram of PerClot or SuperClot was added to 19.3mL and 10mL of 0.9% NaCl, respectively. These mixtures were incubated at 37°C for 72 hours and then centrifuged. The resulting supernatant (0.2mL) was applied to one eye each of 10 New Zealand rabbits. Saline (0.9% NaCl) was applied to the adjacent eye, as well as to one eye of 5 additional rabbits as a control. Eye irritation was graded using an Integral Index Form at 8, 24, 48, and 72 hours. Recovery of the eyes occurred on days 4 and 7 post-treatment.

The eye irritation scores were 0 for all animals at all time points except for 24 hours. The mean eye irritation scores at 24 hours were 0.4, 1.6, and 1.6 for the control, PerClot, and SuperClot animals, respectively. The PerClot and SuperClot animals had a small amount of secretion from the eye at 24 hours, but no irritating effects.

3.2.4 Hemostatic Effects in a Rat Tail Clip Hemorrhagic Model (non GLP)

Fifty rats were divided into 5 equal groups to receive PerClot, SuperClot, Arista, native starch, or a blank control. Tails were clipped off at about 2cm from the tip. A clamp was applied to each tail and 50mg of hemostat was applied to the bleeding. At 1 minute, the clamps were released and the wound was observed. If the wound was still bleeding at 1 minute, the clamps were reapplied and the wound was observed after another 3 minutes.

Bleeding stopped completely at 1 minute for all animals in the PerClot and Arista groups. Bleeding stopped completely at 4 minutes for all animals in the SuperClot group. Bleeding failed to stop after 15 minutes for all animals in the native starch and blank control groups.

3.2.5 Hemostatic Effects in a Liver Hemorrhagic Model of New Zealand Rabbits (non GLP)

Thirty rabbits were divided into 5 equal groups to receive PerClot, SuperClot, Arista, fibrin glue, or a blank control. A circular wound was created in the liver of all animals with a diameter of 1.5cm and a depth of 0.3cm. Hemostatic treatment was applied to the liver injury (200mg each of PerClot, Super, and Arista; 0.2mL of fibrin glue; and gauze for blank controls). Bleeding was monitored for a total of 60 minutes and blood loss was

calculated. Animals were sacrificed at 24 hours and starch material remaining in the wound was examined with iodine staining.

Bleeding stopped completely at 1 minute in all animals in the PerClot, SuperClot, Arista, and fibrin glue groups. The amount of blood loss was not different between the PerClot, SuperClot, Arista, and fibrin glue animals ($p>0.05$). Bleeding continued for more than 1 minute and the amount of blood loss was significantly greater for the control animals compared to the experimental animals ($p<0.01$). No starch material was detected using iodine staining at 24 hours in any of the experimental animals.

3.2.6 Hemostatic Effects in a Liver and Spleen Hemorrhagic Model of Bama Miniature Pigs (non GLP)

Twelve pigs were divided into 3 equal groups to receive PerClot, Arista, or native starch. "+" shape wounds were created in both the liver and spleen of all animals. The wounds were 2 x 2cm and had a depth of 1.5cm. One gram of hemostatic product was applied and the wounds were suppressed with gauze. Pressure was applied for 2 minutes. Bleeding was monitored for a total of 30 minutes and the amount of blood loss was calculated. Animals were sacrificed at 7 days and iodine staining was performed to assess if there were any intact starch molecules present at the initial site of application. Tissue histology was also performed.

Bleeding stopped completely after 2 minutes in all animals in the PerClot and Arista groups. Bleeding continued for more than 2 minutes in the native starch animals. No starch material was detected using iodine staining at 7 days.

Histopathology of the PerClot animals revealed:

- Chronic fibrotic granulomatous inflammation;
- Hemostatic material with mild surrounding fibrosis at the site of injury;
- Thrombosis in one small hepatic vessel and one vessel in the spleen; and
- Mild congestion, but no other significant abnormalities.

Histopathology of the Arista animals revealed:

- Chronic fibrotic granulomatous inflammation;
- Hemostatic material with mild surrounding fibrosis at the site of injury; and
- Mild congestion, but no other significant abnormalities.

The results of the study show that PerClot has hemostatic effects comparable to those of Arista and that small amounts of test material may remain in the site of application at 7 days, but with minor tissue response.

3.2.7 Hemostatic Effects in an Abdominal Aortic Hemorrhagic Model of Bama Miniature Pigs (non GLP)

Sixteen pigs were divided into 4 equal groups to receive PerClot, SuperClot, Arista, or native starch. The abdominal aorta of all animals was clamped and punctured using a needle 0.3cm in diameter. One gram of treatment was applied to the wound and pressure was applied for 5 minutes. The clamps were then released and bleeding was monitored for

30 minutes. Animals were sacrificed at 7 days and starch material remaining in the wound was examined using iodine staining. Tissue histology was also performed.

Bleeding stopped completely at 5 minutes for all animals in the PerClot, SuperClot, and Arista groups. None of the animals in the native starch group survived the procedure. No starch material was detected using iodine staining. Histopathology revealed thrombi attached to the arterial wall in all animals; no other changes were found in any animals.

The results of the study show the PerClot has hemostatic effects comparable to those of Arista.

3.2.8 Absorption Capacities, Hemostatic Effects on Liver and Abdominal Aorta, and Effects on Intestinal Adhesion and Bone Regeneration (non GLP)

The absorption capacities of Arista, PerClot, and SuperClot were calculated using 0.3g of hemostat and 10mL of double distilled water. The absorption capacities of Arista, PerClot, and SuperClot were 7, 21, and 16g/mL, respectively. The PerClot samples had a significantly higher absorption capacity than the Arista samples ($p<0.01$).

Twelve rabbits were divided into 4 equal groups to receive PerClot, SuperClot, Arista, or control (pressure alone). Three injuries 8 x 8mm in diameter and 3mm in depth were created on each liver. The wounds were allowed to bleed freely for 20 seconds before treatment. The treatments consisted of application of the prescribed hemostat and pressing with gauze for 5 minutes or application of the prescribed hemostat and pressing with gauze for 2 minutes. All injuries were hemostatic by 5 minutes.

In these same animals, the abdominal aorta was punctured using a needle 1.2mm in diameter. The hemostatic material was applied and either pressure was applied for 2 minutes with gauze or 1-3 drops of saline were used to wet the hemostatic material. All injuries were hemostatic by 5 minutes.

The effect of different hemostatic materials on intestinal adhesion formation was also examined. Sixty total rats were divided into 5 equal groups to receive PerClot, SuperClot, Arista, control, or sodium hyaluronate. A 2cm incision in the lower abdomen was performed, the cecum serosa was scuffed until bleeding was observed, ethanol was dropped onto the wound surface, and temporary ischemia was obtained by clamping the mesenteric artery. The prescribed hemostatic agent was then applied to the wound surface. The animals were sacrificed at 14 days and intestinal adhesions were graded as follows:

- Grade 0: no adhesion;
- Grade 1: an adhesion band between internal organs or between abdominal walls;
- Grade 2: two adhesion bands between internal organs or between abdominal walls;
- Grade 3: more than two adhesion bands but internal organs not directly adhered to the abdominal wall; or
- Grade 4: internal organs directly adhered to the abdominal wall.

The mean adhesion grades were 3.72 for control, 1.42 for PerClot, 3.00 for SuperClot, 1.82 for Arista, and 1.18 for sodium hyaluronate. The mean adhesion grades for PerClot, Arista, and sodium hyaluronate were significantly less than that for the control ($p<0.05$). Histopathological examination revealed a few inflammatory cells in the PerClot and Arista

groups, a mild inflammatory reaction in the SuperClot group, and a strong inflammatory reaction in the sodium hyaluronate group.

Twenty New Zealand rabbits were divided into 5 equal groups to receive PerClot, SuperClot, Arista, bonewax, or control. Two holes 6mm in diameter were drilled on either side of the skull in each animal and the hemostatic materials were applied in the defects. The animals were sacrificed at 6 weeks and the bone healing scores were graded:

- 0: no visible defects;
- 1: less visible defects;
- 2: moderate visible defects; or
- 3: extensive visible defects.

The mean bone healing scores were 2.14 for the control, 1.23 for PerClot, 1.14 for SuperClot, 1.44 for Arista, and 1.86 for bonewax. PerClot, SuperClot, and Arista had significantly better bone healing scores than the control group. The mineral apposition rate was significantly higher for PerClot, SuperClot, Arista, and bonewax than the control. The osteoid rate was significantly greater for PerClot, SuperClot, and Arista when compared to the control. The mineralization bone rate was significantly greater for PerClot, SuperClot, Arista, and bonewax when compared to the control. The defect area rate was significantly less in the PerClot, SuperClot, and Arista groups when compared to the control.

3.2.9 PerClot & SuperClot Encephalic and Abdominal Degradation in Rat (non GLP)

Twenty-four rats were randomized to receive either PerClot or SuperClot. One hundred µL of 10% (mass:volume) PerClot or SuperClot suspensions were injected under the dura mater. The animals were sacrificed at 30, 60, and 120 minutes after the procedure and their brains were removed and disseminated with iodine solution or saline. The samples were then centrifuged and the absorbance of the supernatant was used to determine starch polysaccharide content and calculate residual amounts. The residual rates of starch polysaccharide were 38.62%, 3.95%, and 0.282% at 30, 60, and 120 minutes, respectively. Another study was similarly performed on brain tissue homogenate from twenty-four rats. Samples contained 0.01, 0.03, 0.1, 0.3, or 1µg of PerClot or SuperClot. Samples were incubated at 37°C for 30 minutes and then fully mixed with 0.1mL iodine solution. Absorbance was used to determine starch polysaccharide content and calculate residual amounts. The residual rates were 0%, 0%, 61.0%, 57.3%, and 60.7% for 0.01, 0.03, 0.1, 0.3, and 1µg, respectively.

Twenty-four animals were randomized to receive either PerClot or SuperClot. One hundred µL of 10% (mass:volume) PerClot or SuperClot suspensions were injected into the abdominal cavity. The abdominal cavities were washed with 4mL of saline at 30, 60, and 120 minutes after the procedure. These saline solutions were mixed with an iodine solution and the absorbance was used to determine starch polysaccharide content and calculate residual amounts. The residual rates of starch polysaccharide were 65.68%, 31.57%, and 1.69% at 30, 60, and 120 minutes, respectively.

The *in vitro* degradation of PerClot and SuperClot by tissue homogenate was also examined. One gram each of brain, liver, kidney, and lung were taken from twenty-four anesthetized rats and added to 4mL saline. The samples were centrifuged and the supernatant was combined with 2µg of PerClot or SuperClot. Samples were incubated

at 37°C for 30 minutes. Absorbance was used to determine starch polysaccharide content and calculate residual amounts. The residual rates were 48.77%, 21.71%, 40.59%, and 34.67% in the brain, liver, kidney, and lung, respectively.

3.2.10 Effects of PerClot on the Healing of Full-Thickness Skin Wounds in Rats (non GLP)

This study evaluated the effects of PerClot on wound healing in a rat model. Full-thickness skin wounds were created on the back of 24 rats. PerClot, raw starch, or no treatment controls were applied to the skin wounds. Wound closure was monitored and histological examination was performed at 7 and 14 days. Wound closure was significantly accelerated by the local application of PerClot. PerClot-treated wounds showed significantly increased fibroblast numbers, newly formed capillaries, and collagen regeneration.

3.2.11 GLP Abdominal Aorta Model

A GLP preclinical evaluation of the effectiveness and safety of PerClot to achieve hemostasis was performed for an abdominal aorta lesion in the pig. The objectives of the study were to:

- Evaluate the efficacy of PerClot in achieving hemostasis of an abdominal aorta lesion compared to a comparator device; and
- Evaluate the safety of PerClot in a cardiovascular application compared to a comparator device through:
  - The evaluation of animal morbidity and mortality;
  - Blood testing at multiple time points; and
  - Biocompatibility, healing, and presence of the device through histopathological evaluation.

The achievement of hemostasis was observed and documented at 1, 3, 5, and 10 minutes after application of the test or control article (Gelfoam® Plus[viii]). The primary efficacy endpoint was hemostasis of the treatment site within 5 minutes after hemostat application. Animals were survived to 14 + 3 days postoperatively. There was a single animal in the PerClot group that was terminated at 5 days postoperatively due to dehiscence of the midline incision.

Five of the eight animals implanted with PerClot were hemostatic by 1 minute; the remaining animals were hemostatic by 3 minutes. All six animals implanted with Gelfoam Plus were hemostatic by 1 minute. Therefore, all animals in both treatment groups met the primary efficacy endpoint. Clinical pathology (blood testing and animal morbidity and mortality) did not indicate a negative response to the implant of either PerClot or Gelfoam Plus.

Treatment of the abdominal aorta lesion sites with either PerClot or Gelfoam Plus, followed by observation period of 14 to 17 days, showed complete bioresorption and optimal biocompatibility of PerClot. Gelfoam Plus was incompletely bioresorbed and provoked an on-going mild to moderate foreign body response. Neither group showed gross or microscopic evidence of test site bleeding and both groups showed complete mural healing.

[viii] A porcine collagen hemostatic agent containing human thrombin manufactured by Baxter International, Inc. (Deerfield, IL).

3.2.12 GLP Partial Nephrectomy Model

A GLP preclinical evaluation of the effectiveness and safety of PerClot to achieve hemostasis was performed for a partial nephrectomy model in the pig. The objectives of the study were to:

- Evaluate the efficacy of PerClot in achieving hemostasis of a kidney injury compared to a comparator device; and
- Evaluate the safety of PerClot in a nephrectomy application compared to a comparator device through:
  - The evaluation of animal morbidity and mortality;
  - Blood testing at multiple time points; and
  - Biocompatibility, healing, and presence of the device through histopathological evaluation.

The achievement of hemostasis was observed and documented at 1, 3, 5, and 10 minutes after application of the test or control article (Gelfoam Plus). The primary efficacy endpoint was hemostasis of the treatment site within 5 minutes after hemostat application. Animals were survived to 14 + 3 days postoperatively, with the exception of three animals that received PerClot (one terminated early due to poor health, one found dead, and one terminated early due to incision dehiscence). The cause of death was not determined in the single animal in the PerClot group that died on postoperative day 9, but the death was deemed unrelated to the test article.

PerClot was implanted in a total of nine animals; 4 animals were hemostatic at 1 minute, 1 animal was hemostatic at 3 minutes, 1 animal was hemostatic at 5 minutes, 2 animals were hemostatic at 10 minutes, and 1 animal was not hemostatic until after 10 minutes. For the 9 animals, the cumulative effectiveness rate was 44% at 1 minute, 56% at 3 minutes, 67% at 5 minutes, and 89% at 10 minutes. The first animal in this study underwent removal of the lower pole, which resulted in such profuse bleeding that it did not allow for contact of the test article with the wound; this animal did not achieve hemostasis until after 10 minutes. The surgical model was amended to a round divot cut approximately 1cm in diameter and 0.3cm in depth. Six animals underwent implantation of the control article; 2 were hemostatic at 1 minute, 2 were hemostatic at 3 minutes, 1 was hemostatic at 5 minutes, and 1 was not hemostatic until after 10 minutes, for a cumulative effectiveness rate of 33% at 1 minute, 67% at 3 minutes, and 83% at 5 minutes. Therefore, 67% of the test animals met the primary efficacy endpoint of hemostasis by 5 minutes and 83% of the control animals met this primary efficacy endpoint. Clinical pathology (blood testing and animal morbidity and mortality) did not indicate a negative response to the implant of either PerClot or Gelfoam Plus.

Treatment of nephrectomy sites with Gelfoam Plus and PerClot, followed by an observation period of 14 to 17 days, showed complete bioresorption and optimal biocompatibility of PerClot. Gelfoam Plus was incompletely bioresorbed and a provoked an on-going minimal to moderate foreign body response. Neither group showed microscopic evidence of test site bleeding and both groups showed complete healing of the surgical sites albeit with very significant differences in scar extent and quality. The PerClot group had no inflammation and limited scarring, where the Gelfoam Plus group had a significant inflammatory reaction with thicker fibrous capsule formation.

3.2.13 GLP Liver Biopsy Model

A GLP preclinical evaluation of the effectiveness and safety of PerClot to achieve hemostasis was performed for a liver biopsy model in the pig. The objectives of the study were to:

- Evaluate the efficacy of PerClot in achieving hemostasis of an abdominal aorta lesion compared to a comparator device; and
- Evaluate the safety of PerClot in a cardiovascular application compared to a comparator device through:
  - The evaluation of animal morbidity and mortality;
  - Blood testing at multiple time points; and
  - Biocompatibility, healing, and presence of the device through histopathological evaluation.

The achievement of hemostasis was observed and documented at 1, 3, 5, and 10 minutes after application of the test or control article (Gelfoam Plus). The primary efficacy endpoint was hemostasis of the treatment site within 5 minutes after hemostat application. Animals were survived to 14 + 3 days postoperatively. There was an animal in the PerClot group that died upon surgery completion due to cardiovascular failure, likely due to a pre-existing multisystemic vasculitis with cardiac involvement. There was another animal in the PerClot group that was prematurely terminated on the first postoperative day due to dehiscence of the midline incision.

PerClot was implanted in a total of 13 animals and 16 wounds. Seven wounds were hemostatic by 1 minute, 2 were hemostatic by 3 minutes, 2 were hemostatic by 5 minutes, 2 were hemostatic by 10 minutes, and 3 did not achieve and maintain hemostasis until after 10 minutes. This gives a cumulative success rate of 44% at 1 minute, 56% at 3 minutes, 69% at 5 minutes, and 81% at 10 minutes. Six animals underwent implantation of the control article; 5 were hemostatic at 1 minute and 1 was hemostatic at 3 minutes, for a cumulative effectiveness rate of 83% at 1 minute and 100% at 3 minutes. Therefore, 69% of the test animals met the primary efficacy endpoint of hemostasis by 5 minutes and 100% of the control animals met this primary efficacy endpoint. Clinical pathology (blood testing and animal morbidity and mortality) did not indicate a negative response to the implant of either PerClot or Gelfoam Plus.

Multiple sizes and shapes of wounds were used in this study. The original "+" shape of the injury created on the liver presented problems with the appropriate application of the test article. There were multiple deep corners of the injury in which granule contact with the entire surface was not achieved or could not be determined. Because the test article works best when in direct contact with the source of bleeding, the shape of the surgical injury was changed so that delivery of the test article to the entire surface of the wound could be ensured. The "+" shape wound was changed to a divot injury (3.4cm in diameter and 0.75cm deep, giving approximately the same surface area), which also presented problems because the level of bleeding that was created by these wounds did not allow the test article to stay in place. Based on this the profuse bleeding seen with this size injury, the divot wound size was decreased to 1cm in diameter and 0.3cm in depth. This wound size produced sufficient bleeding, but the bleeding was not as profuse as was seen in the larger divot injury (3.4cm in diameter and 0.75cm deep). Three animals received 2 wounds each were used to show effectiveness in this surgical model; all six wounds in these animals were hemostatic by 1 minute and maintained hemostasis throughout the 10 minute

evaluation period. An evaluation of hemostasis in animals where it was determined that the test article was in full contact with the entire surface of the wound and where the bleeding was not so profuse as to prevent the test article from coming into full contact with the wound demonstrated a cumulative success rate of 100% at 1 minute.

The experience from this study demonstrates the importance of direct contact of the test article with the source of bleeding.

Treatment of the liver injury sites with PerClot showed complete bioresorption and optimal biocompatibility. The liver injury sites treated with Gelfoam Plus showed incomplete resorption and on-going mild to moderate foreign body response. Neither group showed gross or microscopic evidence of test site bleeding, and both groups showed complete healing of the surgical sites, albeit with very significant differences in scar extent and quality. The PerClot group had no inflammation and limited scarring, where the Gelfoam Plus group had a significant inflammatory reaction with thicker fibrous capsule formation.

3.2.14 GLP Evaluation of the Effectiveness of Two Plant Based Hemostats in a Pig Bleeding Model

A GLP preclinical study was performed to evaluate the effectiveness of PerClot and Surgicel in a pig bleeding model.

The primary objective for the 10-minute bleeding evaluation group was to evaluate the amount of blood loss in 30 seconds and 10 minutes resulting from pre-determined sized liver injuries.

The primary objectives for the hemostat evaluation groups were to:

- Evaluate the effectiveness of two different plant based hemostats (PerClot vs. Surgicel) when applied to liver injuries of varying bleeding severities.
  - Primary endpoint was the achievement of hemostasis by 5 minutes post hemostat application.
  - Secondary endpoints were the achievement of hemostasis at the site of application evaluated at 1, 3, 7, and 10 minutes.
- Determine the severity of bleeding at which the hemostats are effective;
- Assess the amount of blood loss resulting from pre-determined sized liver injuries using various bleeding severity assessment methods.
- Examine the relationship between the bleeding severity assessment methods and hemostatic efficacy.
- Examine the relationship between bleeding severity and the amount of hemostat applied.

For the 10-minute bleeding evaluation group, total blood loss throughout the entire evaluation period ranged from 1.22g to 163.18g.

PerClot and Surgicel performed similarly in meeting the primary efficacy endpoint of hemostasis by 5 minutes (88.89% and 91.67%, respectively).

For the injuries treated by PerClot, 52.78%, 72.22%, 94.45%, and 97.23% were hemostatic at 1, 3, 7, and 10 minutes. For the injuries treated by Surgicel, 27.78%, 44.45%, 91.67%, and 97.23% were hemostatic at 1, 3, 7, and 10 minutes.

For at least 1.0 gram and no more than 10.0 grams of fluid mass collected on a 15-stack of gauze held with light pressure for 30 seconds, both PerClot and Surgicel were at least 90% efficacious for the achievement of hemostasis by 5 minutes.

A strong linear correlation was found between mass of fluid collected and calculated blood volume based on hemoglobin concentration measurement. The mass of fluid and calculated blood volume collected over 30 seconds have a significant effect on the achievement of hemostasis by 5 minutes. This suggests that an objective measure, such as fluid mass loss, can be accurately applied when assessing the severity of bleeding for an injury. Further, the efficacy of both PerClot and Surgicel has been determined for a range of bleeding severities assessed using this method.

There were no strong relationships between bleeding severity and the amount of PerClot or Surgicel applied.

3.2.15 GLP Evaluation of the Safety of PerClot on Cranial Bone Healing in a Rabbit Model

A GLP preclinical evaluation was performed to assess the safety of PerClot on cranial bone healing in a rabbit model.

The objectives of this study were as follows:

- Evaluate the safety of PerClot compared to clinical available hemostatic agents (i.e. bone wax),
  - Evaluate bone healing and regrowth using histology; and
  - Compare effect(s) of PerClot on bone healing and regrowth to effect(s) of bone wax on bone healing and regrowth.

A total of 34 rabbits were utilized for evaluation in this study. Each animal underwent a surgical procedure to create two circular cranial injuries (7mm diameter) at the mid-point of each parietal bone through the full thickness of the skull. A test article, control article (bone wax) or no-treatment control was applied to each injury. At 0 (acute), 42 (+3) and 70 (+3) days post-operation, designated animals were euthanized and injury sites were excised and fixed in 10% neutral buffered formalin. Fixed tissues underwent histopathological processing and evaluation.

Microscopic evaluation of cranial injury sites implanted for 0 (acute), 42 (+3) and 70 (+3) days (actual duration 0, 42, 47, 48, 70 or 71 days) revealed the following:

- There was abundant residual bone wax present at both time points, while very little of the test article, PerClot, was present at either day 42 or day 70, with most sites having no residual material at either time point.
- Both residual bone wax and PerClot were associated with a foreign body inflammatory response. This response was greater overall for the bone wax.

- The general inflammatory response for the bone wax and PerClot groups was generally attributable to the foreign body response. There was no general inflammation observed in the no-treatment control group.
- At both days 42 and 70, the percentage of bone within the defect area, the percentage of bone bridging, and the degree of bone maturity was considered to be comparable between the no-treatment control and the PerClot test article, and somewhat greater than that seen with bone wax.

In conclusion, based upon light microscopic evaluation of craniotomy sites left untreated, treated with bone wax, or treated with PerClot, bone healing and regrowth was comparable between the PerClot and untreated control, while PerClot demonstrated superior bone healing and regrowth to that of bone wax. Unlike bone wax, which had marginal resorption even at day 70, PerClot was nearly completely resorbed by day 42. Inflammation for any of the treatment groups was generally limited to a foreign body response to residual test or control article.

3.2.16 Non-GLP Evaluation of Starch-Based Hemostatic Agents Irradiated to Different Doses in a Porcine Liver Bleeding Model

This study was performed to determine if starch-based hemostatic agents irradiated to different doses displayed any difference in hemostatic efficacy. The primary efficacy endpoint of this preclinical evaluation was the achievement of hemostasis at the site of application at 5 minutes following a single application of the prescribed hemostatic agent.

A total of 9 pigs underwent midline laparotomy and each received 12 injuries on the liver. The injuries were randomized to receive one of three treatments.

The primary efficacy endpoint, hemostasis within 5 minutes, was met in 100.0% of the Treatment A samples, compared to 100.0% of the Treatment B samples and 91.7% of the Treatment C samples. The mean time to hemostasis in Treatment Group A was 2.06 ± 0.43 minutes, compared to 2.00 ± 0.00 minutes for Treatment Group B and 2.25 ± 0.87 minutes for Treatment Group C. The difference in mean time to hemostasis was not statistically significant between treatment groups ($p = 0.161$). Treatment A is PerClot irradiated at 25kGy, Treatment B is PerClot irradiated at 40 kGy, and Treatment C is Arista.

This study demonstrates that there is no difference in performance between the starch-based hemostatic agents irradiated to different doses in this porcine liver model of bleeding.

3.2.17 GLP Assessment of Blood Glucose Levels During Degradation of Starch Based Hemostatic Agents in a Rabbit Model

A total of fifteen New Zealand White rabbits were enrolled in this study. All animals enrolled in the study were intact males with a weight range of 3.2 – 3.8kg at time of implant. The animals were enrolled randomly into the following groups: Six animals received PerClot granules; six animals received HemoStase particles; and three animals were sham operated controls. On the day of implantation, rabbits were anesthetized and an incision was made over the abdomen to access the intraperitoneal space. Animals enrolled in either PerClot or HemoStase groups received a pre-weighed (50 gram) amount of the appropriate hemostat delivered directly into the peritoneal cavity. Animals in the sham operated group were immediately closed following access to the peritoneal cavity. Blood

glucose levels were measured at baseline, 1, 2, 4, 6, 9, 12, 24, 72, and 96 hours after delivery of PerClot, HemoStase, or sham operation. Following the measurement of blood glucose at 96 hours, all animals were euthanized and the peritoneal cavity was examined grossly for any remaining hemostat as well as using the iodine test for starch.

Mean baseline blood glucose levels were similar for all three groups (138.56 mg/dL, 147.33 mg/dL, and 139.33 mg/dL for PerClot, HemoStase, and sham groups, respectively). Blood glucose levels 1 hour post-operatively were significantly higher than baseline blood glucose for all three groups ($p<0.05$), with glucose levels remaining significantly higher at 2 hours post-operatively for animals treated with PerClot or HemoStase. The 1 hour and 2 hour glucose levels in animals treated with PerClot or HemoStase were significantly higher than the sham operated control animals with HemoStase treated animals having higher glucose levels than PerClot treated animals 2 hour post-operatively. By 48 hours, glucose levels for all three groups were similar and remained so for the remainder of the study. At the time of necropsy, no remaining test article was grossly observed in any of the animals treated with either PerClot or HemoStase. Overall, no adverse events were noted in response to implanted test article for any animals for the duration of the study.

3.2.18 GLP Determination of Systemic Blood Glucose Levels During Degradation of Starch Based Hemostatic Agents in a Rabbit Model

A total of fifteen New Zealand rabbits were enrolled randomly into the following groups: six animals received PerClot; six animals received Arista; and three animals underwent sham operated procedure. On the day of implantation, rabbits were anesthetized and an incision was made over the abdomen to access the intraperitoneal space. Animals enrolled in either PerClot or Arista groups received a pre-weighed amount (10 grams) of the appropriate hemostat delivered directly into the peritoneal cavity. Animals enrolled in the sham operated group were immediately closed following access to the peritoneal cavity. Blood glucose levels were measured at baseline (fasted levels), and at 1 hour, 2 hours, 4 hours, 6 hours, 9 hours, 12 hours, 24 hours, 48 hours, 72 hours, and 96 hours after delivery of either PerClot, Arista, or sham operation. Following the measurement of blood glucose at 96 hours post-operation, all animals were euthanized and the peritoneal cavity was examined grossly for any remaining hemostat as well as using the iodine test for presence of any residual starch based material.

Baseline blood glucose levels were similar for all three groups (153.61 mg/dL, 148.17 mg/dL, and 141.89 mg/dL for PerClot, Arista, and Sham groups, respectively) and all three treatment groups had mean baseline blood glucose levels within normal range for New Zealand White rabbits (100 – 190 mg/dl). Blood glucose levels 1 hour post-operatively were significantly higher than baseline blood glucose for all three groups ($p<0.05$), with glucose levels remaining relatively high at 2 hours post-operatively for animals treated with PerClot or Arista. Glucose levels of PerClot and Arista animals at 2 hours were almost equivalent while slightly higher than glucose levels in Sham operated control animals. By 4 hours, glucose levels for all three groups were similar and remained normal for the remainder of the study.

It was concluded that known structural differences in the polysaccharide molecules and the rates of breakdown of the two products did not result in elevated systemic blood glucose levels during the degradation of PerClot and Arista in a rabbit model. As all groups experienced brief elevation of blood glucose levels at 1 and 2 hours post-surgery, post-operative stress and excitement most likely attributed to those slight elevations.

Furthermore, no residual starch based material was found in the peritoneal cavity in any of the study rabbits at 96 hours post application.

3.2.19 A Preclinical GLP Evaluation of Effectiveness and Safety of PerClot in an Endoscopic ENT Application

The objectives of this study were to test the efficacy, degradation, safety and healing of PerClot® Topical Hemostatic Powder (CryoLife Inc., Kennesaw, GA), herein referred to as PerClot Topical, when compared to NexStat Topical Hemostat Powder (Hemostasis, LLC., St. Paul, MN), herein after referred to as NexStat, and standard of care (pressure alone). Effectiveness was evaluated by determining hemostatic achievement by 5 minutes after application. Safety and healing were evaluated by histological analysis at an implant time of 21-22 days. Degradation was evaluated by implant time of 48 (±3) hours and 72 (±4) hours using iodine stain to determine if any of the PerClot Topical granules remained at the implant site.

Twenty-two (22) goats were used for this study. Six (6) animals were used in the degradation groups, and 16 animals were used in the chronic healing and safety groups.

A uniformly sized (8mm x 4mm) abrasion was created on the inferior turbinate using a drill in each nostril. The drill was turned on and held in place for 10 seconds to cause bleeding. The injury was consistent in size throughout the study and study groups. After 10 seconds, the excess fluid was removed using suction and gauze. Pre-weighed gauze (4"x4" squares) were held over the injury for 10 seconds and then removed and weighed. The difference was calculated to gauge the amount of fluid/blood loss at the injury site.

Depending on the study group, treatment was applied according to its respective IFU, and hemostasis recorded at 1, 3 and 5 minutes. If the wound did not reach hemostasis by 5 minutes, alternative methods (i.e. manual pressure) were used to reach hemostasis.

Animals were survived to their pre-determined end points of 48 (±3) hours, 72 (±4) hours and 21 (±2) days.

For animals in the degradation study groups (48±3 hours and 72±4 hours) a necropsy was performed by a board certified pathologist. Tissue samples were collected at the discretion of the pathologist. At the site of implant, Lugals iodine was used to detect any presence of starch.

For animals survived out to 21-22 days, a necropsy was performed and tissues samples were collected to evaluate healing and safety. Adhesions at the application site were evaluated and graded.

The study pathologist evaluated the implant site for the following via histology: granuloma formation, ciliary loss, presence of a foreign body, fibrosis of the lamina propria, osteoneogenesis of underlying bone, inflammation, and serous gland presence. Any sign of infarct was evaluated as a potential embolism of the test or control article and described histologically by the study pathologist.

A gross observation was made by the pathologist in regards to any inflammation of the respiratory tract that could be a sign of the test or control article being inhaled. Any indication of infarct in the major organs was documented, collected, and analyzed histologically.

Blood was drawn prior to implant and then prior to termination. There were minimal changes and nothing that would indicate a problem with the test or control article.

Two groups were included in the study to evaluate the degradation of PerClot Topical at 48±3 hours (n=6) and 72±4 hours (n=6). All sites of device application were negative for the presence of starch in animals survived to both time points.

PerClot Topical when compared to NexStat proved to be more effective. Comparing the study groups that went to 21-22 days, there were 14 sites treated with PerClot Topical, 14 sites treated with NexStat, and 4 sites treated using Standard of Care (direct pressure).

Effectiveness for the test article was 86% with 12 of 14 injuries achieving hemostasis by 5 minutes. At 1 minute there was 36% (total of 5 / 14) achievement of hemostasis. At 3 minutes there was 64% (total of 9 / 14) achievement of hemostasis.

Effectiveness for the control group was 64% with 9 of 14 sites achieving hemostasis by 5 minutes. At 1 minute 2 of 14 sites (14%) were hemostatic and at 3 minutes 7 of 14 sites (50%) were hemostatic.

The standard of care group had 3 of 4 sites that achieved hemostasis by 5 minutes; this effective rate is 75%. At 1 minute 1 of 4 sites (25%) was hemostatic at 3 minutes only 1 site was hemostatic.

All animals that were implanted under this protocol survived to their study end point, giving the study a 0% mortality rate. Histologically there was no difference between the test and control groups at 21 – 22 days post-implant

All testing for the presence of starch at necropsy for the 48 (±3) and 72 (±4) hour test groups were negative therefore in regards to degradation, PerClot Topical was not found at the site of implant as early as 48 hours after implant

In regards to morbidity and mortality rates, the test article has proven to be safe with a 100% survival rate. When compared to the control article and standard of care the test article was proven to be more effective when applied to a nasal abrasion in an ENT application.

In regards to healing and safety, there were no significant differences between the test and control articles. Neither the test article nor control article had any unexpected findings.

3.2.20 Non-GLP Evaluation of Performance of PerClot in a Porcine Model

The aim of this study was to evaluate the performance of PerClot lot # MS14J04, and compare it to other lots of PerClot to determine if it was an outlier. We evaluated the performance of PerClot lot # MS14J04 on 12 pigs in 4 difference sets of experiments. PerClot manufactured by SMI and Arista were also used for reference.

The data showed the MS14J04 lot performed, as the other PerClot lots examined on that day, equivalently to the control articles (Arista and SMI-manufactured PerClot) at 7 min, which is the primary endpoint.

Animal to animal variation of success rate was observed in the study. To possibly explain this phenomenon, veterinary analysis and clinical pathology review of the animals enrolled

in this study were undertaken. Neither was able to point to a specific physiological or pharmacological parameter as the cause of the variation.

In conclusion, lot MS14J04 is not an outlier and its performance is similar to that of other PerClot lots and the control articles.

3.3 Clinical Experience

3.3.1 Clinical Trial of Absorbable Polysaccharide Haemostatic Chongqing and Xian, China

A total of 142 patients from two investigational sites undergoing a surgical procedure (60 orthopedic and 82 general surgery) were randomized to receive PerClot (n=44), SuperClot (n=54), or Arista (n=44) as an adjunct hemostatic treatment. The efficacy endpoint was achievement of hemostasis within 3 minutes of hemostatic agent application. The safety endpoint consisted of the occurrence of adverse events.

The three groups (PerClot, SuperClot, and Arista) were statistically homogeneous with respect to age, gender, height, ethnicity, occupation (manual vs. non-manual labor), medical history, and physical examination. There was no statistical difference in the amount of bleeding observed at each identified lesion prior to hemostat application. Hemostasis was achieved in all patients and in all treatment groups by 3 minutes. None of the patients in the PerClot and Arista groups experienced any adverse events. A single patient in the SuperClot group (1.96%) experienced one adverse event (a fever that resided 24 hours after surgery) that was deemed unrelated to the hemostatic device.

The safety and efficacy profile of PerClot is non-inferior to the safety and efficacy profiles of SuperClot and Arista.

3.3.2 PerClot for Bleeding Control of the Sternum Vogtareuth, Germany

Twenty-one patients undergoing coronary surgery had sternal bleeding controlled with PerClot application. Electrocautery to the periosteum was used sparingly, PerClot was applied to each side of the sternal spongiosa, and towels were immediately wrapped around the applied PerClot.

Effective control of sternal bleeding was observed in 18 patients. In two cases, additional applications of PerClot were required to achieve hemostasis. In one case, continuous mild bleeding continued throughout the surgical procedure but did not require additional intervention. No adverse events were observed and there were no mortalities out to 3 months.

3.3.3 Clinical Evaluation of Hemostatic Performance in Splenectomy for Portal Hypertension Xian, China

The purpose of this prospective, randomized, comparative, non-inferiority clinical evaluation was to evaluate and compare the safety and efficacy of PerClot with absorbable gelatin sponge and Arista in achieving hemostasis in actively bleeding wounds during hepatic surgery. Forty-five patients undergoing splenectomy for portal hypertension were

randomized to receive PerClot, absorbable gelatin sponge, or Arista (n=15 each). All patients were evaluated at 24 hours postoperatively, 3 days postoperatively or at discharge (whichever was earlier), and at 30 days postoperatively.

The primary efficacy endpoint was hemostasis of the first treated wound within 5 minutes of hemostat application. The primary safety endpoint was the occurrence of serious device-related adverse events within 30 days postoperatively. Secondary objectives consisted of the time to hemostasis, the number of applications of hemostat required to achieve hemostasis within 5 minutes, and all adverse events.

No significant difference in primary efficacy endpoint, hemostasis within 5 minutes, was found between the PerClot and Arista groups (86.7% versus 80.0%, respectively). The 5 minute hemostatic success rate for the gelatin sponge group (40.0%) was significantly lower than the hemostatic success rates of the PerClot and Arista groups ($p<0.05$).

The mean times to hemostasis were 2.25 ± 0.93 minutes, 2.38 ± 1.19 minutes, and 4.17 ± 0.98 minutes for the PerClot, Arista, and absorbable gelatin sponge groups, respectively. One application of PerClot per wound was required to achieve hemostasis within 5 minutes.

No clinically significant adverse reactions occurred in any of the three treatment groups.

3.3.4 A Post-Market Surveillance Study Evaluating the Safety and Effectiveness of PerClot to Control Mild Bleeding in Subjects Undergoing Endoscopic Sinus Surgery

This was a prospective, single center, single-arm study designed to collect clinical data to support the safety and effectiveness of PerClot when used in patients undergoing endoscopic sinus surgery. All patients were treated with PerClot in at least one nostril and followed up 2 weeks after surgery. The effectiveness endpoints for this study were the achievement of hemostasis in each nostril (yes/no) after the application of the PerClot and time to hemostasis in each nostril (in minutes). The safety endpoints consisted of intraoperative blood product administration, use of alternative means to achieve hemostasis after PerClot application, incidence of reoperation for bleeding, post-operative infection, and post -operative wound healing.

Of the 12 patients enrolled in the study 10 (83%) were male. The average age of the group was 43 years ± 17 years. 42% had undergone previous ENT surgery and 2 patients (17%) were noted to having a predisposition to developing post-operative adhesions or developing post- operative bleeding. 2 patients (17%) were current smokers and a further 2 patients (17%) had a history of allergy. All patients were documented as being ASA grade 1 or 2 making them low anaesthetic risk patients.

All 12 patients underwent endoscopic sinus surgery with the application of 3 grams of PerClot to control bleeding. Fifty percent of patients had bilateral surgery and therefore required PerClot in both nostrils and 50% of patients underwent unilateral surgery therefore only requiring an application of PerClot to one nostril.

Fifty percent of patients were reported as having mild bleeding, 42% moderate bleeding and 1 patient (8%) was reported as having severe bleeding prior to the application of PerClot. Of all the surgical sites to which PerClot was applied 94% achieved hemostasis

within a mean time of 1.82 minutes ± 0.71 minutes. One patient required an additional hemostat (Nasopore) to achieve hemostasis. A further patient did achieve hemostasis within 3 minutes; however, as this patient had a history of severe epistaxis Nasopore was inserted prophylactically.

No patients required the use of intra-operative blood products and the mean surgical time was 34.33 ± 18.33 minutes. One adverse event (AE) was documented intra-operatively. This event occurred prior to the application of PerClot and was therefore reported as not related.

Prior to discharge no patients showed any clinical signs of bleeding or required reoperation for a bleeding event. No evidence of post-operative infection was noted and no patients reported any adverse events.

At the 14 day follow up visit no patients required reoperation for bleeding. There were no cases of post-operative infection or evidence of adhesion formation. Two patients (20%) reported bleeding since discharge. Patient 3 reported epistaxis's 4 days post-surgery which did not require treatment. Patient 12 had mild bleeding for 5 days post-surgery which was reported as an adverse event. It should be noted that patient 12 was reported as having a predisposition to post-operative bleeding and was the only patient who was reported as having severe bleeding during surgery. In comparison Shorman *et al (2009)* measured bleeding in the week following FESS using a non- validated patient questionnaire. Patients were asked to give a score from 0 (no bleeding) to 10 (major bleeding). The mean bleeding score for Nasopore was 3.67 (min 0, max 10). This indicated that PerClot is comparable if not advantageous to Nasopore for the prevention of post-operative bleeding.

3.4 Publications

3.4.1 Modern Topical Hemostatic Agents–A Breakthrough in Vascular Surgery[8]

One hundred and six patients were treated with either Fibrillar® (n = 65), PerClot® (n = 26), or Surgiflo® (n = 15) in difficult cases (primary arterial anastomoses and anastomosis with synthetic prostheses) to stop bleeding. The topical hemostatic agents reduced blood loss and shortened the operative time in 95% of cases.

3.4.2 Polysaccharide hemostatic system reduces blood loss in high-body-mass-index patients undergoing simultaneous bilateral total knee arthoplasty[9]

The purpose of this study was to investigate the efficacy of a topically applied hemostatic agent used to reduce blood loss in patients undergoing bilateral total knee arthroplasty.

A total of thirty two patients undergoing single-stage bilateral total knee arthroplasty were enrolled into the study and divided into two group with a body mass index of <30 (Group 1) and >30 (Group 2). A total of 3 grams of a polysaccharide hemostatic agent was applied to the right knees of each patient. The left knee was used as the control.

There was a significant increase in the amount of blood loss ($p = 0.027$) for patients with a higher body mass index. The local treatment of the right knee with a polysaccharide hemostatic agent significantly reduced the amount of blood loss (314 ± 151 ml) for the right knee versus 468 ± 140 ml for the left knee in Group 1 and in Group 2 (420 ± 251 ml

and 620 ± 229 ml, respectively. There was no difference in blood loss reduction between the right and left knees ($p = 0.173$).

The authors concluded that the use of a polysaccharide hemostatic agent can be of value as an adjunctive therapy in blood management procedures in major joint-replacement surgery.

4 Risks and Benefits

4.1 Potential Benefits

Overall, advancement of medical and scientific knowledge that may benefit future patients may be realized from this study.

4.2 Potential Risks

There are possible risks, complications, and discomforts associated with surgery in general. The more common and serious possible risks and/or complications of surgeries include, but are not limited to, the following:[10, 11]

- Abscess formation;
- Adhesion formation;
- Allergic reactions to any drugs given during surgery;
- Anesthesia complications;
- Arrhythmia;
- Atelectasis;
- Bleeding;
- Death;
- Deep vein thrombosis;
- Fluid collection;
- Hematoma;
- Hemothorax;
- Hypoxemia;
- Infection;
- Myocardial infarction;
- Pain;
- Paralysis;
- Pneumothorax;
- Pulmonary embolism;
- Reoccurrence of chest pain;
- Stroke; or
- Tissue necrosis.

Furthermore, there are possible risks, complications, and discomforts specifically associated with the three therapeutic areas (cardiac, general, and urological). The more common and serious risks and/or complications associated with these three therapeutic surgical areas include, but are not limited to, the following:

Cardiac[12, 13, 14, 15]

- Brain damage;
- Graft failure;
- Infection of the inner tissue lining of the heart (endocarditis);
- Infection of the mediastinum, the cavity between the lungs (mediastinitis);
- Inflammation (pericarditis);
- Irregular heart rhythm; or
- Post-pericardiotomy syndrome.

General[16, 17]

- Ascites;
- Biliary leakage;
- Hernia formation;
- Necrotizing pancreatitis;
- Pleural effusion; or
- Pneumonia.

Urological[18, 19, 20]

- Epididymitis;
- Fistula;
- Sexual dysfunction;
- Unanticipated loss of renal function;
- Ureteral injury;
- Urinary incontinence; or
- Urinary leak.

Subjects that are randomized to the control group are exposed to increased risks associated with the use of Arista™AH (Medafor, Inc.; Minneapolis, MN; hereinafter referred to as Arista). Possible adverse events that could be associated with the use of Arista may include, but are not limited to, the following:[21]

- Act as foci for calculus formation when used in renal pelvis or ureters;
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid;
- Compression necrosis of surrounding tissues due to swelling;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Effect on glucose load;
- Embolization; and
- Paralysis and nerve damage when used in or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.

Subjects that are randomized to the investigational device group are exposed to the increased risks associated with PerClot. Possible adverse events that could be associated with the use of the investigational device may include, but are not limited to, the following:

- Adhesions or fibrosis;
- Anaphylaxis;
- Blockage of the bladder or ureteral lumen;

- Blockage of the bypass system;
- Cancer recurrence and/or progression;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Embolism;
- Failure of deep or superficial wound healing;
- Failure to obtain hemostasis;
- Fever;
- Hemorrhage;
- Infection;
- Peri-operative hyperglycemia;
- Exacerbation of surgical procedure-associated adverse events;
- Swelling and compression of pressure-sensitive tissues and structures;
- Thromboembolism;
- Thrombosis; and
- Toxicity.

There may also be other unforeseen risks.

There are also risks or inconveniences specific to participation in this investigation that may include, but are not limited to, the following:

- Additional blood draws preoperatively, intraoperatively (including a blood draw from an artery), and postoperatively;
- Pregnancy test (females) performed preoperatively;
- Assessment for intraoperative hemostasis maintenance 12 minutes after device application and just prior to surgical closure.

Risks and benefits of participating in the clinical investigation are also listed in the sample Subject Informed Consent Form (ICF), included as Appendix B.

4.3 Risk Mitigation

Risk mitigation steps taken to reduce the risks associated with the use of PerClot include material specifications, biocompatibility and animal testing, and labeling. Please refer to the PerClot IFU, attached as Appendix A.

All efforts will be made to minimize these risks by selecting investigators who are experienced and skilled in their respective areas of surgery and who have been adequately trained in the use of PerClot and the control hemostatic device. In addition, efforts will be made to ensure that the treatment and follow-up of all subjects is consistent with the best current medical practice.

4.4 Risk/Benefit Rationale

The Sponsor and reviewing surgeons have determined that this investigation is justified because its potential benefits outweigh its potential risks. Appendix C contains the Risk Analysis performed by the Sponsor.

5 Objectives of the Clinical Investigation

5.1 Objectives

The primary objective of this clinical investigation is to demonstrate non-inferiority in the achievement of hemostasis of the treated bleeding site at 7 minutes in subjects receiving PerClot compared to those receiving a control hemostatic device. The secondary objective of this investigation is to compare the achievement of hemostasis of the treated bleeding site at 5 minutes for subjects receiving PerClot compared to those receiving a control hemostatic device.

5.2 Intended Performance of the Investigational Device

The intended use for PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.

6 Design of the Clinical Investigation

6.1 General

6.1.1 Clinical Investigation Overview

This is a prospective, multicenter, multidisciplinary, controlled clinical investigation evaluating the safety and efficacy of PerClot in achieving intraoperative hemostasis compared to a similar marketed hemostatic device.

6.1.2 Bias

In order to ensure that bias is not being introduced into the investigation, each investigational site will keep a subject pre-screening log and a screening and enrollment log, drafts of which are included as Appendix D. All subjects who are considered for study participation will be documented on the pre-screening log. All subjects who sign the Informed Consent Form will be documented on the subject screening and enrollment log.

Randomization procedures are detailed in Sections 6.4.3.3, 6.6.6 and Appendix N: Operative Steps.

If any subject meeting the intraoperative eligibility criteria is not enrolled in this investigation (due to technical failures, i.e., contraindications, misdiagnosis, or intraoperative death prior to treatment, etc.), the reason(s) will be documented on the screening and enrollment log. This log will be monitored by the Sponsor or Sponsor representative. Any investigational site determined to be introducing bias into the investigation may be subject to further training or suspension from the investigation.

6.1.3 Endpoints

The primary efficacy endpoint of this investigation is the achievement of hemostasis for the treated bleeding site at 7 minutes following the application of the prescribed hemostatic agent. The secondary efficacy endpoint for this investigation is hemostasis for the treated bleeding site at 5 minutes.

The safety endpoints will consist of:

- Total operative time;
- Hemostasis at 5 and 7 minutes;
- Hemostasis maintenance;
- Total intraoperative estimated blood loss;
- Alternative means required to achieve hemostasis (where applicable);
- Units of blood transfused intraoperatively and postoperatively (where applicable);
- Incidence of reoperation;
- Total hospitalization time;
- The incidence of procedure complications; and
- The incidence of adverse events through final follow-up, including, but not limited to:
  - Adhesions or fibrosis;
  - Anaphylaxis;
  - Blockage of the bladder or ureteral lumen;
  - Blockage of the bypass system;
  - Cancer recurrence and/or progression;
  - Compromised attachment of prosthetic devices to bone or tissue;
  - Death;
  - Embolism;
  - Failure of deep or superficial wound healing;
  - Failure to obtain hemostasis;
  - Fever;
  - Hemorrhage;
  - Infection;
  - Peri-operative hyperglycemia;
  - Exacerbation of surgical procedure-associated adverse events;
  - Swelling and compression of pressure-sensitive tissues and structures;
  - Thromboembolism;
  - Thrombosis; and
  - Toxicity.

Any procedure complications/adverse events through final follow-up will be reported as per Common Terminology Criteria for Adverse Events (2009): CTCAE-2009.[22]

6.1.4 Replacement Subjects

The efficacy endpoints are collected intraoperatively; therefore no adjustment is made for attrition. However, the sample size is increased to 54 subjects per treatment group within each therapeutic group (Section 6.3, Figure 1) to account for the possibility of up to 5% loss within either group. This is discussed further in Section 6.6.5.

6.2 Investigational and Comparator Devices

6.2.1 PerClot – Investigational Device

Please refer to Section 2.

6.2.2 Comparator Devices

When a subject is randomized to the control group, he or she will receive Arista on the qualified bleeding site. This hemostatic agent was chosen as the control because it is a medical device, as is PerClot, is plant-based, and does not contain any pharmaceutical components such as thrombin or fibrinogen. Arista has a comparable indication for use as the intended use of PerClot for this clinical trial, and thus would not limit its use in this investigation.

Arista is a medical device intended for application to surgical wound sites as an absorbable hemostat. This technology incorporates hydrophilic, flowable, microporous particles synthesized by cross-linking purified plant starch through a proprietary process; Arista is a 100% plant based polysaccharide. Arista contains no human or animal components. Arista is a fine, dry, sterilized white powder that is biocompatible, non-pyrogenic, and is typically absorbed within 24 to 48 hours.

Arista particles are hydrophilic molecular sieves that enhance natural hemostasis by concentrating blood solids such as platelets, red blood cells, and blood proteins on the particle surfaces to form a gelled matrix. The concentrated gel matrix provides a barrier to further blood loss and is formed regardless of the patient's coagulation status. The concentration of clotting factors and platelets in the gel serves to enhance normal clotting reactions and creates stable hemostatic plugs. The absorption process begins immediately and is dependent on several factors, including the amount applied and site of use.

The use of Arista as the control in this investigation has been approved by FDA.

6.2.3 Other Medical Devices

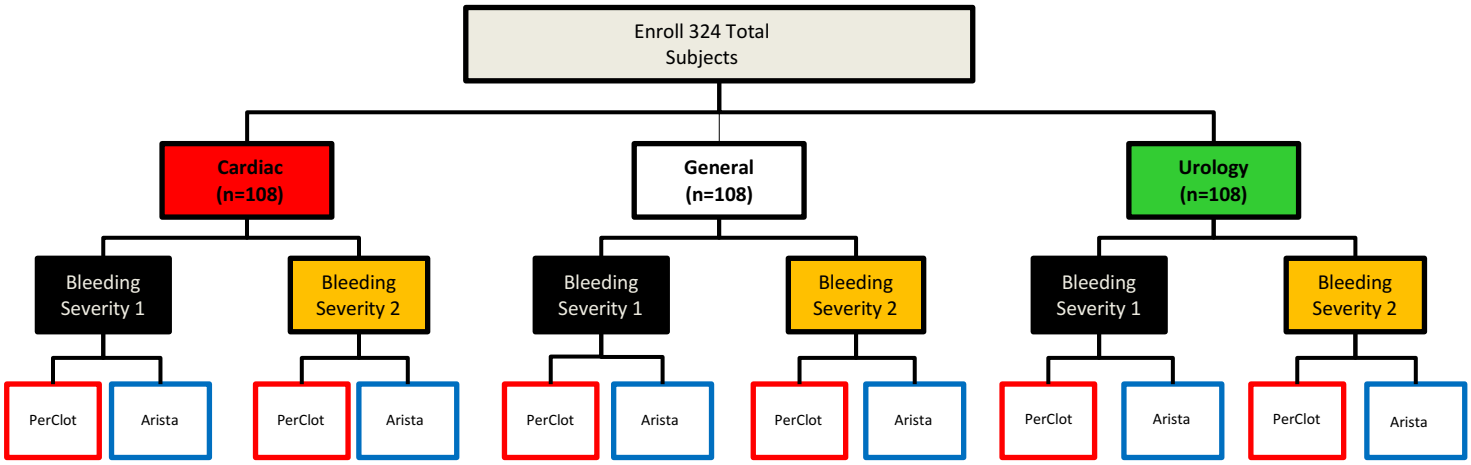
Other medical devices to be used in enrolled subjects will be at the discretion of the investigator, but must be medical devices that are currently approved for the intended use. However, the surgeon will only be allowed to use the prescribed hemostat (PerClot or identified control device) that the subject has been randomized to for the evaluation of hemostasis of the bleeding site that meets the intraoperative inclusion/exclusion criteria. Any other additional hemostatic measures, either due to failure of hemostasis at 7 minutes or during the additional 5 minute observation (12 minutes post-application) or the evaluation just prior to surgical closure for hemostasis maintenance at the target application site, or a site that does not meet the intraoperative inclusion/exclusion criteria, will consist of hemostatic measures other than PerClot or Arista. Alternative means used to achieve hemostasis of the bleeding site will be documented and analyzed as a safety endpoint. PerClot or Arista can be used on a bleeding site meeting intraoperative inclusion/exclusion criteria and when the anatomic site is less than or equal to 25cm² and when the anatomic application site is less than or equal to 47cm^2, for the evaluation of hemostasis at 5 and 7 minutes. Use of any blood modifiers/insulin or blood-sugar lowering medications will also be documented. A list of blood modifiers/insulin or blood-sugar lowering

medications, including reversal drugs, is provided in Appendix L: Blood Modifiers and Appendix K: Insulin or Blood Sugar Lowering Medications.

6.3 Subjects

A total of 324 subjects undergoing open elective cardiac, general, and urological surgical procedures will be enrolled across a maximum of 25 investigational sites. Each investigational site is expected to enroll approximately 13-40 subjects. All investigational sites will be located in the U.S. These subjects will be intraoperatively randomized to receive either PerClot or the control hemostatic device after the intraoperative eligibility criteria are confirmed. Randomization will also be stratified by bleeding severity score. See Figure 1 below. The maximum expected duration of the clinical investigation, from the first subject enrolled to the last subject discontinued, is 28-32 months. The estimated enrollment period is 18 months. The expected duration of each subject's participation in this investigation can range from 28-56 days, based on the visit windows presented in Table 3 (Section 6.4.7). For oncologic subjects, overall survival data will be collected at 24 months.

Figure 1. Subject Allocation



6.3.1 Subject Informed Consent

Each subject must sign and date the current IRB-approved version of the ICF prior to screening.

A subject will be provided ample time and opportunity to inquire about the details of the trial and decide whether to participate before informed consent is obtained. Coercion or undue influencing of a subject for participation must be avoided; a subject's legal rights must not be waived. An ICF will be given to each prospective subject to include an explanation of the trial and its duration, expected benefits, risks or inconveniences, an explanation of alternative treatments, medical record access and subject anonymity. The ICF will contain non-technical language. Informed consent shall be documented by the dated signatures of the subject and the individual obtaining informed consent. The Principal Investigator or specified designee will be responsible for obtaining the ICF.

A sample of the ICF is presented in Appendix B.

Each investigational site will keep a subject pre-screening log and a screening and enrollment log, drafts of which are included as Appendix D. All subjects who are considered for study participation will be documented on the pre-screening log. All subjects who sign the Informed Consent Form will be documented on the subject screening and enrollment log.

6.3.2 Subject Eligibility

The following eligibility assessments will occur no more than1 month (30 days) prior to surgery. Subjects must meet all of the following criteria to be enrolled in the study:

Preoperative Inclusion Criteria

- Subject is undergoing one of the following open elective cardiac, general, or urological surgical procedures;
  - Cardiac procedure (Epicardium);
  - Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line);
  - Liver resection;
  - Total splenectomy;
  - On-clamp partial nephrectomy; or
  - Radical nephrectomy.
- Subject is willing and able to give prior written informed consent for investigation participation; and
- Subject is $\geq$ 22 years of age.

Preoperative Exclusion Criteria

- Subject with known sensitivity to starch or starch-derived materials;
- Subject who has a clinically significant coagulation disorder or disease, defined as a platelet count <100,000 per microliter, International Normalized Ratio >1.5, or a PTT more than 1.5 times outside the laboratory's normal reference range;
- Subject who used corticosteroids (excluding inhalers, eye-drops, and dermatologic corticosteroids) within 6 weeks prior to surgery;
- Subject who has been treated with an investigational product and has not completed the entire follow-up period for that investigational product;
- Subject who is pregnant (as confirmed by a pregnancy test), planning on becoming pregnant during the follow-up period, or actively breast-feeding; and
- Subject with poor blood glucose control as per glycosylated hemoglobin > 9%.

NOTE: For subjects with more than one laboratory report available, the values closest to the time of implant of the test or control articles should be evaluated to determine eligibility.

NOTE: A pregnancy test is not required for subjects who have undergone a total hysterectomy.

Record laboratory values on the Laboratory eCRF.

Intraoperative Inclusion Criteria

- Subject is undergoing one of the following elective procedures:
  - Cardiac procedure (Epicardium);
  - Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line);
  - Liver resection;
  - Total splenectomy;
  - On-clamp partial nephrectomy; or
  - Radical nephrectomy
- Subject in whom all visible vessels or suture holes, greater than or equal to 2mm in diameter have been ligated, or suture line gaps greater than or equal to 2mm have been ligated;
- Subject in whom there is bleeding at the specified area for each surgical procedure after any applicable conventional means for hemostasis are attempted as specified by the intraoperative protocol;
- Subject in whom the anatomic site is equal to or less than 25cm²;
- Subject in whom the anatomic application site is equal to or less than 47cm²; and
- Subject in whom the bleeding flux from the identified bleeding site is $> 0.000040[g/(cm^2 \cdot s)]$ and $\leq 0.013[g/(cm^2 \cdot s)]$.

Bleeding Severity Score	Bleeding Flux
0=No Bleeding	0-0.000040
1=Ooze	>0.000040-0.0056
2=Slight Bleeding	>0.0056-0.013
3=Moderate Bleeding	>0.013-0.041
4=Severe Bleeding	>0.041-0.063
5=Life-Threatening Bleeding	>0.063

Verbal description of each score on the bleeding severity scale:

a. A score of 0 denotes no active bleeding. The surgical field is completely dry with no blood or the surgical field is stained with blood, but this blood is completely stagnant.

b. A score of 1 denotes oozing. The rate of bleeding is slow. This is what one may expect from capillary, venular, or arteriolar bleeding.

c. A score of 2 denotes slight bleeding. The rate of bleeding is slightly faster than oozing. There is no pulsatile flow present. This is what one may expect from capillary, venular, or arteriolar bleeding.

d. A score of 3 denotes moderate bleeding. There may be a weak pulsatile flow present. If there is a pulsatile flow, the rate of blood flow is similar to the rate of flow for a score of 2. If there is no pulsatile flow, the rate of blood flow is faster than slight bleeding.

e. A score of 4 denotes severe bleeding. For the most part, pulsatile flow is present. If there is no pulsatile flow, then the rate of blood flow is extremely rapid.

f. A score of 5 denotes life-threatening bleeding. A strong pulsatile flow is always present and the rate of blood flow is extremely rapid.

Intraoperative Exclusion Criteria

- Subject undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis);
- Subject in whom any major intraoperative bleeding incidences during the surgical procedure occurred (i.e., subject with assignment of an American College of Surgeons Advanced Trauma Life Support Hemorrhage Class of II, III, or IV Hemorrhage)[x];
- Subject who has an active or potential infection at the surgical site, or whose surgical wound is defined as a wound classification of CO (Contaminated) or D (Dirty or Infected) based upon the Center for Disease Control and Prevention's wound classification system;[ix]
- Subject who has undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery.

Investigators will be trained on bleeding severity assessment and the appropriate application of PerClot and the control device prior to the enrollment of any subjects.

All patients presenting to the investigator for elective (non-emergent) surgical procedures are potential study candidates and should be screened for eligibility. Subjects who do not meet all eligibility criteria will not be enrolled.

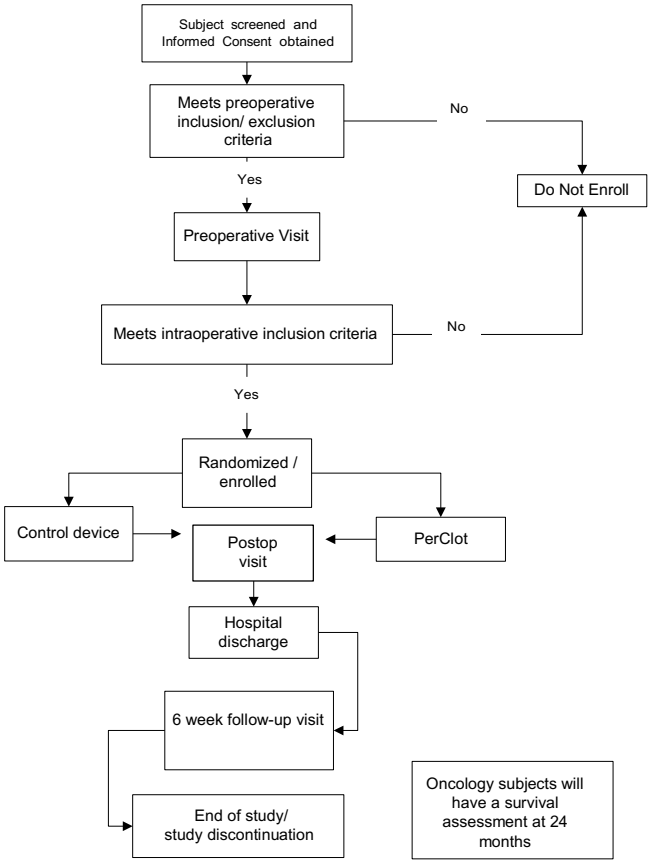
Enrollment occurs when a subject meets the preoperative inclusion/exclusion criteria, signs the ICF, meets the intraoperative eligibility criteria, and is randomized to a treatment arm.

6.3.3 Subject Randomization

Once a subject has met the intraoperative eligibility criteria, he or she will be randomized to either the control group or PerClot group for each surgical specialty. See Figure 2 below. Subjects will be randomized on a 1:1 basis at each investigational site.

[ix] Please see the Glossary (Section 13) for the Center for Disease Control and Prevention's wound classification system and the American College of Surgeons Advanced Trauma Life Support Hemorrhage classification system.

Figure 2. Subject Enrollment and Discontinuation



6.3.4 Subject Withdrawal

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

A withdrawn subject's ongoing follow-up treatment will not be compromised in any way subsequent to withdrawal. If a subject elects to withdraw prior to completing the trial, an effort will be made to collect final data and information regarding the reason for withdrawal. Subject withdrawal information will be recorded on the appropriate electronic case report form (Completion/Discontinuation eCRF).

6.3.5 Subject Death

If a subject death occurs during the study, the Sponsor and Sponsor representative should be contacted immediately and the applicable regulatory authorities and IRBs notified as required by the regulations (also see Section 10.4.2). The subject death should be documented on the Adverse Event eCRF and the Completion/Discontinuation eCRF. Ancillary information regarding the subject's death and its relationship to the investigational product, such as autopsy reports, should also be provided if available.

6.4 Procedures

6.4.1 Subject Registration and Numbering

Subjects who meet the preoperative eligibility criteria will be asked to sign and date the current IRB-approved ICF. Informed consent must be obtained for all subjects who are potential study candidates before any study-specific tests or procedures are performed. Upon giving written informed consent, all subjects will be assigned a unique four digit subject identification number according to the order of screening. The first two digits will identify the investigative site; the remaining two digits identify subjects in order of screening. The two sets of digits will be separated by a dash.

Study personnel should explain that even if a subject agrees to participate in the study, they may not meet the eligibility criteria for enrollment in the study. During the intraoperative period, only those who meet the intraoperative eligibility criteria will be enrolled into the study.

After the subject has agreed to participate in the study and signed the ICF, the following information will be documented on the Subject Screening eCRF:

- Subject gender;
- Subject date of birth;
- Subject ethnicity and race; and
- Confirmation of all preoperative inclusion and exclusion criteria.

The Laboratory eCRF will be completed as applicable. Sample CRFs are provided in Appendix E.

6.4.2 Preoperative Evaluations

The following baseline data will be taken and recorded and will occur no more than 1 month (30 days) prior to surgery:

- Physical exam, including the subject's height, weight, temperature, diastolic and systolic blood pressure;
- Indication for surgery, reoperation information, and concomitant procedures;
- Use of any blood modifiers, insulin or blood sugar lowering and/or reversal drugs;
- Complete blood count and coagulation status (platelet count, PTT, INR, and fibrinogen) and Complement C3;
- Medical history, including smoking habits, use of oral contraceptives, diabetes and type, if applicable, and the presence of any malignancies (including if the subject has undergone chemotherapy within the last 6 months and date of last treatment, if applicable, and if the subject is undergoing surgery for this malignancy); and
- Thromboembolism Risk Assessment.

NOTE: For subjects with more than one laboratory report available, the values most proximal to the time of implant of the test or control articles should be evaluated to determine eligibility.

This information will be recorded on the Preoperative eCRF and Laboratory eCRF. The Blood Modifiers/Blood Sugar Lowering eCRF should be completed as applicable.

6.4.3 Intraoperative Procedures and Evaluations

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

6.4.3.1 Surgical Procedures

Subjects undergoing the following elective open, surgical procedures will be eligible for investigation enrollment:

- Cardiac procedure (Epicardium)
- Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line);
- Liver resection;
- Total splenectomy;
- On-clamp partial nephrectomy; or
- Radical nephrectomy.

For each of these procedures, a bleeding site meeting intraoperative inclusion/exclusion criteria and whose anatomic site is less than or equal to 25cm² and whose anatomic application site is less than or equal to 47cm^2, will be evaluated for bleeding flux and satisfaction of the intraoperative eligibility criteria.

For each of these procedures, PerClot should not be allowed to enter into cell saver devices, extracorporeal cardiopulmonary bypass circuits or autologous blood salvage circuits. Granules of PerClot or fragments of gelled PerClot may pass through 40 micron transfusion filters of blood salvaging systems.

For cardiac procedures, the site of evaluation for satisfaction of intraoperative eligibility criteria will be any bleeding sites on the epicardium, along an aortic anastomotic suture line, or an aortotomy suture line. For example, the surgeon will perform dissection of adhesions per his or her conventional methods and bleeding will be controlled using means continually employed by the surgeon prior to surgical closure. Prior to application along an aortic anastomotic suture line or an aortotomy suture line, suture line gaps $\geq$ 2mm and large needle holes $\geq$ 2mm will be ligated prior to assessment of intraoperative eligibility criteria. Any bleeding site on the epicardium, or along an aortic anastomotic suture line, or an aortotomy suture line meeting the eligibility criteria will be evaluated for satisfaction. PerClot should be applied after drug reversal and the patient is taken off by-pass.

For liver resection procedures, the resected liver surface will be the site of evaluation. The surgeon will perform resection of the diseased portion of the liver per his or her conventional methods. Bleeding from discrete vessels will be controlled using means conventionally employed by the surgeon. Vessels $\geq$ 2mm in diameter will be ligated and any observed bile leaks controlled prior to assessment of intraoperative eligibility criteria. Any bleeding site on the exposed parenchymal surface will be evaluated for satisfaction of the eligibility criteria.

For total splenectomy procedures, the site of evaluation for satisfaction of the intraoperative eligibility criteria will be the retroperitoneal surface. The surgeon will perform the splenectomy per his or her conventional methods. Vessels ≥ 2mm in diameter will be ligated prior to assessment of intraoperative eligibility criteria. Any bleeding site on the retroperitoneal surface/cavity will be evaluated for satisfaction of the eligibility criteria.

For on-clamp partial nephrectomies, the site of evaluation will be the kidney bed surface. The surgeon will perform resection of the kidney per his or her conventional methods. Vessels ≥ 2mm in diameter will be ligated and entries into the collecting system controlled prior to assessment of intraoperative eligibility criteria. Any bleeding site on the kidney bed will be evaluated for satisfaction of the eligibility criteria after clamp release.

For radical nephrectomies, the site of evaluation will be the retroperitoneal surface/cavity. The surgeon will perform the procedure per his or her conventional methods. Vessels ≥ 2mm in diameter will be ligated prior to assessment of intraoperative eligibility criteria. Any bleeding site on the retroperitoneal surface/cavity will be evaluated for satisfaction of the eligibility criteria.

A description of the surgical procedure performed, including type of implant of graft used, any concomitant procedures, and bleeding sites to be evaluated will be captured. All conventional method(s) used for hemostasis prior to assessment of intraoperative eligibility criteria will be documented on the Operative eCRF.

6.4.3.2 Intraoperative Inclusion

The intraoperative eligibility criteria must be satisfied for the subject to be enrolled and randomized, if applicable, into the investigation.

A subject must meet the following intraoperative eligibility criteria (bleeding severity assessment) to be enrolled into the investigation:

Intraoperative Inclusion Criteria

- Subject is undergoing one of the following open, elective cardiac, general, or urological surgical procedures:
  - Cardiac procedure (Epicardium);
  - Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line);
  - Liver resection;
  - Total splenectomy;
  - On-clamp partial nephrectomy; or
  - Radical nephrectomy.
- Subject in whom all visible vessels or suture holes, greater than or equal to 2mm in diameter have been ligated, or suture line gaps greater than or equal to 2mm have been ligated;
- Subject in whom there is bleeding at the specified area for each surgical procedure after any applicable conventional means for hemostasis are attempted as specified by the intraoperative protocol;
- Subject in whom the anatomic site is equal to or less than 25cm^2;
- Subject in whom the anatomic application site is equal to or less than 47cm^2; and
- Subject in whom the bleeding flux from the identified bleeding site is >0.000040[g/(cm^2·s)] and ≤0.013[g/(cm^2·s)].

Bleeding Severity Score	Bleeding Flux
0=No Bleeding	0-0.000040
1=Ooze	>0.000040-0.0056
2=Slight Bleeding	>0.0056-0.013
3=Moderate Bleeding	>0.013-0.041
4=Severe Bleeding	>0.041-0.063
5=Life-Threatening Bleeding	>0.063

Verbal site description of each score on the bleeding severity scale:

a. A score of 0 denotes no active bleeding. The surgical field is completely dry with no blood or the surgical field is stained with blood, but this blood is completely stagnant.

b. A score of 1 denotes oozing. The rate of bleeding is slow. This is what one may expect from capillary, venular, or arteriolar bleeding.

c. A score of 2 denotes slight bleeding. The rate of bleeding is slightly faster than oozing. There is no pulsatile flow present. This is what one may expect from capillary, venular, or arteriolar bleeding.

d. A score of 3 denotes moderate bleeding. There may be a weak pulsatile flow present. If there is a pulsatile flow, the rate of blood flow is similar to the rate of flow for a score of 2. If there is no pulsatile flow, the rate of blood flow is faster than slight bleeding.

e. A score of 4 denotes severe bleeding. For the most part, pulsatile flow is present. If there is no pulsatile flow, then the rate of blood flow is extremely rapid.

f. A score of 5 denotes life-threatening bleeding. A strong pulsatile flow is always present and the rate of blood flow is extremely rapid.

Intraoperative Exclusion Criteria

- Subject undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis);
- Subject in whom any major intraoperative bleeding incidences during the surgical procedure occurred (i.e., subject with assignment of an American College of Surgeons Advanced Trauma Life Support Hemorrhage Class of II, III, or IV Hemorrhage);
- Subject who has an active or potential infection at the surgical site, or whose surgical wound is defined as a wound classification of CO (Contaminated) or D (Dirty or Infected) based upon the Center for Disease Control and Prevention's wound classification system;[x]
- Subject who has undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery.

The surgeon will perform conventional means for hemostasis as specified in Section 6.4.3.1 for the identified bleeding site. Vessels ≥ 2 mm in diameter or suture line gaps ≥ 2 mm will be ligated.

[x] Please see the Glossary (Section 13) for the Center for Disease Control and Prevention's wound classification system.

If there is bleeding that meets the predefined criteria for inclusion in the study, the surgeon will blot the bleeding site with clean gauze to remove blood and any other fluid from the study site; ligate any vessels ≥ 2mm diameter or suture line gaps ≥ 2 mm . Using a millimeter-incremented tool, measure the 2 longest perpendicular distances of the bleeding site and multiply those two values to calculate the Anatomic Site. Add 1cm to each of the 2 recorded longest perpendicular distances of the bleeding site to calculate Anatomic Application Site. Blot the bleeding site with clean non-weighed gauze before placing 2 of available 10 pre-weighed 4 inch by 4 inch Covidien™ Vistec™ X-ray Detectable sponges, 16 ply (hereinafter referred to as pre-weighed gauze), onto the bleeding site and hold them with gentle pressure (enough to hold the pre-weighed gauze and capture all the blood without deforming the pre-weighed gauze or the tissue) in place until blood is seen on the top layer or for 10 seconds, timed using a timing device that can be stopped in increments of seconds. The stacks of blood-stained gauze will be weighed with the unused gauze and gauze packaging on a pre-calibrated scale (in grams, to 3 decimal places) to determine blood mass collected, and the bleeding flux will be calculated (2 significant digits after the decimal point).

The scale will be calibrated in accordance with the Calibration Plan. Calibration will be documented on the eCRF.

Bleeding Flux [g/(cm²·s)] = [Blood Mass Collected (g)]/ [Anatomic Site (cm²) · time gauze held (s)]

If the bleeding flux is > 0.000040[g/(cm²·s)] and ≤ 0.013[g/(cm²·s)], then the subject will be enrolled into the investigation. If the bleeding flux is ≤0.000040[g/(cm²·s)] or >0.013[g/(cm²·s)], then the subject will not be enrolled into the investigation.

Bleeding flux and site description will be documented on the Operative eCRF.

Confirmation of all the intraoperative eligibility criteria will be documented on the Operative eCRF.

6.4.3.3 Intraoperative Randomization

After confirmation of the intraoperative eligibility criteria, the subject will be randomized to receive an adjunct application of PerClot or the control device. The randomization schedule will be stratified by site, therapeutic area and bleeding severity score, Subjects will be randomized on a 1:1 allocation to either PerClot or the control group via envelope randomization. The Randomized Study Device (RSD) will be provided in a manner which will maintain product sterility.

There may be cases in which a subject is randomized but expires before the prescribed hemostatic agent can be applied. In such cases, this will be documented on the screening and enrollment log. Also see Section 6.1.2.

After randomization, the following data will also be collected and documented on the Operative eCRF:

- Identifier number;
- Surgeon;

- Technical failures;
- Diastolic and systolic blood pressure;
- Pulse;
- Core body temperature;
- Use of any blood modifiers, insulin or blood sugar lowering medications; and
- Blood glucose measurement.

6.4.3.4 Hemostat Application

The prescribed hemostatic agent will be applied according to the respective product Instructions for Use. Any device malfunctions will be recorded on the Device Malfunctions eCRF using FDA CDRH (Center for Devices and Radiological Health) Event Reporting nomenclature.[23] This will be a single-blinded trial. The subjects will be blinded as to the hemostatic treatment received. Unblinding will be permitted after a subject has completed his or her 6 week follow-up visit evaluation.

The anatomic site is defined as the approximate surface area of bleeding site, measured by multiplying the greatest perpendicular distances of the bleeding site. The anatomic application site is defined as the approximate surface area of the target application site, measured by adding one (1) centimeter to both greatest perpendicular distances of the bleeding site and multiplying the two values. The anatomic site and anatomic application site must meet all intraoperative eligibility criteria noted in Section 6.4.3.2. The anatomic site must not exceed 25cm². The anatomic application site must not exceed 47cm². Anatomic site and anatomic application site will be calculated and documented for the bleeding site on the Operative eCRF.

NOTE: The actual resection site may be larger than the anatomic site and/or anatomic application site (e.g., a liver resection site may be 5 inches by 4 inches, however you will only be allowed to evaluate investigational product on a 25cm² anatomic site).

The investigator will be allowed to use the entire contents of up to two 5 gram bellows of PerClot per investigational subject. Each box of PerClot supplied will contain five separate packages. Only two 5 gram bellows (packages) can be used per subject. Sites will be instructed to bring two packages of PerClot and two packages of the control product into the operating room on the day of the surgery. Application of investigational product will be addressed during investigator training. The exact amount of investigational product applied will be determined by weighing the device(s) before and after use.

The site of bleeding should be thoroughly covered with the granules. It is important that the PerClot granules come into direct contact with the bleeding surface. Gentle manual pressure will be applied until hemostasis is achieved in accordance with Appendix A: PerClot Instructions for Use and Appendix N: Operative Steps; any gauze used when applying pressure must be carefully removed for hemostasis evaluation. Wetting of the gauze with saline will facilitate this process. If gauze is adhered to the formed blood clot, the gauze should be fully saturated with saline, and then gently and slowly peeled away.

Gentle manual pressure using dry gauze will be applied immediately after application and held for 5 minutes. Gentle manual pressure using dry gauze will be re-applied after the 5 minute hemostatic assessment point and held until the 7 minute evaluation. If at the 7 minute evaluation, hemostasis is achieved, the surgeon will continue to observe the site for an additional 5 minutes (12 minutes post-application) to assess for hemostasis

maintenance. If, at any time after the 7 minute evaluation, hemostasis is not achieved or maintained, the surgeon will be allowed to use alternative measures to control bleeding.

Time of device application will be documented.

The Arista IFU will be followed for the application of control product. Application of Arista will also be addressed during investigator training and in the Operative Steps (Appendix N). The amount of hemostatic product applied in each subject will be determined by recording the mass in grams of the device(s) before and after application.

The surgeon will also be asked to estimate the amount of device left in the patient in relation to the original amount applied (percentage) after saline irrigation and aspiration of excess material, if applicable. The amount of irrigation fluid used during the irrigation and aspiration of excess material will be documented. Dislodgement of RSD, during gauze removal, will be assessed at the 5 minute and 7 minute hemostatic evaluations. The surgeon will document if the dislodgement is perceived to be the sole reason for any observed hemostatic failure. If hemostasis is observed at 7 minutes, maintenance of hemostasis will be assessed for an additional 5 minutes (12 minutes post-application) and again just prior to surgical closure.

Information regarding hemostat application will be documented on Operative eCRF.

6.4.3.5 Intraoperative Evaluations and Assessment of Hemostasis

All subjects will undergo the same intraoperative investigation evaluations unless otherwise stated. Intraoperative is defined as the time interval from when the subject enters the surgical suite until the subject exits the surgical suite. Hemostatic evaluation time points will be measured on a continuum with time zero being the time of hemostat application. The treated bleeding site will be observed and evaluated at each of the pre-defined time points regardless of when hemostasis is achieved. For example, if hemostasis is achieved at 5 minutes, the surgeon will still evaluate the application site at 7 minutes to ensure that hemostasis has been maintained. If hemostasis is observed at 7 minutes, an assessment will be made to ensure hemostasis maintenance for an additional 5 minutes (12 minutes post-application) and again just prior to surgical closure.

Success/failure criteria will be defined as follows:

- If the surgeon visually observes complete cessation of bleeding, this will be considered successful hemostasis;
- If the surgeon visually observes bleeding egressing from the RSD, this will be considered a failure of hemostasis;

If hemostasis is not achieved at 7 minutes after test or control hemostat application, the surgeon may use alternative means necessary to achieve hemostasis (i.e., other approved and marketed hemostatic devices for the applicable therapeutic area). Additionally, if hemostasis is achieved at 7 minutes after test or control hemostat application, but is not maintained at any point during the additional 5 minute observation period (12 minutes post-application) or bleeding is observed at the target application site just prior to closure, the surgeon may use alternative means necessary to achieve hemostasis (i.e., other approved and marketed hemostatic devices for the applicable therapeutic area). Any alternative

means used to achieve hemostasis will be documented. The test or control hemostat will not be allowed to be re-applied after the 7 minute hemostatic evaluation time point.

A sample Operative Worksheet is attached as Appendix F; this worksheet will assist in the collection of intraoperative data and will act as the source document for intraoperative evaluations. All intraoperative data will be recorded.

The following intraoperative parameters will also be collected after the 7 minute hemostasis endpoint and prior to closure:

- Diastolic and systolic blood pressure;
- Pulse;
- Core body temperature; and
- Use of any blood modifiers, insulin, or blood sugar lowering medications.

Other data to be collected intraoperatively include:

- Surgical procedure(s) to be performed, including any concomitant procedures;
- Placement of a drain and time of placement, if applicable;
- Total operative time (from skin incision to skin closure);
- Total intraoperative estimated blood loss;
- Hemodilution (i.e. crystalloids, colloids, urine output, other);
- Intraoperative blood products administered (i.e. red blood cells, platelets, fresh frozen plasma, cryoprecipitate);
- Use of blood modifiers, insulin, or blood sugar lowering medications and other products known to affect bleeding or glucose levels;
- Other topical hemostatic agents used during procedure, if applicable;
- The incidence of any device malfunctions;
- NNIS Risk Index;
- The incidence of any complications/adverse events; and
- The incidence of any deviations from protocol.

Once the subject is randomized to a treatment group and undergoes hemostatic agent application and intraoperative evaluations, the Operative eCRF must be completed and the Product Accountability Log updated. The screening and enrollment log should also be filled out to document if a subject satisfies the eligibility criteria. A draft screening and enrollment log is provided in Appendix D.

6.4.4 Postoperative Evaluations

All subjects will undergo the following assessments within 24 hours postoperatively:

- Clinical signs or symptoms of bleeding;
- Any blood product administration;
- Reoperation;
- Use of any blood modifiers insulin, or blood sugar lowering medications or reversal drugs;
- Drainage volume within the first 24 hours postoperatively and time of drain volume measurement, as applicable;

- Complete blood count, coagulation status (platelet count, PTT, INR, and fibrinogen) and Complement C3;
- Incidence of any complications/AEs;
- Clinical signs or symptoms of embolism or thrombosis; and
- Thromboembolism Assessment.

All subjects will undergo a blood glucose assessment at the following time points:

- After randomization (prior to application of study device);
- Within 1 hour following study device application;
- 6 hours (± 30 min) following study device application;
- 12 hours (± 30 min) following study device application; and
- 24 hours (± 30 min) following study device application.

Note: Blood glucose measurements should be evaluated with venous blood draw or the Nova StatStrip blood glucose meter. Blood glucose measurements should not be evaluated with any other blood glucose meter.

The Postoperative eCRF and Laboratory eCRF must be completed for the postoperative evaluation. The Blood Modifiers/Insulin or Blood Sugar Lowering Medications eCRF, Adverse Event eCRF, and Reoperation eCRF should also be completed as applicable.

6.4.5 Discharge Evaluation

Discharge evaluations will occur at hospital discharge or between 24 hours and 14 days postoperatively. Discharge evaluations consist of:

- Clinical signs or symptoms of bleeding;
- Reoperation;
- Use of any blood modifiers, insulin, or blood sugar lowering medications or reversal drugs;
- Total hospitalization time;
- Incidence of any complications/AEs;
- Drainage volume, as applicable;
- Time of drain volume measurement, as applicable;
- Time of drainage removal, as applicable; and
- Deep Vein Thrombosis (DVT) prophylaxis methods and duration.

The Discharge eCRF must be completed at discharge. The Blood Modifiers/Insulin or Blood Sugar Lowering Medications eCRF, Adverse Event eCRF, and Reoperation eCRF should also be completed as applicable.

6.4.6 Follow-up Evaluation

A follow-up evaluation will be performed at 6 weeks postoperatively (between 28-56 days). Unscheduled follow up evaluations are at the discretion of the investigator and may occur at any time prior to the 6 week follow up evaluation.

The Follow-Up eCRF must be completed for the follow-up evaluation. The Blood Modifiers/Insulin or Blood Sugar Lowering Medications eCRF, Adverse Event eCRF, and Reoperation eCRF should also be completed as applicable. The completion/ discontinuation eCRF will be completed for each subject at the completion of the 6 week follow-up visit or whenever applicable (i.e., upon subject death or subject withdrawal).

6.4.6.1 Six-week Postoperative Follow-Up Evaluation

- Clinical signs or symptoms of bleeding;
- Clinical signs or symptoms of embolism or thrombosis
- Reoperation and Re-Hospitalizations;
- Use of any blood modifiers, insulin, or blood sugar lowering medications or reversal drugs;
- Thromboembolism Assessment;
- DVT prophylaxis methods and duration; and
- Incidence of any complications/AEs.

6.4.6.2 24 Month Postoperative Follow-Up Evaluation (***for oncologic subjects only***)

- Assessment of Overall Survival: At 24 months, overall survival will be conducted. This may be completed by a medical records review, confirmation of an obituary, or other contact (phone call, email, letter, etc.). If there is no response after 3 documented attempts (one of which must be a certified letter), the subject will be considered lost to follow up.

6.4.7 Evaluation Schedule

Table 3 summarizes the acceptable visit windows for each evaluation time point.

Table 3. Visit Windows for Evaluations

Visit Type	Timing
Preoperative	Within 1 month (30days) before operative visit
Operative	Day 0
Postoperative	Within 24 hours postoperatively
Follow-Up: Discharge	Within 24 hours of hospital discharge or between 24 hours and 14 days postoperatively
Follow-Up: 6 Week	28-56 days postoperatively
Follow-Up: 24 Months*	23-25 months (700-760 days) postoperatively

*for oncologic subjects only

Table 4 summarizes the eCRFs that need to be completed at each time point.

Table 4. Completion of eCRFs

eCRF	Screening	Preoperative	Operative	Postoperative	Discharge	Follow-Up Visit(s)	Discontinuation
1: Subject Screening Form	X						
2: Preoperative Form		X					
3: Operative Form			X				
4: Postoperative Form				X			
5: Discharge Form					X		
6: Follow-Up Form						X	
7: Blood Modifiers Form	*Where Applicable*						
8: Laboratory Form		X		X			
9: Reoperation Form	*Where Applicable*						
10: Adverse Event Form	*Where Applicable*						
11: Discontinuation Form	*Where Applicable*						
12: Protocol Deviation Form	*Where Applicable*						
13: Equipment Calibration Form			*X*				

6.5 Monitoring Plan

Monitoring of the clinical trial will be a continuous, interactive process overseen by the Sponsor or Sponsor representative to ensure that high-quality data are obtained. Appropriately trained personnel designated by the Sponsor or Sponsor representative will monitor all subjects at the investigational site. Monitoring will be conducted according to 21 CFR Part 812, 21 CFR Part 50, ICH E6, as recognized by FDA, and by the Sponsor or Sponsor representative's applicable standard operating procedures (SOPs) and under the guidelines specified in the Monitoring Plan. In addition, the Sponsor or Sponsor representative may conduct an internal audit of the trial for quality assurance. Other inspections by regulatory authorities may include on-site inspections and source data verification.

6.5.1 Pre-Trial/Qualification Visit

The Sponsor or Sponsor representative will conduct a pre-trial (or qualification) visit to review the clinical protocol and regulatory requirements with the Investigator and trial personnel to assure the following:

- The site understands the investigational use of the device;
- The site understands the protocol;
- The site understands and accepts the obligation to conduct the clinical investigation in compliance with the protocol, the Sponsor and/or Sponsor representative policies and procedures, applicable laws, regulations and good clinical practices;
- The site understands and accepts the obligation to obtain informed consent in accordance with applicable regulations;
- The site understands and accepts the obligation to obtain IRB approval before the clinical investigation is initiated, ensures continuing review of the trial by the IRB, and keeps the Sponsor or Sponsor representative informed of the IRB approval and actions concerning the trial;
- The site has access to an adequate number of eligible subjects to participate in the trial;
- The site has adequate facilities and resources to conduct the trial; and
- The site has sufficient time to carry out the responsibilities of the trial.

A report of this visit will be completed. The site will be notified of any concerns or required follow-up items from the pre-trial visit. Resolution of these will be documented.

A Study Initiation Visit will be conducted prior to the enrollment of any subjects.

6.5.2 Periodic Monitoring Visits

Monitoring visits during the trial are necessary to assess the Investigator's adherence to the protocol, agreement, and applicable regulations. Monitoring will occur at a mutually agreeable time. One hundred percent (100%) of the data will be monitored for this trial.

6.5.3 Closeout Visits

A closeout visit will be conducted once a site is no longer enrolling and patient follow-up is complete, the trial is completed, or site activities have been terminated by the Sponsor and/or applicable regulatory agency. There may be instances where a phone call close-out may occur (e.g.., for a site that did not enroll any subjects). During the study closeout, the monitor will address administrative and regulatory record requirements.

6.5.4 Study Monitors

The Sponsor will be responsible for monitoring this study. Qualified Sponsor employees or qualified Sponsor representatives may represent the Sponsor for monitoring purposes. Questions about monitoring or other study issues may be directed to:

IMARC
22560 Lunn Road
Strongsville, OH 44149
Phone: (440) 801-1540
Fax: (440) 801-1542

6.5.5 Source Document Verification

To ensure accurate and complete data are collected, 100% source document verification will be performed on all subjects at each site. This verification requires all data to be reviewed in the source documents and in the eCRF.

Only site staff listed on the Delegation of Responsibilities Log is authorized to enter data or make corrections to eCRFs.

6.5.6 Protocol Deviations/Violations

The Investigator will not deviate from the protocol without the prior written approval of the Sponsor except in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the investigation or in cases to eliminate immediate hazards to a subject. Prior approval for protocol deviations will not be required in such cases; however, protocol deviations will be documented on the applicable Protocol Deviation Log eCRF provided by the Sponsor or Sponsor Representative.

For the purposes of this investigation, protocol violations are defined as entry of a subject into the investigation against inclusion/exclusion criteria without prior Sponsor approval. Deviations are defined as less severe protocol non-compliance such as visits occurring outside the visit time window. Sites should be instructed to follow their local IRB rules and any other applicable requirements for reporting protocol deviations/violations.

6.6 Statistical Considerations

Sections below provide detail on statistical aspects of the study design. Additional detail is provided in the Statistical Analysis Plan for the study.

6.6.1 Trial Objectives and Endpoints

The primary objective of this clinical investigation is to demonstrate non-inferiority in the achievement of hemostasis of the treated bleeding site at 7 minutes in subjects receiving PerClot compared to those receiving a control hemostatic device. The primary endpoint is the proportion of subjects achieving hemostasis of the treated lesion at 7 minutes in each treatment group.

The secondary objective of this investigation is to compare the achievement of hemostasis of the treated bleeding site evaluated at 5 minutes for subjects receiving PerClot compared to those receiving a control hemostatic device. The secondary endpoint is the proportion of subjects achieving hemostasis of the treated bleeding site at 5 minutes in each treatment group.

6.6.2 Primary Efficacy Hypothesis

The primary efficacy hypothesis for this clinical investigation is that the proportion of subjects achieving hemostasis of the treated bleeding site at 7 minutes in the overall PerClot group is non-inferior to the proportion of subjects achieving hemostasis at 7 minutes in the overall control group.

H_0: $P_{PerClot} < P_{Control} - \delta$
H_a: $P_{PerClot} \geq P_{Control} - \delta$

where $P_{PerClot}$ is the proportion of PerClot subjects achieving hemostasis at 7 minutes, $P_{Control}$ is the proportion of control subjects achieving hemostasis of the treated bleeding site at 7 minutes, and δ is the non-inferiority margin, with $\delta = 0.10$.

The primary efficacy endpoint measure will also be reported by therapeutic area (subgroup): open elective cardiac, general, or urological surgical procedures. The proportion of PerClot and control subjects achieving hemostasis at 7 minutes will be reported, along with the absolute difference between the groups. A poolability analysis will also be performed on the therapeutic area subgroups. See Section 6.6.12. There are no labeling claims being sought out for this subgroup analysis.

Additionally, the number of subjects in whom hemostasis is achieved at 7 minutes, but have a re-bleed during the 5 minute observation period following the 7 minute assessment will be summarized. A sensitivity analysis of the endpoint will be conducted where all subjects that achieved hemostasis at 7 minutes, but did not maintain it for the 5 minutes following the assessment or any time after the observation period, will be counted as 'failures' in the analysis.

For subgroups, with an overall enrollment of 324 subjects in the study in the treatment and control cohorts, it is expected that there will be data on approximately 108 subjects in each subgroup. At a minimum, the study will enroll 50 subjects within a specific therapeutic area subgroup. At a maximum there will be 224 subjects in a single subgroup. A minimum of 50 subjects in each subgroup would lead to approximately 25 treatment subjects per subgroup. For a success rate of 92% (23/25), the distance from the observed rate of 92% to the lower bound of the two-sided 95% confidence interval is 18.0%. This planned minimum subgroup size would provide a reasonable degree of statistical precision for estimation of the treatment performance within subgroups.

6.6.3 Secondary Efficacy Hypothesis

The secondary efficacy endpoint will be evaluated at 5 minutes in a manner similar to the primary efficacy analysis. The secondary hypothesis for this clinical investigation is that the proportion of subjects achieving hemostasis of the treated lesion at 5 minutes in the overall PerClot group is non-inferior to the proportion of subjects achieving hemostasis of the treated bleeding site at each evaluation time point in the overall control group.

H_0: $P_{t,PerClot} < P_{t,Control} - \delta$
H_a: $P_{t,PerClot} \geq P_{t,Control} - \delta$

where $P_{tPerClot}$ is the proportion of PerClot subjects achieving hemostasis of the treated bleeding site at time point *t*, $P_{t,Control}$ is the proportion of control subjects achieving hemostasis of the treated bleeding site at time point *t*, and δ is the non-inferiority margin, with $\delta = 0.10$.

The secondary efficacy endpoint measure will also be reported by therapeutic area (subgroup): open elective cardiac, general, or urological surgical procedures. The proportion of PerClot and control subjects achieving hemostasis at 5 minutes will be reported, along with the absolute difference between the groups. These analyses are descriptive in nature, and as such there are no formal hypothesis tests. There are no labeling claims being sought out for this subgroup analysis.

Additionally, the number of subjects in whom hemostasis is achieved at 5 minutes, but has a re-bleed after the 5 minute assessment will be summarized. A sensitivity analysis of the endpoint will be conducted where all subjects that achieved hemostasis at 5 minutes, but did not maintain it after the assessment will be counted as 'failures' in the analysis.

6.6.4 Safety Analysis

Safety data will be summarized by incidence of each adverse event type along with 95% exact confidence intervals. Adverse event rates will be reported as the proportion of subjects who experience an event and the total number of each event type occurring. Adverse events will be summarized by relatedness, seriousness, and severity. The comparison of the safety between treatment arms will be based on Fisher's exact tests for the proportion of subjects with serious device-related adverse events, unanticipated adverse device effects, and frequent adverse events (≥ 5% overall incidence) in the two treatment groups.

Additionally, supportive descriptive analyses will be performed on adverse event data within each therapeutic area: open elective cardiac, general, or urological surgical procedures.

The other following safety endpoints will also be summarized using descriptive statistics:

- Total operative time;
- Hemostasis at 5 and 7 minutes;
- Hemostasis maintenance;
- Total intraoperative estimated blood loss;
- Alternative means required to achieve hemostasis (where applicable);
- Units of blood transfused intraoperatively and postoperatively (where applicable);
- Incidence of reoperation;
- Total hospitalization time;
- Incidence of procedure complications;
- Incidence of adverse events through final follow-up, including, but not limited to:
  - Adhesions or fibrosis;
  - Anaphylaxis;
  - Blockage of the bladder or ureteral lumen;

- Blockage of the bypass system;
- Cancer recurrence and/or progression;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Embolism;
- Failure of deep or superficial wound healing;
- Failure to obtain hemostasis;
- Fever;
- Hemorrhage;
- Infection;
- Peri-operative hyperglycemia;
- Exacerbation of surgical procedure-associated adverse events;
- Swelling and compression of pressure-sensitive tissues and structures;
- Thromboembolism;
- Thrombosis; and
- Toxicity.

6.6.5 Sample Size Justification

The sample size was calculated based on the following assumptions:

- One-sided $\alpha = 0.025$;
- Minimum 80% power;
- Non-inferiority margin $\delta = 0.10$;
- Expected 7 minute hemostatic success rate in the PerClot group is 90%;
- Expected 7 minute hemostatic success rate in the control group is 90%; and
- Randomization allocation of 1:1.

A sample size of 154 subjects in each group will provide > approximately 80% power to reject the hypothesis of the inferiority of PerClot to the control by a 10% margin, using a one-sided 97.5% confidence interval. As the primary endpoint data is collected intraoperatively, no adjustment is made for attrition; however, the sample size was increased to account for the possibility of up to 5% loss within either group due to technical failures (i.e., contraindications, misdiagnosis, or intraoperative death prior to treatment, etc.), or subjects not treated according to randomization assignment, resulting in a sample size of 162 per arm to ensure >80% power in the overall sample including all three therapeutic areas. Thus, a total of 324 subjects will be enrolled across the three therapeutic areas. It is expected that there will be approximately equal numbers randomized within each of the three therapeutic areas, with an approximate 108 subjects in each therapeutic cohort.

A non-inferiority margin of 10% is consistent with the margins used in other controlled clinical trials involving hemostatic agents.[24, 25] A non-inferiority margin $\delta = 0.10$ was chosen for this study because excluding a 10% difference between the treatments would be supportive of non-inferior performance of PerClot compared to the control.

6.6.6 Blinded Sample Size Re-estimation

In order to protect against lower than planned power due to misspecification of the assumed success rates, blinded sample size re-estimation will be performed.[26] The initial sample size

calculation will be repeated based on the observed pooled efficacy rate (i.e. the proportion of all subjects, regardless of randomization assignment, with 7 minute hemostatic success) rather than the initially assumed rate of 90%.

The re-estimation will be performed using the efficacy results of the first 20% and 50% of the minimum planned enrollment of 324(i.e. 64 and 162 subjects) pooled across randomized arm. The re-estimated sample size after 20% enrollment will provide an initial re-calibration of the sample size. The re-estimated sample size after 50% enrollment will determine the final sample size, which may be lower or higher than the re-estimated sample size after 20% enrollment.

The sample size calculation will result in an increase in sample size if the observed efficacy rate is less than 90%. The loss rate at the interim analysis will be estimated and provided to the DSMB. In making a sample size recommendation, the DSMB may adjust the re-estimated sample size by up to 5% for the loss rate. The minimum sample size for the trial, regardless of the observed efficacy and loss rates, is the initially planned sample size of 324. A maximum sample size is set at 536 (510 with a 5% loss adjustment) for any observed efficacy rate ≤ 80%. The table below provides examples of the revised sample size before adjusting for loss based on hypothetical results.

Table 5: Re-estimated sample size based on blinded efficacy rate before adjusting for loss

Blinded Efficacy Rate	Re-estimated Sample Size
90%	308
89%	332
88%	352
87%	374
86%	394
85%	414
84%	434
83%	454
82%	474
81%	492
80%	510

Because the sample size re-estimation is blinded and based only on a nuisance parameter, there is no impact on the Type I error rate. Larger sample sizes are required due solely to greater variability in the binomial outcome when the equal PerClot and control efficacy rates are closer to 50%, at which point variability is at a maximum.

If the observed efficacy rate is ≤ 60% when the blinded sample size re-estimation is performed at 20% of enrollments or ≤ 64% when the blinded sample size re-estimation is performed at 50% of enrollments, the DSMB will evaluate the overall study data and make a recommendation regarding whether to stop the study prematurely due to an unacceptable efficacy rate. The boundaries of 60% and 64% were selected based on those observed rates have <5% chance of being observed if the population efficacy rate is 70% or higher.

6.6.7 Trial Success Criteria

Trial success will be the rejection of the primary efficacy null hypothesis, with the upper bound of the 97.5% one-sided confidence interval for the difference in proportions of subjects achieving hemostasis at 7 minutes between overall treatment groups ($P_{Control}$-$P_{PerClot}$) being less than 0.10, in the As Treated population.

6.6.8 Randomization and Blinding

The randomization schedule is a set of lists of sequential randomization assignments. The schedule will be stratified by site, therapeutic area and bleeding severity score. Stratifying the randomization is performed in order to help ensure that randomization is balanced between the two arms within each stratum. Therefore each site will have its own set of randomization envelopes for each bleeding severity score and therapeutic area that are independent of other sites. In creating the randomization schedule, the list of randomization assignments is composed of a series of permuted random blocks with each block consisting of two or four randomization assignments. The size of each block in the sequence is selected at random. The random permuted block method ensures that as subjects are randomized, the randomization returns to balance once each sequential block is filled, thus ensuring that the size of any imbalance is limited throughout the accrual of subjects into the study. Subjects will be randomized on a 1:1 allocation to either PerClot or the control group. A subject may agree to participate and sign the ICF, but ultimately not be enrolled due to failure to meet the intraoperative eligibility criteria. Only subjects meeting the intraoperative eligibility criteria will be randomized and enrolled.

This will be a single blinded trial. The subjects will be blinded as to the hemostatic treatment received. Unblinding will be permitted after a subject has completed his or her 6 week follow-up visit evaluation.

6.6.9 Analysis Populations

Analysis populations are defined as follows:

- The Intent-to-Treat (ITT) population includes all randomized subjects, regardless of treatment received;
- The As Treated population includes all subjects who were randomized and treated with either PerClot or Arista, with subjects assigned to the treatment group for the treatment received (even if this differs from randomization assignment); and
- The Per Protocol population includes all subjects who were randomized and treated with either PerClot or Arista, and had no major protocol deviations, where major protocol deviations are defined as:
  - Failure to meet any preoperative inclusion/exclusion criteria;
  - Failure to meet any intraoperative inclusion/exclusion criteria; or
  - Any informed consent violation.

All efficacy analyses and summary statistics will be performed on the ITT, As Treated, and Per Protocol populations. Safety analyses will be performed on the ITT population.

No subject will be removed from the study once randomization occurs. All randomized subjects with available outcome data will be included in the analysis, according to the defined analysis population.

Study success will be evaluated on the As Treated population. Effectiveness analyses of the ITT and Per Protocol populations will be supportive of the As Treated analysis. Any clinically significant differences in effectiveness results between the analysis populations will be examined relative to protocol deviations and discussed.

6.6.10 Descriptive and Summary Statistics

Demographics, baseline characteristics, and the comparability of the PerClot and control group subjects will be assessed by tabulations of mean, median, range, standard deviation and analyses using t-tests of means or Wilcoxon tests for continuous factors. For categorical factors, frequency, percent and Fisher's exact tests of proportions will be carried out. Achievement of hemostasis for all treated bleeding sites will be assessed by tabulating frequency of success as a percentage and analyses using Chi-square test.

6.6.11 Covariate Analysis Methods

Covariate analyses will be performed to assess the association with certain study parameters on the primary efficacy endpoint. For these analyses, logistic regression models will be used. Covariates will be tested univariately for inclusion in the multivariate model. Covariate assessments may consist of, but are not limited to, the following variables:

- Demographic measures such as age, gender, ethnicity, and BMI;
- Medical history;
- Therapeutic area;
- Use of blood modifiers or products known to affect bleeding (including aspirin and colloids);
- Administrations of blood products;
- Fluids administered (including colloids and crystalloids);
- Surface area of the anatomic site;
- Initial bleeding severity (as continuous measure);
- Indication for surgery;
- Complete blood count and coagulation status;
- Complement C3;
- Smoking history;
- Use of oral contraceptives;
- Diabetes;
- Presence of any malignancies;
- Amount of hemostat applied;
- Core body temperature;
- Level of glycosylated hemoglobin;
- Other hemostatic efforts made;
- Procedure type;
- NNIS risk index;
- Blood glucose at randomization;
- Blood glucose within 1 hour of device application;

- American Society of Anesthesiologists Classification;
- Total operative time;
- Placement of wound drain;
- Drainage volume within 24 hours postoperatively;
- Total drainage volume;
- Total drainage duration; and
- Volume of fluid used to rinse away excess study device.

6.6.12 Poolability Analyses

It is expected that data will be poolable across trial sites and therapeutic areas, as all sites and Investigators will follow a common protocol with identical inclusion/exclusion criteria and defined objective efficacy parameters. Additionally, it is expected that data will be poolable across therapeutic areas. Potential variability in time to hemostasis between therapeutic areas is mitigated by limiting the types of procedures and bleeding severities for which subjects can be enrolled into the investigation.

Treatment effect will be evaluated by the proportion of subjects achieving hemostasis at 7 minutes by site, and again by therapeutic area. Each of these measures will be tested as a covariate in a logistic regression model, with the primary endpoint measure as the outcome. Additional logistic regression models will be fit to test treatment by site and treatment by therapeutic area interaction effects.

In the case that poolability across site or therapeutic areas is confirmed, as indicated by statistical significance at alpha > 0.15, the assumption of homogeneity will be accepted.

In the case that poolability across site or therapeutic areas is questionable, as indicated by statistical significance at alpha $\leq$ 0.15, the assumption of homogeneity will be rejected. An additional primary efficacy analysis will be fit in order to ascertain the treatment effect after adjustment for site or therapeutic area. The reasons for any differences in outcome across these measures will be investigated and reported.

6.6.13 Missing Data

Every effort will be made to collect all data points in the study. The amount of missing data will be minimized by appropriate management of the clinical study, training of participating investigators and study coordinators, and sufficient monitoring of study sites. As the primary efficacy endpoint data is collected intraoperatively, missing data is expected to be minimal, and subject withdrawal and loss to follow-up during the follow-up period is not expected to impact the efficacy analysis.

To assess the impact of missing data on the primary endpoint, a sensitivity analysis will be conducted. The primary endpoint analysis will be repeated under two scenarios: one in which all missing endpoints are assumed to be successes for the PerClot group and failures for the control group, and another in which all missing endpoints are assumed to be failures for the PerClot group and successes for the control group. If these scenarios do not impact the conclusion of the analysis, then the impact of missing data will be considered inconsequential. The reason for any significant differences between scenarios will be investigated and reported.

6.7 Data Collection and Data Management

The handling of data will comply with regulatory guidelines and the Sponsor or Sponsor representative's SOPs and work instructions. Data management activities specific to this study will be described in a Data Management Plan. All steps and actions taken regarding data management and quality assurance will be documented in the Sponsor representative's SOPs and data handling guidelines.

Data will be collected via electronic data capture (EDC) screens referred to as eCRFs, designed specifically for this investigation. The Principal Investigator at each investigational site will review and approve all completed eCRFs.

Data collected must be supported by source documents found at the site, and subject medical records, hospital charts, operative reports, laboratory and diagnostic testing results, office visits, source document worksheets as supplied by the Sponsor, etc. will be utilized for the collection of relevant data. Completed eCRFs will undergo 100% source documentation verification and will be checked visually by the study monitor for completeness and consistency.

Electronic data queries will be created for identified errors on eCRFs that have been submitted to ensure errors/omissions are corrected. New and previous findings and recommended corrective and preventative actions, if they exist, will be communicated with the study staff during monitoring visits, and will also be addressed in a final letter that will be sent to the Investigator after each monitoring visit.

6.7.1 Data Retention

Clinical investigation records will be stored in a confidential manner so as to protect the confidentiality of subject information.

All correspondence related to this clinical investigation will be kept in appropriate investigational files. Records of subjects, source documents, eCRFs, device inventory, IRB and Sponsor correspondence, and Investigator correspondence pertaining to the investigation must be kept on file. All original subject, laboratory, and device inventory records (electronic and/or hard copies) relating to this investigation (to include the Informed Consent document, research records and data, and research specimens) shall be retained for no less than 2 years after the latter of the following dates: the date on which the investigation is terminated, the date on which the investigation is completed, or the date that records are no longer required for the purposes of supporting the pre-market approval expansion application (PMA). The Sponsor shall be contacted prior to the destruction of any records pertaining to this investigation to ensure that they no longer need to be retained. The Sponsor must approve the destruction of any investigational records.

6.7.2 Study Audits

The Sponsor, the Sponsor representative, and the reviewing IRB may audit the study centers and regulatory authorities may inspect any study center to evaluate the conduct of the study. Such audits will require access to all study records, including source documents for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit. The Investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

6.8 Protocol Amendments and Deviations

Amendments to this clinical investigation protocol will be identified by protocol reference number and amendment number. All amendments will be accompanied by a title page that identifies the changes being made and the protocol section(s) affected. The protocol reference number and amendment number will be placed on the title page and every subsequent page of an amendment.

A protocol amendment will not be implemented before all necessary reviews and approvals have been obtained, including Sponsor approvals, Investigator signatures, and IRB approvals, as applicable.

7 Statement of Compliance

FDA regulations (21 CFR Parts 50, 54, 56, and 812) and ICH E6 Good Clinical Practices (GCP), as recognized by FDA, are being followed in the conduct of this clinical investigation.

This clinical investigation shall not begin until the required approvals are obtained from the IRB and all applicable regulatory authorities.

Subjects will not be paid to participate in the clinical trial. However, reasonable travel expenses may be reimbursed; the reimbursement amount will be subject to respective IRB approvals. It is not expected that subjects will incur any additional cost due to their participation in the trial.

If a subject experiences a medical emergency and has followed the directions of the Investigator or other study staff, and if the Sponsor determines that the emergency is related to PerClot, the Sponsor will pay for whatever emergency care is required.

8 Informed Consent Process

All subjects must voluntarily provide signed informed consent prior to receiving any pre-investigation assessments that would not have been performed as part of normal subject care. Informed consent must be obtained in accordance with FDA regulations 21 CFR Part 50, 45 CFR Part 46 and ICH E6 Good Clinical Practices (GCP), as recognized by FDA.
Also see Section 6.3.1.

9 Adverse Events

9.1 Adverse Event Definitions

An adverse event is any untoward medical occurrence in a clinical study subject. An adverse event would be any unfavorable or unintended sign, symptom, or disease that appears or worsens during the clinical study regardless of the relationship to the device. Adverse events will be collected for all subjects after they are enrolled in the trial.

An abnormal laboratory value is clinically significant if the investigator determines that it requires treatment, or if he/she would collect the laboratory value at a later date to verify normalization.

A serious adverse event (SAE) is an adverse event which results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly or birth defect; and/or;
- Other, as determined by the investigator.

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Assessing Adverse Events

Adverse events will be documented by the Investigator on the appropriate source document(s) at the investigational site and will also be recorded onto the Adverse Event eCRF. All adverse events will be monitored until they are adequately resolved or explained.

Adverse events are to be recorded and dated according to when they are first observed. The respective treatment(s) should also be documented. An event should be recorded on the eCRF only once unless there are multiple occurrences of that event. As an example, a stroke reported once with sequelae still present at subsequent visits should not be reported again. However, a second stroke should be reported on a second eCRF.

The following should be determined and recorded on the Adverse Event eCRF:

- Accepted medical term for the event;
- Description of the event;
- Duration of the event (dates of onset and resolution);
- Outcome;
- Severity of the event;
- The relationship of the event to the investigational device or the control device;
- Description of the action taken; and
- Determination of whether or not the event was a serious adverse event.

All procedure complications/adverse events through final follow-up will be reported and graded as per Common Toxicity Criteria for Adverse Events (2009): CTCAE-2009.[22]

The CDRH guidance for adverse event data will be followed.
(www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm)

The severity of the event will be graded as follows by the Investigator:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- Grade 4: Life-threatening consequences; urgent intervention indicated; or
- Grade 5: Death related to AE.

Every effort should be made to determine the cause of each adverse event, since a judgment must be made as whether or not it is related to the investigational device or comparator device. The relation to PerClot or control hemostatic device will be graded and recorded on the Adverse Event eCRF by the Investigator using the following definitions:

- Not related – The adverse event is due to the underlying disease state or is due to concomitant medications or therapy not related to the use of the device;
- Possibly related – The adverse event has a reasonable temporal relationship to the use of the device but alternative etiology is equally or more likely compared to the potential relationship to the use of the device;
- Probably related – The adverse event has a strong temporal relationship to the use of the device and alternative etiology is less likely compared to the potential relationship to the use of the device; or
- Definitely related – The adverse event has a strong temporal relationship to the use of the device, follows a known response pattern and cannot reasonably be explained by known characteristics of the subject's clinical state or other therapies.

9.3 Reporting Adverse Events

9.3.1 UADE Reporting

All UADEs noted during the investigation will be immediately reported by the Investigator to the Sponsor and/or Sponsor representative (within 24 hours of awareness of the event). The investigation's medical monitors and/or medical expert will assist the Sponsor in the investigation and evaluation of UADEs and determining the appropriate course of action. The preferred method for notifying the Sponsor and Sponsor's representative is in writing via fax or e-mail (to provide written confirmation by the Investigator); contact information is provided on the cover page of this protocol.

The Sponsor shall report the results of their evaluation of UADEs to the FDA, all reviewing IRBs, and all participating Investigators within 10 working days after the Sponsor first receives notice of the UADE. The Investigator will be responsible for reporting the evaluation of UADEs to their applicable IRB within 10 working days or as required by IRB policy.

9.3.2 SAE Reporting

Serious adverse events shall be reported by the Investigator to the Sponsor and/or Sponsor representative within 24 hours of awareness of event.

9.3.3 Subject Death

Subject deaths shall be reported by the Investigator to the Sponsor and/or Sponsor representative and to their applicable IRB within 24 hours of awareness of event.

9.4 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be constituted prior to subject enrollment and the names, affiliations, and academic backgrounds of all members will be provided to FDA. The DSMB will provide expert advice to the Sponsor regarding the implementation and progress of the clinical investigation and will review accumulation trial data to monitor the safety of PerClot while the investigation is in progress.

The DSMB will make recommendations based on safety concerning continuation, suspension and/or termination of the investigation at the conclusion of each data review meeting. The DSMB will recommend actions to be taken in light of critical safety findings, including expected and unexpected adverse events and adverse device effects. The minutes of any DSMB meeting in which the DSMB recommends changes to the protocol and/or device will be immediately (within 2 working days of receipt by the Sponsor) provided to FDA.

10 Study Conduct

As the trial Sponsor of this clinical study, CryoLife, Inc. has the overall responsibility for the ethical conduct of the trial, including assurance that the trial meets the regulatory requirements of the FDA. This trial will be performed in accordance with this protocol and also in accordance with 21 CFR Parts 50, 54, 56, and 812, applicable ICH guidelines, and applicable local regulatory requirements and laws.

This clinical investigation shall not begin until the required approvals are obtained from the IRB. Any additional requirements imposed by the IRB or regulatory authority shall be followed.

10.1 Investigator Selection

The Investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor and the IRB.

10.2 Investigator Agreements

Investigators and any designated sub-investigators are responsible for conducting the investigation in compliance with the protocol and all regulations guiding clinical research. These responsibilities are specifically outlined in the Investigator's Agreement (Appendices H and I), which must be signed by all Investigators and designated sub-investigators prior to investigation initiation. In addition, Investigators are required to prepare and submit to the Sponsor the following reports in an accurate and timely fashion as specified below in Section 10.4.

10.3 Confidentiality

The Sponsor and Sponsor representative will keep all subject research documents confidential. Each enrolled subject will receive a subject identification number; any samples taken will also be identified using a subject's assigned number. All records used will not contain any patient-identifying information (e.g. names) such that the confidentiality of these records is maintained.

10.4 Investigator Records and Reports

10.4.1 Investigator Records

Per 21 CFR 812.2(b), 812.140(a) and/or the Investigator Agreement (a sample Principal Investigator Agreement is attached as Appendix H), the Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- All correspondence pertaining to the investigation with other Investigators, the reviewing IRB, the Sponsor, the Sponsor representative, and FDA;
- Records of receipt, use or disposition of a device;
- Subject case history records relating to use of the device, including signed consent forms, eCRFs, operative worksheets, medical records, progress notes, nurses notes, relevant observations relating to the device, etc.;
- The protocol and documentation of the date and reason for any deviation from the protocol; and
- A signed Investigator's Agreement, Financial disclosure, medical license, and curriculum vitae.

Records are subject to FDA inspection and must be retained for a period of at least two years after the latter of the two dates: 1) the date on which the investigation is terminated or completed, or 2) the date that the records are no longer required for purposes of supporting an application to the FDA to market the device.

10.4.2 Investigator Reports

Per 21 CFR 812.2(b), 812.150(a) and/or the Investigator Agreement, and/or IRB procedures, the Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 6. These are also subject to regulatory authority inspection and the retention requirements described in Section 6.7.1.

Table 6. Investigator Reports

Report	Submit To	Time	Description
Unanticipated Adverse Device Effect (UADE)	Sponsor*	24 hours of awareness	The Investigator must notify the Sponsor, in writing, of any UADE within 24 hours of awareness of event.
	Local IRB	10 working days or less as required by local IRB policy	The Investigator must submit to the reviewing IRB a report of any UADE as soon as possible but not more than 10 working days after the Investigator first learns of the effect.
Serious Adverse Event (SAE)	Sponsor*	24 hours of awareness	The Investigator must notify the Sponsor, in writing, of any SAE within 24 hours of awareness of event.
	Local IRB	10 working days or less as required by local IRB policy	The Investigator must submit to the reviewing IRB a report of any SAE as soon as possible but not more than 10 working days after the Investigator first learns of the effect.
Withdrawal of IRB approval	Sponsor*	5 working days	The Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Deviation from protocol in emergency	Sponsor*	24 hours of awareness	Deviations from the study protocol that are made to protect the life or physical well-being of a patient in an emergency situation must be reported within 24 hours of awareness of event after the emergency occurred.
	Local IRB	5 working days or less as required by applicable IRB policy	Deviations from the study protocol that are made to protect the life or physical well-being of a patient in an emergency situation must be reported within 5 working days after the emergency occurred.
Deviation from protocol that affects the scientific soundness of the study plan or the rights, safety, or welfare of human subjects	Sponsor*	Prior approval	Prior approval by the Sponsor is required when a deviation of this nature is anticipated.
Failure to obtain informed consent	Sponsor*	5 working days	If a study device was used without obtaining informed consent, the Investigator must notify the Sponsor within 5 working days of the use of the device.
	Local IRB	5 working days	If a study device was used without obtaining informed consent, the Investigator must notify the IRB within 5 working days of the use of the device.
Final report	Sponsor*	3 months	The Investigator must submit this report to the Sponsor within 3 months after the termination or completion of the study, or after the Investigator's participation in the study is complete.
	Local IRB	3 months	The Investigator must submit this report to the IRB within 3 months after the termination or completion of the study, or after the Investigator's participation in the study is complete.

*Sponsor and/or Sponsor representative

10.5 Sponsor Records and Reports

10.5.1 Sponsor Records

Per 21 CFR 812.2(b) and 812.140(b), the following records must be maintained in one location and available for regulatory authority inspection:

- All correspondence pertaining to the investigation with another Sponsor, Investigators, the reviewing IRB, the Sponsor representative, and FDA;
- Records of shipment and disposition of a device;
- Signed Investigator Agreements, financial disclosure, and curriculum vitae;
- The name and intended use of the device;
- The objectives of the investigation;
- A brief explanation of why the device is not a significant risk device;
- The name and address of each Investigator;
- The name and address of each IRB;
- A statement of the extent to which the good manufacturing practices (21 CFR 820) were followed in manufacturing the device; and
- Records concerning complaints and adverse device effects whether anticipated or not.

10.5.2 Sponsor Reports

Per 21 CFR 812.2(b) and 812.150(b), the Sponsor is responsible for the reports listed in Table 7.

Table 7. Sponsor Reports

Report	Submit To	Timeline	Description
Unanticipated Adverse Device Effect (UADE)	FDA, all reviewing IRBs, and Investigators	10 working days	The Sponsor must report the results of an evaluation of a UADE to FDA and all reviewing IRBs and Investigators within 10 working days after the Sponsor first receives notice of the adverse effect.
Withdrawal of IRB approval	FDA, all reviewing IRBs, and Investigators	5 working days	The Sponsor must notify FDA and all reviewing IRBs and participating Investigators of the withdrawal of IRB approval of an investigation (or any part of an investigation) within 5 working days of receipt of the withdrawal of approval.
Progress report	Reviewing IRBs	Annually	At regular intervals and at least yearly, the Sponsor must provide progress reports to all reviewing IRBs.
Final report	Reviewing IRBs	6 months	For a non-significant risk device, the Sponsor must submit a final report to all reviewing IRBs within 6 months after completion or termination.
Recalls and device disposition	FDA and all reviewing IRBs	30 working days	The Sponsor must notify FDA and all reviewing IRBs of any request that an Investigator return, repair, or dispose of any investigational device. The notice must be made within 30 working days after the request is made and must state why the request was made.
Significant risk device determination	FDA	5 working days	If an IRB determines that the device is a significant risk device and not a non-significant risk device as the Sponsor had propose to the IRB, a report must be submitted to FDA within 5 working days after the Sponsor learns of the IRB determination.

11 Publication Policy

The conduct and results of this investigation will be documented in investigation reports prepared by the Sponsor or Sponsor representative. Because this investigation is a multicenter investigation, it is intended that the combined clinical data from all participating sites will be presented at an academic meeting and/or published. Individual Investigators will not publish or present results prior to publication of the combined results, without prior written consent from the Sponsor, which may be withheld by the Sponsor in its sole discretion.

12 Bibliography

Please see Appendix O for a list of publications referenced within this protocol.

13 Glossary

Adverse Event (AE)
An adverse event is any untoward medical occurrence in a clinical study subject. An adverse event would be any unfavorable or unintended sign, symptom, or disease that appears or worsens during the clinical study regardless of the relationship to the device. An adverse event would include any clinically significant laboratory value, as determined by the investigator, for routine laboratory results. An abnormal laboratory value is considered clinically significant if the investigator determines that the subject requires treatment, or if he/she would
conduct a repeat test to verify normalization.

Adverse Event Reports
Investigator reports of all serious adverse events, injuries, and deaths given to the Sponsor, the IRB, and the FDA or appropriate regulatory body.

Allergic Reaction
The body's response to an allergic stimulus. This can be localized to one area or generalized and may include rash, itching, hives, swelling, difficulty breathing, and/or low blood pressure.

Anatomic Application Site
Approximate surface area of the target application site, measured by adding one (1) centimeter to both greatest perpendicular distances of the bleeding site and multiplying the two values.

$$Anatomic\ Application\ Site\ (cm^2) = (greatest\ perpendicular\ length, cm + 1\ cm) \cdot (greatest\ perpendicular\ width, cm + 1\ cm)$$

Anatomic Site
Approximate surface area of bleeding site, measured by multiplying the greatest perpendicular distances of the bleeding site.

$$Anatomic\ Site\ (cm^2) = (greatest\ perpendicular\ length, cm) \cdot (greatest\ perpendicular\ width, cm)$$

Bleeding Site
True surface area of wound, or lesion from which blood egress is observed..

Blood Modifiers
Drug category that includes agents that modify properties of human blood (anticoagulants, antiplatelet agents, hemostatics, heparin antagonists, thrombolytic agents).

Case Report Form (CRF)
A form designated to record all of the protocol-required information that is to be reported to the Sponsor on a clinical investigation subject.

Clinical Investigation
A systematic study designed to evaluate a product (drug, device, or biologic) using human subjects in the treatment, prevention, or diagnosis of a disease or condition as determined by the product's benefits relative to its risks.

Clinical Research
Study of a drug, biologic, or device in human subjects with the intent to discover potential beneficial effects and/or determine its safety and efficacy.

Clinical Research Associate (CRA)
Person employed by the Sponsor or CRO to monitor a clinical study at all participating sites. See also "monitor."

Clinical Research Coordinator (CRC) or Coordinator
Site administrator for the clinical investigation. Duties are delegated by the Investigator. Also called research, study, or healthcare coordinator, and data manager, research nurse, or protocol nurse.

Clinical Trial
Any investigation in human subjects intended to determine the clinical effects of an investigational agent and/or to identify any adverse reactions to an investigational agent to assess the agent's safety and efficacy.

Closure
Terminus of the operative procedure, signified by suturing or stapling the initial skin incision(s).

Common Terminology Criteria for Adverse Events (CTCAE)-2009
All procedure complications/adverse events through final follow-up will be reported and graded as per CTCAE-2009:

- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living;
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living;
- Grade 4: Life-threatening consequences; urgent intervention indicated; or
- Grade 5: Death related to AE.

Completion/Discontinuation Form
A form designated to inform the Sponsor that a subject has discontinued from/completed the clinical investigation. This form should be faxed to the Sponsor immediately after a subject's discontinuation or completion.

Complication
An undesirable or unexplained clinical event that results in death, injury, or invasive intervention. Complications may or may not be related to the investigational device.

Contaminated
Procedures in which gross contamination is present at the surgical site in the absence of obvious infection. Contaminants are the bacteria that are introduced by gross soilage of the surgical field.

Contract Research Organization (CRO)
A person or an organization contracted by the Sponsor to perform one or more of a Sponsor's investigation-related duties and functions.

Control Group
A comparison group of study subjects who are not treated with the investigational agent. The subjects in this group may receive no therapy, a different therapy, or a placebo.

Data
Factual information (such as measurements or statistics) used as a basis for reasoning, discussion, or calculation.

Death
All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Demographic Data
Refers to the characteristics of study participants, including sex, age, family medical history, and other characteristics relevant to the study in which they are enrolled.

Device
An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is intended for use in the diagnosis, cure, treatment or prevention of disease. A device does not achieve its intended purpose through chemical action in the body and is not dependent upon being metabolized to achieve its purpose.

Device Accountability Records Log
Required documentation for material accountability, quantity used and left over, and date of disposal.

Device Malfunction
A product malfunction or user error, which caused an adverse event.

Dirty
A surgical procedure performed when an active infection is already present.

Discharge Form
A form designed to collect the required protocol information obtained at subject discharge.

Documentation
All forms of records that describe or document study methods, conduct and results, including any adverse events and actions taken.

eCRF
Electronic case report form.

Efficacy
A product's ability to product beneficial effects on the duration or course of a disease. Efficacy is measured by evaluating the clinical and statistical results of clinical tests.

Embolism
The lodging of an embolus, a blockage-causing piece of material, inside a blood vessel. The embolus may be a blood clot, a fat globule, a bubble of air or other gas, or foreign material.

Enrollment
Enrollment in the study occurs when a patient meets the general inclusion/exclusion criteria, signs the informed consent form, meets the intra operative inclusion criteria and is randomized in the study.

eGFR
Estimated Glomerular Filtration Rate.

Food and Drug Administration (FDA)
Department within the United States Department of Health and Human Services. Enforces Food, Drug and Cosmetics Act and related federal public health laws. Grants IND, IDE, PMA, and NDA approvals.

Good Clinical Practice (ICH E6/GCP)
International ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing, and reporting studies. Ensures that data reported is credible and accurate, and that subject's rights and confidentiality are protected.

Hemorrhage
Blood flow external to an intact blood vessel lumen. The American College of Surgeons Advance Trauma Life Support Hemorrhage Classification System is as follows: Class I Hemorrhage involves up to 15% of blood volume. There is no change in vital signs and fluid resuscitation is not usually necessary. Class II Hemorrhage involves 15-30% of total blood volume. A patient is often tachycardic (rapid heartbeat) 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. The patient may exhibit slight changes in behavior. Volume resuscitation with crystalloids (saline solution or Lactated Ringer's solution) is all that is typically required. Blood transfusion is typically not required. Class III Hemorrhage involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral perfusion (shock), such as capillary refill worsens, and the mental status worsens. Fluid resuscitation with crystalloid and blood transfusion are usually necessary. Class IV Hemorrhage 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.

Hemostasis
Complete cessation of bleeding.

Hemostasis Maintenance
Continued cessation of bleeding for a minimum of 5 minutes after the 7 minute endpoint evaluation.

Human Subject
A patient or healthy individual participating in a research study. A living individual about whom an Investigator obtains private information or data through intervention or interactions.

IDE
Investigational Device Exemption.

Inclusion Criteria
Refers to the characteristics that must be met by a subject in order to participate in a clinical investigation, as outlined in the protocol.

Infection
The state produced by the establishment of an infective agent in or on a suitable host. The Centers for Disease Control and Preventions' wound classification system is as follows: Clean [Class C (I), an uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered] and Clean-contaminated [Class CC (II), operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination] are allowed. Contaminated [Class CO (III), open, fresh, accidental wounds, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in the category.] and Dirty or Infected (Class D (IV) old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera] will be excluded.

Inflammatory and Immune Responses
The reaction of the body to foreign material mediated through the blood supply.

Informed Consent (IC)
The voluntary verification or a patient's willingness to participate in a clinical trial, along with the documentation thereof. This verification is requested only after complete, objective information has been given about the trial, including an explanation of the objectives, potential benefits, risks and inconveniences, alternative therapies available, and of the subject's rights and responsibilities.

Informed Consent Form (ICF)
A written document that contains relevant information about the clinical investigation and that is signed and date by the subject.

Injury to Normal Tissue
Cellular necrosis or damage.

INR
International Normalized Ratio – a calculated made to standardize prothrombin time.

Institution or Site
Location of research. Retains ultimate responsibility for human subject regulation compliance.

Institutional Review Board (IRB)
An independent body consisting of medical professionals and non-medical members responsible for reviewing and providing initial and continuing approval of research in human subjects and verifying that the safety, integrity, and human rights of subjects participating in a particular clinical investigation are protected.

Intraoperative
Skin incision to skin closure.

Investigator
A medical professional, usually a physician, under whose direction an investigational device is administered.

Ischemia
Lack of delivery of oxygen and other nutrients to tissue.

Ligation
Tying a duct or blood vessel with a ligature.

Local tissue necrosis or injury
Morphological changes indicative of cell death and caused by the progressive degradation action of enzymes. It may affect groups of cells or part of a structure or an organ.

Monitor
Person employed by the Sponsor or CRO who reviews study records to determine that a study is being conducted in accordance with the protocol. A monitor's duties may include, but are not limited to, helping to plan and initiate an investigation, and assessing the conduct of investigations. Monitor work with the clinical research coordinator to check all data and documentation from the investigation. See also Clinical Research Associate (CRA).

Monitoring
Reviewing a clinical investigation, ensuring conduct, proper records and reports are performed as stated in the clinical protocol, standard operating procedures, GCP and by regulatory requirements.

National Nosocomial Infections Surveillance (NNIS) System
An ongoing collaborative surveillance system sponsored by the Centers for Disease Control (CDC) to obtain national data on nosocomial infections.

Overall Survival
An assessment to determine whether a patient is alive or deceased..

Patient
Individual seeking medical care.

Postoperative
The time interval from skin closure until hospital discharge.

Preclinical testing
Before a drug or device may be tested on humans, preclinical studies must be conducted either *in vitro* but usually *in vivo* on animals to determine that the drug or device is safe.

Preoperative Form
A form designed to collect the required protocol information obtained during the preoperative period.

Principal Investigator
An individual responsible for the conduct of the clinical investigation at an investigational site. In the event the investigation is conducted by a team of individuals at the investigational site, the Principal Investigator is the responsible leader of the team.

Protocol
A detailed plan that sets forth the objectives, study design, and methodology for a clinical trial. A study protocol must be approved by an IRB before investigational drugs or devices may be administered to or used in humans.

Protocol Amendment
Changes or clarifications made in writing to the original protocol.

PTT
Partial thromboplastin time.

Quality Assurance
Systems and procedures designed to ensure that a study is being performed in compliance with Good Clinical Practice (GCP) guidelines and that the data being generated is accurate.

Randomization
Investigation participants are usually assigned to groups in such a way that each participant has an equal chance of being assigned to each treatment (or control) group. Since randomization ensures that no specific criteria are used to assign any patients to a particular group, all the groups will be equivalent.

Randomized Study Device (RSD)
Investigational device (PerClot) or control device (Arista).

Regulatory Affairs
In clinical trials, the department or function that is responsible for ensuring compliance with government regulations and interacts with the regulatory agencies.

Research
Systematic investigation designed to develop or contribute to generalizable knowledge. Includes Clinical Research.

Risk-Benefit Ratio
Risk to individual subjects versus potential benefits.

Safety Reports
FDA or other regulatory body reports required by Investigator for any serious and unexpected adverse experience.

Serious Adverse Event (SAE)
An adverse event which results in any of the following outcomes: 1) death, 2) a life-threatening adverse event, 3) inpatient hospitalization or prolongation of existing hospitalization, 4) persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, 5) a congenital anomaly or birth defect, or 6) other, as determined by the investigator.

Signs or Symptoms of Adhesion Formation
Possible signs or symptoms of adhesion formation include pain with deep breathing, pain during exercise or when stretching, chest pain, or bowel obstruction.

Signs or Symptoms of Bleeding
Possible signs or symptoms of bleeding include tissue inflammation and pain; weakness; lightheadedness; shortness of breath; decreased blood pressure; increased pulse; blood in stool; blood in urine; and blood in vomit.

Sponsor
An individual, company, governmental agency, academic institution, private organization, or organization that takes responsibility for and initiates a clinical investigation.

Standard Operating Procedure (SOP)
Official, detailed, written instructions for the management of clinical trials. SOPs ensure that all the functions and activities of a clinical trial are carried out in a consistent and efficient manner.

Standard Treatment
The currently accepted treatment or intervention considered to be effective in the treatment of a specific disease or condition.

Sub-Investigator
Helps conduct investigation at a study site.

Subject
Participant in an investigation. See "Human Subject."

Subject Log
A log designed to document all subjects who undergo a surgical procedure in which bleeding is observed and are enrolled into either the treatment or control arm.

Suture
To unite, close, or secure with a strand of fiber.

Target Application Site
True surface area intended for RSD application in accordance with its Instructions For Use (IFU).

Thrombosis
Local coagulation or clotting of the blood in a part of the circulatory system.

Thromboembolism
Obstruction of a blood vessel by a blood clot that has become dislodged from another site in the circulation.

Total Hysterectomy
Surgical removal of the body, fundus, and cervix of the uterus.

Unanticipated Adverse Device Effect (UADE)
Any serious adverse effect on health or safety or 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 investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Well-being
Subject's physical and mental soundness.

Appendix A: PerClot Instructions for Use

PerClot® Polysaccharide Hemostatic System
Instructions for Use [L6421.014]

Caution: Investigational Device. Limited by United States Law to Investigational Use.

Read *Instructions for Use* prior to using this product.

Device Description

PerClot® Polysaccharide Hemostatic System (hereinafter referred to as PerClot) is a medical device composed of absorbable polysaccharide granules and delivery applicators. The granules are biocompatible, non-pyrogenic and derived from purified plant starch. The granules do not contain any human or animal components. PerClot granules have a molecular structure that rapidly absorbs water, forming a gelled adhesive matrix that provides a mechanical barrier to further bleeding and results in the accumulation of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.). One gram of PerClot absorbs at least 19 mL of water. The gelled adhesive matrix thus promotes the normal, physiological clotting cascade. PerClot granules are enzymatically degraded by alpha-amylase and glucoamylase and by macrophages. Based on preclinical studies, absorption normally requires several days and is dependent on the amount of material applied on the wound and the site of use.

Intended Use

The intended use for PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.

Contraindications

- Do not inject or place PerClot into blood vessels as potential for embolization and death may exist.
- Do not inject into bladder or ureteral lumen.
- Do not use in patients who have known sensitivity to starch or starch-derived materials.

Warnings

PerClot should not be used:

- In subjects undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis);
- In subjects who have a clinically significant coagulation disorder or disease, defined as a platelet count <100,000 per microliter, an International Normalized Ratio >1.5, or a PTT more than 1.5 times outside the laboratory's normal reference range;
- In subjects who used corticosteroids (excluding inhalers, eye-drops, and dermatologic corticosteroids) within 6 weeks prior to surgery;
- In subjects who have undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery;

- In subjects who have been treated with an investigational product and have not completed the entire follow-up period for that investigational product;
- In subjects who are pregnant (as confirmed by a pregnancy test), planning on becoming pregnant during the follow-up period, or actively breast-feeding;
- In subjects with poor blood glucose control as per glycosylated hemoglobin > 9%. and
- In subjects with an active or potential infection at the surgical site, or whose surgical wound is defined as wound classification CO (Contaminated) or D (Dirty or Infected) based upon the Centers for Disease Control and wound classification system.

NOTE: PerClot is predicted to activate Complement C3 because of its activity and fluid absorption capacity.

NOTE: The expected rate of absorption will vary depending on anatomic location. Elevated peri-operative blood glucose levels may also be associated with increased rate of wound infection. Elevated blood glucose levels in the immediate postoperative period may affect wound healing.

NOTE: The safety and effectiveness of PerClot have not been clinically evaluated in pediatric patients, on ophthalmic or neurologic tissues, or in laparoscopic cases.

NOTE: Once hemostasis is achieved, excess PerClot should be removed from the site of application by irrigation and aspiration. In an in vitro study where PerClot was agitated to ensure complete hydration, the average maximum swell capacity for each gram of PerClot in deionized water, saline, and blood were 59.7 mL, 27.1 mL, and 11.0 mL, respectively. Under these conditions the time to maximum swelling was 10 minutes. Dry, white PerClot should be removed. The possibility of the product interfering with normal function and/or causing compression necrosis of surrounding tissues due to swelling is reduced by removal of excess dry material.

Precautions

- PerClot is not recommended as a primary treatment for coagulation disorders.
- PerClot is intended to be used in a dry state. Contact with fluids prior to application will result in the loss of hemostatic properties.
- PerClot is not intended as a substitute for good surgical practice, and in particular, the proper use of conventional procedures (such as ligature) for hemostasis. Blood vessels with a diameter of $\geq$ 2mm, suture line gaps $\geq$ 2mm, and large needle holes $\geq$ 2mm must be ligated prior to PerClot application.
- Combined use of PerClot with other topical hemostatic agents has not been studied in controlled clinical trials.
- Remove excess PerClot granules once hemostasis is achieved. This is particularly important in and around the spinal cord and foramina of the bone since unsaturated granules may swell and compress the surrounding tissues.
- PerClot should not be mixed with methyl methacrylate or other acrylic adhesives as it may reduce the adhesive strength and compromise the attachment of prosthetic devices to bone tissue. Excess granules should be fully removed from bony surfaces by irrigation prior to the use of adhesives.
- As with other hemostatic agents, do not allow PerClot to enter into cell saver equipment, extracorporeal cardiopulmonary bypass circuits or autologous blood salvage circuits. Granules of PerClot or fragments of gelled PerClot may pass through 40 micron transfusion filters of blood salvaging systems.

Potential Adverse Events

Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following:

- Adhesions or fibrosis;
- Anaphylaxis;

- Blockage of the bladder or ureteral lumen;
- Blockage of the bypass system;
- Cancer recurrence and/or progression;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Embolism;
- Failure of deep or superficial wound healing;
- Failure to obtain hemostasis;
- Fever;
- Hemorrhage;
- Infection;
- Peri-operative hyperglycemia;
- Exacerbation of surgical procedure-associated adverse events;
- Swelling and compression of pressure-sensitive tissues and structures;
- Thromboembolism;
- Thrombosis; and
- Toxicity.

How Supplied

Contents of the PerClot package are supplied sterile for single-patient use only. These contents are sterilized by gamma irradiation and should not be re-sterilized. Discard any unused material from opened or damaged product.

PerClot should be stored between 0°C and 25°C.

PerClot should be used immediately after the package is opened.

Each box of PerClot supplied will contain five separate packages. Only two 5 gram bellows (packages) can be used per subject.

Preparation

1. Visually inspect the sealed packages. If either package has been previously opened or damaged, discard and replace with a new package.
2. Remove the applicator from the package.
3. Remove the granule dispenser (bellows) from its package. Remove the cap using a counter-clockwise turning motion (Fig. 1).
4. Connect the bellows firmly to the end of the applicator handle (Fig. 2). The system is now ready for use (Fig. 3). Pump the particle dispenser/bellows to deliver granules directly to the site of bleeding (Fig. 4).

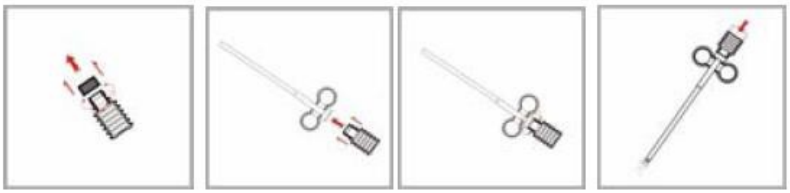


Fig.1 Fig.2 Fig.3 Fig.4

Directions for Use

1. Perform conventional methods for hemostasis, including, but not limited to, pressure and ligature. Ligate any vessels ≥ 2mm, suture line gaps ≥ 2mm, and large needle holes ≥ 2mm in diameter.
2. Confirm that there is bleeding.
3. Determine that there is bleeding which meets the predefined criteria. Remove all excess blood from the intended site by blotting, wiping, or suctioning. Identify and expose the source of bleeding of the wound. Ensure surface to which hemostat is being applied is dry and free from blood/fluid prior to application. Removing excess blood/fluid is critical to maximizing the hemostatic performance as it allows the PerClot granules direct contact with the site and source of active bleeding.
4. Pump the bellows bottle to deliver granules directly to the site of bleeding. Immediately apply a liberal amount of PerClot granules directly to the source of bleeding. Thoroughly cover the lesion with a layer of granules 3 to 4 mm in thickness. Extend the product application to approximately 0.5cm (or 5 mm) beyond the edge of the site of bleeding. The amount of application will depend upon the size of the bleeding site, contour of the bleeding site, and severity of bleeding. The amount of PerClot granules applied will increase with increasing size of the bleeding site and severity of bleeding.

   NOTE: Do not apply more than the entire contents of up to two 5 gram bellows of PerClot implant material per subject.
5. The PerClot granules will help identify the source(s) of active bleeding; granules over source(s) of active bleeding will stain with blood. Additional PerClot granules should be applied to these area(s).
6. When managing deep wounds, the applicator tip must be as close to the source of the bleeding as possible without contacting blood.

   CAUTION: Avoid contacting the applicator tip with blood as this may occlude the applicator. If this occurs, replace applicator tip, if available. If this occurs and a replacement tip is not available, use a stylus to reestablish the delivery pathway by inserting the stylus through the blocked area. Do not attempt to trim the applicator tip.
7. Gentle manual pressure will be applied until hemostasis is achieved. Gentle manual pressure will be applied until the first time point (5 minutes), and again between the first and second time points (7 minutes).

   NOTE: Some materials such as standard gauze may adhere to the formed blood clot. Irrigation with saline before carefully removing the gauze is recommended. If standard gauze is adhered to the formed blood clot, the gauze should be fully saturated with saline, then gently and slowly peeled away. The use of a non-adhering substrate to apply pressure is recommended.

   NOTE: To optimize the hemostatic performance of PerClot, it is important to ensure that the granules come into direct contact with the bleeding surface.
8. Once hemostasis is achieved, remove excess granules carefully and completely by gentle saline irrigation and aspiration.

   NOTE: Following the application of PerClot for epicardial bleeding within the pericardial cavity and achievement of hemostasis, the pericardial cavity should be rinsed with up to 70cc of fluid per 1 gram of PerClot applied, which should be removed with suction, in order to ensure removal of excess particles. Observe the pericardial cavity for a minimum of 10 minutes after initial application for product swelling.

Product Information Disclosure

Handling and storage of this device by the user, as well as factors related to the patient, the patient's diagnosis, treatment, surgical procedures, and other matters beyond manufacturer's control, may directly or indirectly affect this device and the results obtained from its use. This device should not be used except on the order of a physician.

Disclaimer of Warranties, Limits of Liability

CRYOLIFE DISCLAIMS ALL EXPRESS AND IMPLIED WARRANTIES WITH RESPECT TO THIS PRODUCT, INCLUDING BUT NOT LIMITED TO THE EXPRESS AND IMPLIED WARRANTIES OR MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT SHALL CRYOLIFE BE LIABLE FOR INCIDENTAL OR CONSEQUENTIAL DAMAGES. In the event that such disclaimer is found invalid or unenforceable for any reason: (i) any action for breach of warranty must be commenced within one year after any such claim or cause of action accrued and (ii) the remedy for any such breach is limited to the replacement of the product.

1655 Roberts Boulevard, NW
Kennesaw, GA 30144 USA

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Appendix B: Sample Subject Informed Consent Form

Sample Subject Informed Consent Form

Title: Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System

The C.L.O.T. Investigation

Protocol Number: PCT1101.011-C (02/15) Amendment 09

Sponsor: CryoLife, Inc.
1655 Roberts Blvd NW
Kennesaw, Georgia 30144
USA

Monitor: NAMSA
400 Highway 169 South, Suite 500
Minneapolis, MN 55426
USA

IMARC
22560 Lunn Road
Strongsville, OH 44149
USA

This form is called an "Informed Consent Form." It gives you details about the research study. It also tells you what you will need to do if you decide to take part in this research study. The form provides details about the following things listed below about the research study:

- Purpose;
- Research study design;
- Procedures;
- Risks;
- Discomforts; and
- Benefits.

You should read this form carefully. You should also ask any questions before you decide if you want to take part in this research study. Take as much time as you want to decide. You may take this form home before signing it. You can think about it or talk about it with your family, friends, or your family doctor before deciding.

It is important that you understand the basic principles that apply to everyone who takes part in this research study. These principles are listed below.

1. Taking part in the research study is completely voluntary.
2. If you decide not to take part in this research study, the care and treatment you would normally have received will not be limited or taken away.
3. You may withdraw from the research study at any time. The care and treatment you would normally have received will not be limited or taken away. If you decide to withdraw from the

research study, you do not need to give any reasons. If you decide to withdraw from the research study, you will not incur any costs related with the research-related procedures that occurred before you withdrew from the research study.

This consent form may have words that you do not understand. Please ask the study doctor or the study staff to explain anything you do not clearly understand.

Once you read this form and all your questions have been answered, you will be asked if you want to take part in this research study. If you choose to take part, you will be asked to sign this form before any study-related procedures are done. You will be given a signed copy of this form for your records.

What is the purpose of the research study?

You have been asked to take part in this research study because you need surgery. As part of this surgery, your study doctor will need to do things to prevent bleeding. Your study doctor may need to take certain actions to stop bleeding when it occurs (hemostasis). Your study doctor now has different options to stop the bleeding during surgery when control of bleeding by pressure, ligature, or other conventional means is either ineffective or impractical. Currently, the standard treatment for someone who has bleeding during surgery is manual pressure, cautery, and sutures. These are the standard, first attempt treatments applied generally as well as in this trial. A topical hemostat is a material that is applied to stop the bleeding. Some topical hemostats have been approved for use in the United States. PerClot®, which is also a topical hemostat and is being studied in this research study, has not been approved in the United States.

The purpose of this research study is to find out if PerClot is safe and effective as a part of surgery to stop bleeding. PerClot is a device in granule form made from the starch of a potato. The starch has been engineered in a way that the powder absorbs water and helps to form a clot. This kind of device (topical hemostat) is intended for use in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, or other conventional procedures is ineffective or impractical. PerClot is left in your body after surgery. In animal studies, it has been found that PerClot is absorbed by the body in a few days after surgery. This has not been demonstrated in humans and can vary depending on the amount of device applied. This can also depend where it is applied.

This research study will collect follow-up data after PerClot is used. PerClot is an investigational device in the United States. This means it has not been approved by the Food and Drug Administration (FDA). PerClot has been an approved medical device in Europe since 2008.

This research study plans to include about 324 patients. The research study will take place at up to twenty five hospitals in the United States.

What is the design of the research study?

This research study will look at how safe and effective PerClot is compared to another currently approved topical hemostat. If you agree to be in this study and you are undergoing surgery, you will be randomly placed (selected by chance, much like flipping a coin) into one of the two research study groups. Half of the patients will receive PerClot and will be in the 'research group.' The other half of the patients will receive an approved standard topical hemostat and will be in the 'control group.' You have a 50/50 chance of receiving either PerClot or the approved standard topical hemostat.

The approved topical hemostat has been approved by FDA. It is used in the United States.

Even if you qualify to be in this research study before your surgery, there is a chance that you may not be included in this research study. During your surgery, your study doctor first will perform standard methods used to stop bleeding. These methods may include:

- Suture;
- Clips;
- Electrocautery;
- Reversal of coagulopathy, as applicable;
- Argon beam coagulator; or
- Staples.

If there is still bleeding, then you may be included in the research study. If there is no bleeding or too much bleeding, you will not be able to take part in this study. You will be included in the research study only if there is a certain amount of bleeding. You will not know if you were included in this research study until after you wake up from your surgery. You will not know which treatment you receive (research or control) until you complete the research study.

What will I be asked to do if I am in this research study?

The expected length of time that you will be in the research study is about 6 weeks. If you are an oncology patient, you will be contacted by the study doctor's office at 24 months. The expected length of time from informed consent signing to follow-up visit is approximately 2 months. The study will not be completed until the last patient enrolled completes the 6 week follow-up.

To participate in this research study, you must be at least 22 years old. You must also be able to do the things listed below:

1) You must complete the following screening tests and examinations which will determine if you are eligible to take part in this research study.
   - Physical exam and vital signs (height, weight, body temperature, blood pressure);
   - Medical history;
   - Blood tests; and
   - Pregnancy test (females only).

   These tests are usually done on people with your medical condition even if they are not in this research study. After completing these procedures, it may be determined that you are not eligible to take part in this research study. If so, your study doctor will tell you about other treatment options.

2) You will have the following tests performed during your surgery:
   - Vital signs (blood pressure, body temperature); and
   - Blood glucose measurement.

You will have the following tests performed after surgery (prior to your leaving the hospital):

- Vital signs (blood pressure, body temperature);
- Blood glucose will be measured by drawing blood from a vein in your arm or by finger stick at 6 hours, 12 hours, and 24 hours after your surgery;
- Other blood tests; and
- Thromboembolism assessment.

3) You must have a follow-up visit 6 weeks after your surgery. The study will not be completed until the last patient enrolled completes the 6 week follow-up.

   These follow-ups will require you to return to your study doctor's office. During these follow-up visits, your study doctor will ask about or will do some or all of the exams and tests listed below.

   - Make notes of any signs of suspected bleeding;
   - Make notes of any adverse events (side effects, illnesses, or unpleasant experiences);
   - Make notes of any other operations or hospitalizations that you may have had since your last visit; and
   - Make notes of the medications you have taken since your surgery.

4) Below is a table that gives the general overview of the study-related tests that will be done at each visit.

Visit Type	Procedures Performed at Visit
Screening (before surgery)	Physical exam and vital signs, medical history, blood tests, and pregnancy test (females only)
Surgery	Surgery, blood tests, and additional 12 minute intraoperative hemostatic evaluation
Up to 24 hours after surgery	Blood tests
Discharge (no more than 24 hours before you are discharged from the hospital)	Blood tests

   No matter what group you are in, your study doctor may want you to come back to the office at other times for other follow-up visits if needed. For the purpose of this research study, it is important that you return for the follow-up visits. You should report any side effects, illnesses, or unpleasant events that you have experienced.

5) You should also inform your family doctor if you decide to take part in this research study.

Some things that may exclude you from taking part in the study are listed below.

- You are not at least 22 years old;
- You are sensitive to starch or materials derived from starch;
- Your blood tests indicate that your blood may not clot properly;
- You received certain medications or therapies before surgery (corticosteroids, platelet receptor therapy);
- You are taking part in another research study;
- You are pregnant, plan to become pregnant during the research study, or are actively breast-feeding;

- You have poor blood glucose control; or
- You have an active or suspected infection at the site of surgery.

During your surgery, your study doctor will perform standard methods used to stop bleeding. These methods may include:

- Suture;
- Clips;
- Electrocautery;
- Reversal of coagulopathy, as applicable;
- Argon beam coagulator; or
- Staples.

If there is still bleeding, then you may be included in the research study. If there is no bleeding or too much bleeding, then you will not be included in the research study.

Procedures for the Research Group
If you are randomly chosen (much like flipping a coin) to be in the PerClot treatment group (research group), your study doctor will place PerClot at the site of bleeding. The entire contents of up to two 5 gram bellows of PerClot implant material is expected to be applied per subject. This area will be watched for 7 minutes to see how long it takes to stop the bleeding. If bleeding has stopped 7 minutes after PerClot is applied, your study doctor will continue to observe the site for another 5 minutes. After this time, your surgical incision will be closed. If there is still bleeding 7 minutes after PerClot is applied, your study doctor will use any means necessary to stop the bleeding. Your study doctor can explain what other means may be used to stop the bleeding.

Procedures for the Control Group
If you are randomly chosen (much like flipping a coin) to be in the approved standard topical hemostat group (control group), your study doctor will place an approved hemostat at the site of bleeding. This area will be watched for 7 minutes to see how long it takes to stop the bleeding. If bleeding has stopped 7 minutes after the hemostat is applied, your study doctor will continue to observe the site for another 5 minutes. After this time, your surgical incision will be closed. If there is still bleeding 7 minutes after the hemostat is applied, your study doctor will use any means necessary to stop the bleeding. Your study doctor can explain what other means may be used to stop the bleeding.

What are the possible risks of being in the study?

Surgery and products like the ones used in this research study can cause problems. You need to know that your surgery, PerClot (the investigational device), or the approved standard topical hemostat (the control) may cause all, some, or none of these problems. There may be other risks which are unknown at this time. Your study doctor has been chosen to take part in this research study because he or she has the skills and knowledge to perform the research study procedures and this should reduce your risks.

Risks of Surgery

Even if you are not in this research study, there are risks related to having surgery. Your study doctor will discuss the risks of surgery with you. You will be asked to sign a consent form to have the surgery. The risks related with having surgery may be caused or made worse by the use of PerClot or the approved standard topical hemostat.

The more common and serious possible risks of having surgery may include:

- Abscess formation;
- Adhesion formation;
- Allergic reactions to any drugs given during surgery;
- Anesthesia complications;
- Arrhythmia;
- Atelectasis;
- Bleeding;
- Death;
- Deep vein thrombosis;
- Fluid collection;
- Hematoma;
- Hemothorax;
- Hypoxemia;
- Infection;
- Myocardial infarction;
- Pain;
- Paralysis;
- Pneumothorax;
- Pulmonary embolism;
- Reoccurrence of chest pain;
- Stroke; or
- Tissue necrosis.

There are also risks or discomforts specific to being in this research study that may include:

- Extra blood draws before surgery, during surgery and right after surgery;
- Pregnancy test (females);
- Extra hemostatic assessment, increasing surgical time by up to 12 minutes; and
- Extra follow-up visits after surgery.

Risks Associated with Drawing Blood

Risks associated with drawing blood from your arm include pain, bruising, lightheadedness and, on rare occasions, infection.

Risks of the Research Group (PerClot)

Use of PerClot could result in possible side effects or problems such as those listed below.

- Adhesions or fibrosis;
- Anaphylaxis;
- Blockage of the bladder or ureteral lumen;
- Blockage of the bypass system;

- Cancer recurrence and/or progression;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Embolism;
- Failure of deep or superficial wound healing;
- Failure to obtain hemostasis;
- Fever;
- Hemorrhage;
- Infection;
- Peri-operative hyperglycemia;
- Exacerbation of surgical procedure-associated adverse events;
- Swelling and compression of pressure-sensitive tissues and structures;
- Thromboembolism;
- Thrombosis; and
- Toxicity.

PerClot is predicted to activate Complement C3 because of its activity and fluid absorption capacity.

Risks of the Control Group
Use of the approved standard topical hemostat, which is the standard of care, could result in possible side effects or problems such as those listed below.

- Act as a foci for calculus formation when used in renal pelvis or ureters;
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid;
- Compression necrosis of surrounding tissues due to swelling;
- Compromised attachment of prosthetic devices to bone or tissue;
- Death;
- Effect on glucose load;
- Embolization; and
- Paralysis and nerve damage when used in or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.

What are the possible benefits of being in the research study?

It is not possible to predict if you will or will not get any benefit from being in the research study. The information that is obtained from this research study will be studied further and may be helpful to other patients in the future.

Pregnancy Statement

The effects of PerClot on a fetus are unknown. If you become pregnant or father a child while on this research study, an injury to the fetus may occur that has not been seen before or is worse than seen before.

You cannot be pregnant, plan on becoming pregnant throughout the follow-up period, or be actively breast-feeding.

What other treatment options do I have?

Other treatments can be considered in your case. These options include surgery using other topical hemostats to prevent bleeding which is the standard of care. Your study doctor will go over other surgical options or treatment that he or she uses to try and stop any bleeding. You do not have to be in this research study to receive standard of care.

Your study doctor and your family doctor can give you detailed information about your disease. Your study doctor can also tell you about the benefits for the other treatment options. You should feel free to talk about your disease and your possible outcome with your study doctor and your family doctor. Your study doctor will be available to answer any questions you have about this research study. You are also free to ask your study doctor any question that you want about this research study in the future.

Will my privacy be protected?

A record of your progress while in the research study will be kept on confidential forms by:

- Your doctor;
- The corporate headquarters of the Sponsor; or
- The Sponsor representative.

These records will also be kept at these locations after the research study is complete. The privacy of patients who are in this research study will be protected by reasonable means and as required by law. During the research study or after the research study, the following individuals or groups may have access to medical records which contain your identity.

- Representatives or designees of the FDA;
- International regulatory authorities;
- The Sponsor;
- The Sponsor representative;
- Your study doctor;
- Your family doctor; and
- {Institution name}.

They may need access to your medical records to verify clinical trial procedures and/or data, to the extent permitted by law. By agreeing to participate in this research study and signing this Informed Consent Form, you authorize such access and disclosure as described in this Informed Consent Form.

Data from this research study will be used to gain approval from FDA and other international regulatory authorities. Research records will be stored in a confidential manner to protect your identity. To the extent permitted by applicable law, these records will not be made publicly available. If the results of the research study are published, your identity will be confidential. The names of research study participants are not routinely required to be divulged to FDA. If FDA requires such names, FDA will treat such information as confidential. On rare occasions, disclosure to third parties may be required.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Confidentiality

During the conduct of the research study, information about you and your progress will be kept in a private file:

- By your study doctor;
- At the corporate headquarters of the Sponsor; and
- At representatives of the Sponsor.

Research information that identifies you may be shared with those responsible for ensuring that laws and regulations related to research are being followed, including:

- The reviewing Institutional Review Board (IRB);
- A Data Safety Monitoring Board (DSMB);
- The research study monitor;
- Representatives of the Sponsor;
- The FDA;
- The Office of Human Research Protections (OHRP); and
- International regulatory bodies.

Release of Health Information

If you decide to participate in this research study, information about your health may be used or disclosed for the purposes of conduct this research study. The information obtained in this research study may also be used for other regulatory submission and as required by applicable laws, rules and regulations, as described in this Informed Consent Form. This information may include information from your medical records that is related to this research study, such as:

- Your medical history;
- Medications;
- Test results;
- Diagnoses;
- Treatments;
- Operative reports (reports from operations that you have undergone); and
- Discharge summaries.

Information collected by the study doctor and/or research staff for the purpose of this research study could also be used or disclosed. Such information may include:

- Test results;
- Physical examinations; and
- Information about possible side effects.

Individuals that may use or release this information include:

- Your family doctor;
- Your family doctor's office staff;
- Hospital staff;
- The study doctor;
- Authorized members of the study doctor's research staff;
- The Sponsor;
- Representatives of the Sponsor;
- Parties with which the Sponsor contracts to provide services;
- The study monitor;
- Reviewing IRB;
- DSMB;
- FDA representatives; and
- Other regulatory agencies or entities, including those outside of the United States.

The information released to the individuals listed above will not contain your name or social security number. However, some parties may review records containing information that identifies you to make sure that the research study information is correct. These parties may include:

- Authorized representatives of the Sponsor;
- Parties with which the Sponsor contracts to provide services;
- Reviewing IRB;
- DSMB;
- The FDA; and
- Other regulatory agencies.

Because of the need to provide information to these parties, absolute confidentiality cannot be guaranteed.

Use of Information
This information may be used for the following purposes:

- To determine whether you meet all requirements for participation in the research study;
- To monitor your healthcare during the research study;
- To enable the Sponsor to answer the scientific questions for which the research study was designed including with regulatory agencies outside of the United States; and
- To ensure that the research study has been done properly.

Examples of the use of this information are as follows:

- The Sponsor may use the information in submissions to regulatory agencies throughout the world, such as to request approval of the product used in this research study;
- The Sponsor may use the information for reporting adverse events to regulatory agencies, such as the FDA;
- The Sponsor may also transfer the information to business partners or companies it hires to provide research study-related services;

- Both the Sponsor and the study doctor may use the information to prepare reports or publications of the research study results;
- The Sponsor may also provide overall research study results, including your information, to other study doctors; and
- The Sponsor may reanalyze the data from this research study in the future or combine it with data from other studies for analysis.

Once your information has been released, it may no longer be protected by U.S. federal regulations relating to data privacy. It could be used or re-disclosed in ways other than those listed in this section of the Informed Consent Form.

You have the right to see and receive a copy of your records related to the research study for as long as the study doctor has this information in his/her possession. However, you might not be allowed to see these records until after the study has been completed.

Authorization to Disclose
By signing this Informed Consent Form, you authorize disclosure of information to the Sponsor and review of your medical records by the Sponsor and other authorized people, as described in this section of the Informed Consent Form. You do not have to authorize this disclosure of information. However, if you do not, you will not be able to participate in this research study.

Expiration of Authorization - This information is being disclosed for research study use; there is no expiration date for the authorization to disclose and use this information.

Revoking Authorization to Disclose – You may revoke (withdraw) your authorization to disclose at any time. However, once you do so, you can no longer continue to participate in the research study. Revoking your authorization means taking back the permission you gave the study doctor to share information about you to the Sponsor. Once you revoke your authorization, you can no longer continue to participate in the research study. If you decide to stop participating in this research study, you also have the right to revoke your authorization to disclose information.

If you revoke your authorization, your study doctor will not use or release any more information about you after receiving your request. However, your study doctor will tell the Sponsor that you have stopped early and have revoked your authorization. Your study doctor and the Sponsor can still keep and use any information that has already been received.

If you want to revoke your authorization, you must do so in writing to your study doctor. You can get a form for revoking your authorization from your study doctor. You could also write a letter to your study doctor.

Will I be paid if I participate?

The Sponsor will not pay you to be in this research study. However, reasonable travel expenses may be reimbursed. It is not expected that you will incur any additional costs due to your participation in this research study.

Injury Statement

Medical problems, both likely and unlikely, that are not your fault, your study doctor's fault, the hospital's fault, or the study Sponsor's fault, are a possibility of any research study. If you have a medical emergency and you have followed the directions of your study doctor or other study staff

and the Sponsor determines that the emergency is related to PerClot, the Sponsor will pay for whatever emergency care is needed. The Sponsor will provide no other compensation. Payment for lost wages, disability, emotional distress, or discomfort due to injury is not available. However, you are not precluded from seeking to collect compensation for injury(ies) related to malpractice, negligence, fault, or blame on part of:

- The study doctor;
- The hospital;
- The Sponsor; or
- Anyone else involved in the research study.

Research-Related Injury
Your study doctor will make every effort to prevent physical injury that could result from this research. If physical injury occurs as a result of your participation in this research study, you should contact your study doctor immediately {Investigator name, address, and a 24-hour phone number}.

Who do I call if I have questions or a problem?

Your study doctor will answer any questions you have about this research study. You are free to ask your doctor any questions about this research study that you want to in the future. You can also contact the doctor in charge of this research study {Principal Investigator, doctor name, address, and a 24-hour phone number} with any questions or concerns.

You may also contact the Institutional Review Board at {phone number} if you have any questions about your rights as a research subject or about the conduct of this research study.

Significant New Findings

While you are in the research study, you will be told of any important new findings from this research, both good and bad, that might change your mind about being in the research study. You will also be told of any reasons for changes to the research plan that might change your mind about being in the research study.

Refusal or Withdrawal of Participation

You do not have to be in this research study. You may decide to stop being in this research study at any time without giving a reason. Your study doctor will still take care of you. If you decide not to be in the research study, you will not be penalized or lose any benefits to which you are otherwise entitled. Before withdrawing from this research study, notify your study doctor that you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic for tests. If you decide to stop being in this research study, you should notify [Principal Investigator] at [phone number].

Your study doctor may decide to remove you from this research study, without asking you, if at any time he or she feels that the research study is not in your best interest. Some, but not all, of the reasons you may be removed from this research study are listed below.

- You do not follow the instructions of your study doctor;
- You require another surgery; and/or

- You experience an adverse event (side effect, illness, or unpleasant experience).

The Sponsor may decide to end the research study early. You are free to seek care from a doctor of your choice at any time. If you choose not to be in the research study, you will still receive standard medical care for your condition.

I understand that I am considered an Oncologic Patient and agree to be contacted at 24 months post-device application.

Initial and Date

Informed Consent Form

By signing this Informed Consent, you will not give up any legal rights that you may have in the event of negligence or other fault of anyone involved with this research study.

I have read all of the above. I have asked questions and received answers on things I did not understand. I willingly give my consent to be in this research study. I authorize disclosure of my medical records for purposes of this research study as set forth in this Informed Consent Form. I will receive a copy of this signed and dated Informed Consent Form.

_____
(Printed Name of Subject)

_____ _____
(Date) (Signature of Subject)

I have explained the purpose of the research. I have explained the study procedures and identified those that are investigational. I have explained the possible risks and discomforts as well as potential benefits of taking part or participating in this research study. I have answered any questions regarding the research study to the best of my ability.

_____ _____
(Date) (Signature of Person Conducting Informed Consent Discussion)

Appendix C: Risk Analysis

PerClot® Polysaccharide Hemostatic System
Risk Assessment Summary

Prepared by:

Julissa Piña, Risk Management Associate — Date: 01/30/2017

Reviewed and Approved by:

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J. Ferros, Director, Regulatory Affairs — Date: 1/30/2017

A. Wilson, Director, Polysaccharide Hemostats — Date: 01/30/2017

U. Yüksel, Sr. Director, Medical Adhesives, Sealants, and Hemostats — Date: 01/30/2017
Heather M Pegurnt for Ümit Yüksel

W. Matthews, Sr. VP Operations, Quality, and Regulatory — Date: 01/31/2017

K. Bohlman, Associate Director, Global Marketing — Date: 30JAN2017

W. Northrup, VP, Physician Relations and Education — Date: 01/30/2017

S. Saurini, VP, Quality — Date: 30 Jan 2017

PerClot® Polysaccharide Hemostatic System
Risk Assessment Summary

Executive Summary

This document summarizes the risk assessment process for all phases of the PerClot® Polysaccharide Hemostatic System (PerClot) life cycle. The risk assessment was performed using a qualitative model which characterized the effects of foreseeable hazards associated with the entire life cycle of PerClot. The residual risk analysis was also performed using a qualitative model, which provides an overall assessment of the residual risk after mitigation.

This revision to the Risk Management File was completed in January 2017 to update the residual risk communication to be consistent with modifications to the Instructions for Use (IFU). Additionally, the Risk Management File was brought into compliance with the current revision of the Risk Management Package Development procedure, QA0056.015.

The potential and foreseeable risks and hazards of PerClot were identified. A total of 98 hazards were identified; 59 process hazards and 39 product hazards. Each hazard was evaluated and risk control measures were implemented in order to prevent or reduce the likelihood of the occurrence of the hazard as far as possible. Hazard controls included quality inspections, validations, manufacturing and processing procedures, quality testing, quality reviews, and training. Post-production residual risk was communicated to the user in the Clinical Protocol, Instructions for Use and other product labeling, so that PerClot can be used safely and effectively for its intended purpose.

Based on the Risk Assessment, the benefits of PerClot outweigh the potential risks associated with the device. PerClot is acceptable for its intended purpose given its anticipated clinical benefit and low residual risk.

PerClot® Polysaccharide Hemostatic System
Risk Assessment Summary

1. Scope

This Risk Management Summary summarizes the outcome of the risk management activities conducted for PerClot® Polysaccharide Hemostatic System (PerClot). The risk management activities were conducted in accordance with ISO 14971:2007(E) and BS EN ISO 14971:2012. The process, product, and residual risk analyses were performed using a qualitative model of Risk Management. This revision of the Risk Management File was initiated to update the residual risk communication to be consistent with modifications to the Instructions for Use.

2. Device Description

PerClot® Polysaccharide Hemostatic System (hereinafter referred to as PerClot) is a medical device composed of absorbable polysaccharide granules and delivery applicators. The granules are biocompatible, non-pyrogenic and derived from purified plant starch. The granules do not contain any human or animal components. PerClot granules have a molecular structure that rapidly absorbs water, forming a gelled adhesive matrix that provides a mechanical barrier to further bleeding and results in the accumulation of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.). One gram of PerClot absorbs at least 19 mL of water. The gelled adhesive matrix thus promotes the normal, physiological clotting cascade. PerClot granules are enzymatically degraded by alpha-amylase and glucoamylase and by macrophages. Based on preclinical studies, absorption normally requires several days and is dependent on the amount of material applied on the wound and the site of use.

The investigational device product is available in the following configuration:

Table 1: PerClot Product Code

Product Description	Product Code
5 g	PC0005-CR

3. Indications for Use

The intended use for PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.

4. Criteria for Risk Analysis

4.1 Probability and Severity Ratings

The probabilities and severities of risks associated with each hazardous situation were evaluated and assigned a probability/severity rating. Table 2 provides the probability and severity ratings for PerClot. The severity was determined using the Common Terminology Criteria for Adverse Events (CTCAE) scale. The intent of the probability evaluation was that it included detectability of the hazard.

After the probability/severity rating was determined for each risk item, a risk rating (chart value) was assigned. Table 3 provides the risk rating scale for PerClot.

Table 2: Probability and Severity Ratings

Probability Ratings	**Description**
Low	Unlikely to happen, rare, remote
Medium	Can happen, but not frequently
High	Likely to happen, often, frequent
Severity Ratings	**Description**
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

Table 3: Risk Rating Chart Values

Probability Rating	Severity Rating	Chart Value
Low	1	1
Low	2	2
Low	3	3
Low	4	4
Low	5	5
Medium	1	2
Medium	2	4
Medium	3	6
Medium	4	8
Medium	5	10
High	1	3
High	2	6
High	3	9
High	4	12
High	5	15

4.2 Control Measures and Residual Risk

Each risk was evaluated and reduced as far as possible by control measures (see Table 4). The mitigations and the resulting impact to the risk score were documented in the Risk Analysis table. Mitigations were evaluated to determine whether the mitigation introduced a new hazard. Each introduced hazard was also evaluated and reduced as far as possible.

Table 4: Control Measures

Mode of Control	Table Key	Description
Design	D	Hazard mitigation or prevention by design.
Protection	P	Hazard minimization by protection. This includes prevention of the hazard by testing prior to shipment (quality testing, quality inspection, validation), procedures, and training.

Verification that the risk control measures were implemented in the final design is listed in the Risk Control Verification table. The Risk Control Verification table lists the specifications, manufacturing process procedures, quality inspections and product validations identified in the Risk Analysis table.

Process, product risks and residual risk are disclosed in the Risk Analysis Table. Residual Risk associated with the post production phase of the life cycle is communicated to the user so the device can be used safely and effectively for the intended purpose. Post-production residual risk communication includes the Clinical Protocol, Instructions for Use and other labeling. Documents that communicate residual risk are identified on the Residual Risk Communication Table.

4.3 Process Risk Analysis

Each hazardous situation in the process was evaluated and the assigned risk ratings were plotted on a Pre-Mitigation Chart (Figure 1) and then again after mitigation on a Post-Mitigation Chart (Figure 2). The probabilities and severities of risks associated with each hazardous situation was evaluated and reduced as much as possible by inherently safe design and construction. Post mitigation, the risk-benefit analysis for each individual risk and the overall risk-benefit analysis (weighing all risks combined against the benefit) were re-evaluated to determine if the benefits of PerClot outweighed the process residual risk.

Figure 1: Process Hazard Overview Pre-Mitigation

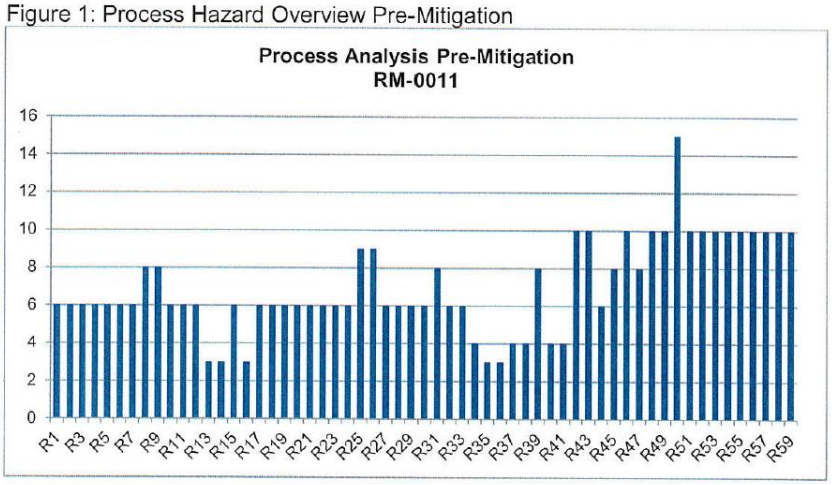
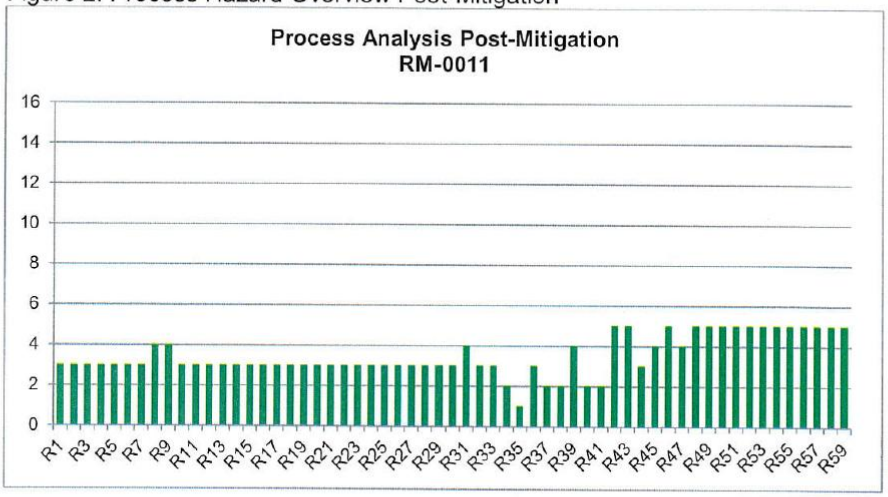


Figure 2: Process Hazard Overview Post-Mitigation



Summaries of mitigations employed:

Raw Materials
Eleven hazards associated with the incoming raw materials utilized in the processing of PerClot were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: incoming inspections and supplier quality audits.

Washing of Raw Starch
Five hazards associated with the washing of the raw starch were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: starch washing procedure, manufacturing processes, and training.

Modification of Starch
Eighteen hazards associated with the modification of the starch were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: modification procedure, manufacturing processes, training, and in-process testing.

Granulation
Two hazards associated with the granulation of the starch were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: manufacturing processes, manufacturing inspections, training, and in-process testing.

Filling
Three hazards associated with the filling of the PerClot bellows were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: weight verifications, quality inspections, and training.

Assembly-Packaging
Eight hazards associated with the packaging of PerClot were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: processing procedures, in-process testing, and line clearance.

Contract Services-Sterilization
Eleven hazards associated with the sterilization of PerClot were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: supplier quality audits, sterilization validation, and quality inspections.

Final Release
One hazard associated with the final release of PerClot was identified. This hazard was evaluated and the following control is in place to lessen/eliminate the hazard: quality control review.

4.4 Product Risk Analysis

Each hazardous situation in the product phase of the life cycle was evaluated and the assigned risk ratings were plotted on a Pre-Mitigation Chart (Figure 3) and then again after mitigation on a Post-Mitigation Chart (Figure 4). The probabilities and severities of risks associated with each hazardous situation were evaluated and reduced as much as possible by inherently safe design and construction. Post mitigation, the risk-benefit analysis for each individual risk and the overall risk-benefit analysis (weighing all risks combined against the benefit) were re-evaluated to determine if the benefits of PerClot outweighed the product residual risk. Residual risk in the post-production phase of the life cycle was communicated to the user in the Instructions for Use and other labeling.

Figure 3: Product Hazard Overview Pre-Mitigation

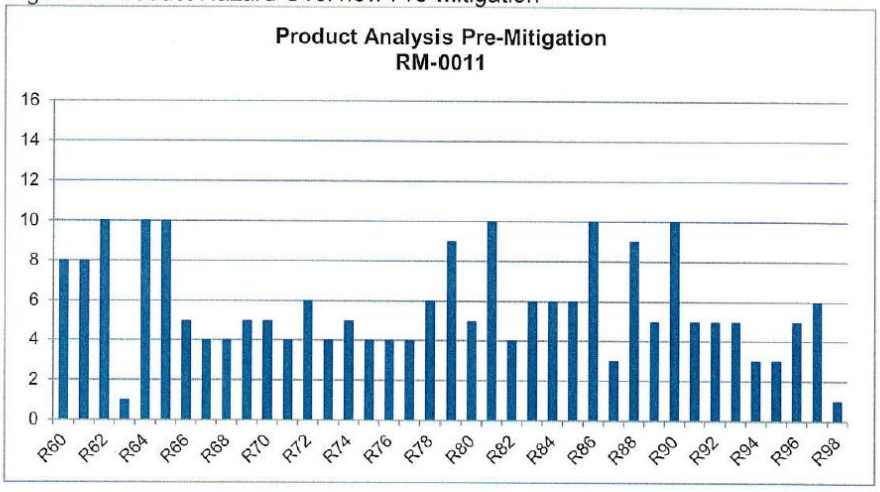
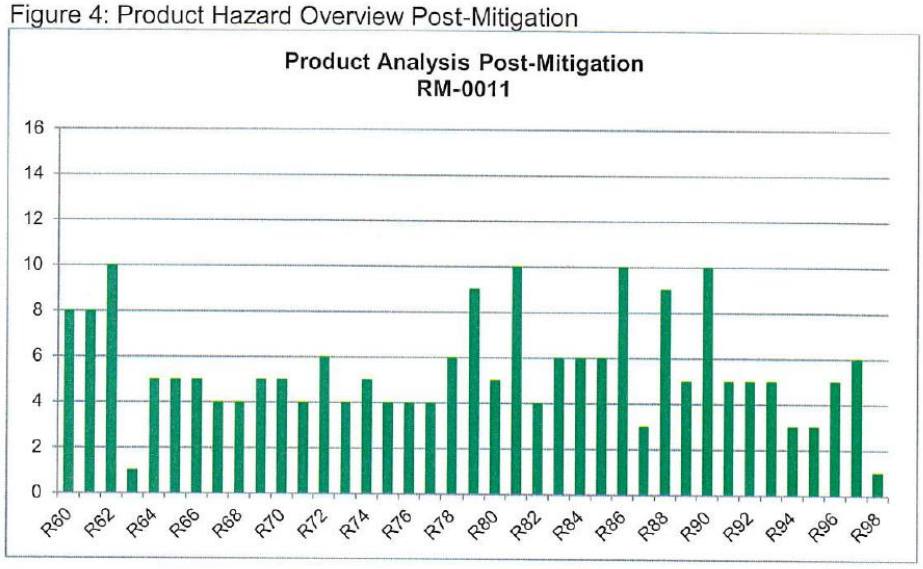


Figure 4: Product Hazard Overview Post-Mitigation



Summaries of mitigations employed:

Storage
Two hazards associated the storage of PerClot were identified. Each hazard was evaluated and the following controls are in place to communicate residual risk: expiry date and storage requirements stated on labeling.

Handling/Transport
Two hazards associated with the handling and transport of PerClot were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazard and to communicate residual risk: investigational device shipping and storage procedures, labeling states not to use if damaged or opened.

Biocontamination
Two hazards associated with biocontamination were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards: terminal sterilization of product and applicators and LAL testing.

Biocompatibility
Three hazards associated with biocompatibility were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards and to communicate residual risk: biocompatibility testing conducted per ISO 10993, and contraindications are identified in labeling.

Misuse
Twenty-two hazards associated with the misuse of PerClot were identified. Each hazard was evaluated and the following controls are in place to communicate residual risk: investigator training, appropriate use described in the IFU, and the clinical protocol.

Patient Selection
Three hazards associated with the patient selection were identified. Each hazard was evaluated and following controls are in place to lessen/eliminate the hazard and to communicate residual risk: clinical protocol, biological risk assessment, and the IFU.

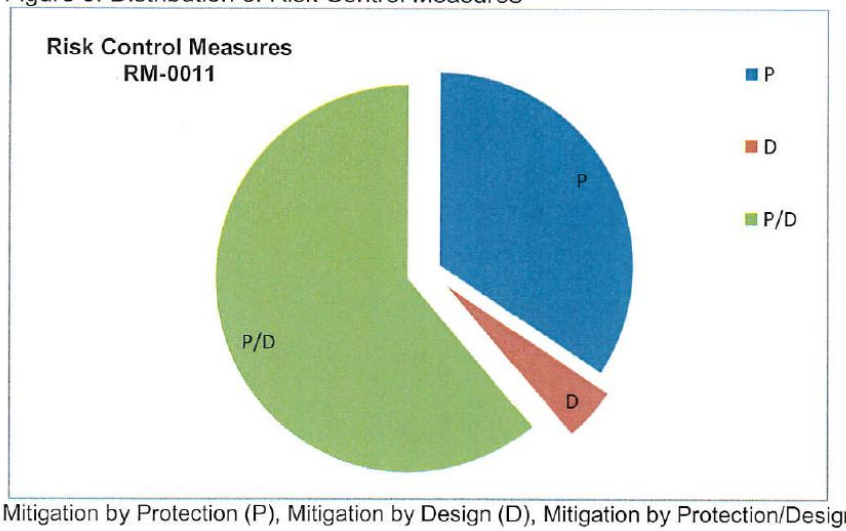
Side Effects
Four hazards associated with side effects were identified. Each hazard was evaluated and the following controls are in place to lessen/eliminate the hazards and to communicate residual risk: clinical protocol, Informed Consent Form, biological risk assessment and the IFU

Disposal
One hazard associated with the disposal of PerClot was identified. This hazard was evaluated and the following controls are in place to communicate residual risk: clinical protocol, investigator training, and the IFU.

5. Residual Risk Overview

While performing the risk analysis, 98 hazards were evaluated and risk control measures were defined where possible. 67 hazards were reduced by control measures. Control measures were not applicable for the remaining 31 hazards. Residual risk was communicated to the end user in the IFU, Clinical Protocol, and other labeling. Figure 5 illustrates the distribution of the assigned risk control measures as documented in the Risk Analysis table.

Figure 5: Distribution of Risk Control Measures



Mitigation by Protection (P), Mitigation by Design (D), Mitigation by Protection/Design (P/D).

6. Overall Statement

The risk/benefit analysis for each risk and the overall risk benefit analyses justify the residual risks of PerClot· Residual risk associated with the post-production phase of the life cycle is communicated to the user so the device can be used safely and effectively for the intended purpose.

As with all products, there are inherent risks and benefits to their use. Based on the Risk Assessment, the anticipated clinical benefits of PerClot to the patient outweigh the residual risks associated with the device. PerClot is acceptable for its intended purpose given its anticipated clinical benefit and low residual risk.

Revision History

Revision Date	Revision Level	Line Item(s)	Change
N/A	000	All	None; existing SMI Risk Analysis
10/2011	001	All	Incorporation of SMI-identified risks and risks related to investigational device. Reformatting of Risk Analysis table to incorporate CTCAE risk evaluation scales for severity.
9/2012	002	All	Replacement of CryoLife mitigations for SMI mitigations; addition of contract services risks.
		R1- R84	Changed mitigations listed in Preventive Action column to accurately reflect procedures performed during CryoLife manufacturing.
		All	Rearranged Risk Category groupings to correspond to manufacturing process
		R25	Removed line item, as pH at this manufacturing stage is an in-process procedure, not a quality procedure
		R27	Removed line item
		R28	Reworded hazard to read "Moisture content following drying not ≤10%"
		R31	Added "Residuals associated with carcinogenic potential" to the Effect of Hazard, and changed the Severity pre- and post-mitigation to D from C.
		Throughout	Corrected Clinical Protocol number from PCT1011.001-C (10/11) to PCT1101.003-C (09/12).
		R56-R84	Changed CryoLife biocompatibility report numbers to Namsa report numbers
		R91	Added "glucose spike" to Effect of Hazard
10/2012	003	R65 and R67	Removal of hazards associated with adhesions and/or malignancies as it has been identified that they are not hazards associated with PerClot. Update tables and graphs accordingly.
10/2012	004	Risk Management Plan: Header Section 1 Section 2 Section 4	Header – Changed RM-0011.003 to RM-0011.004 to reflect revision. Sec 1 – Updated scope to reflect purpose of revision 004. Sec 2 - Clarified language to better describe the currently known mode of action for the product determined from the studies conducted thus far. Sec 4 – Changed "particle" to "granule" to better describe the currently known mode of action for the product determined from the studies conducted thus far.
		Risk Analysis: R36, R60, R68, R76, and R83	Changed "particle" to "granule" to better describe the currently known mode of action for the product determined from the studies conducted thus far.
		Risk Assessment Summary: Header Device Description	Header – Changed RM-0011.003 to RM-0011.004 to reflect revision. Device Desc. - Clarified language to better describe the currently known mode of action for the product determined from the studies conducted thus far.
05/2013	005	Throughout	Risk management plan updated to be compliant with BS EN ISO 14971:2012
		Device Description	Absorption characteristic of PerClot® included in device description
		Throughout	Remove references to acceptable risk

		Table 2 Probability and Severity Table, Table 3 Risk Rating Chart Values and Worksheet D Risk Analysis Table	Severity level changed from alphabetical value to numeric value to be consistent with CTCAE
		Table 3 Control Measures, Worksheet D Risk Analysis Table	Remove Labeling as a Control Measure
		Throughout	Add Residual Risk will be communicated to the end user
		Risk Management File Worksheet F Residual Risk Communication Table	Include Residual Risk Communication Table
		Worksheet D Risk Analysis Table, Worksheet E Risk Verification Table and Worksheet F Residual Risk Communication Table	Add headers to Risk Analysis Table, Risk Control Verification
		Worksheet D Risk Analysis Table	Add R66 Cytotoxicity
		R89	R89 – Use of Product in patients with poor glucose control add effect of the hazard Impaired wound healing and Wound Infection
		Worksheet D Risk Analysis Table and Worksheet E Risk Verification Table	Update reference to PCT1101.003-C(09/12) to PCT1101.004-C(05/13)
09/2013	006	R8	Add MS5923
		Throughout risk management file	Update reference to PCT1011.005-C (09/13)
		R81	Added "DVT, Embolism and Thrombosis" to the effect of the hazard "Product used as substitute for ligation"
		R89	Replace hazard "Use of product in patients with poor glucose control" with hazard "Peri-operative Hyperglycemia/Glucose Spike"
		R90	Add hazard "PerClot applied along suture line"
		R91	Added hazard "PerClot used on a patient who is not enrolled in or does not meet the acceptance criteria for clinical trial"
		R92	Added hazard "Application of PerClot in patients with oncologic disease"
		R93	Added hazard "Adhesions/Fibrosis"
		Risk verification table and risk analysis table	Updated references
02/2014	007	Throughout risk management file	Update reference to PCT1101.006-C (02/14)

		Risk verification table and risk analysis table	Updated references
		R68	Reworded hazard to clarify hazard "Device is sterilized by user"
		Risk Analysis Table	Removed hazard "Product mixed with methacrylate or other acrylic adhesives
		R91	Added hazard "Single use product used on more than one patient"
		R94	Added "Environmental" to the effect of the hazard
		Risk Management Plan and Summary	Updated Indications for Use
07/2014	008	Throughout	Updated reference to PCT1101.008-C (04/14)
		Risk Verification Table	Updated references
		R62	Added hazard "Failure to deliver product on-time and error-free"
		R92	Added hazard "Used where not clinically evaluated"
		R96	Added hazard "Activation of Complement C3 to a level sufficient to trigger immune response"
		Residual Risk Communication Table: R72, R73, R76, R78	Updated residual risk language to be consistent with label modifications
09/2014	009	Throughout	Updated Clinical Trial Protocol reference to PCT1101.009-C (09/14)
		Risk Control Verification Table	Updated references
11/2014	010	Risk Control Verification Table	Updated references
		Residual Risk Communication Table: R72, R73, R74, R75, R87, R91	Updated residual risk language to be consistent with label modifications
04/2016	011	RM Plan and Summary	Updated Intended Use to reflect the IFU revision
		Throughout	Updated Clinical Trial Protocol reference to PCT1101.011-C (02/15) Amend. 1
		R46, R47	Updated Mitigation to "GI4200" (removed Draft status)
		R46, R48-R58, R62	Added "infection" to Effect of Hazard; Increased Severity from 4 to 5
		R47	Reworded Hazard to "Product not labeled/packaged in appropriate configuration based on product code"
		R48, R49, R57	Added "Sterilization Validation" to Preventive Action and corresponding Mitigation
		R51, R53, R57, R58	Added "Quality inspections" to Preventive Action and corresponding Mitigation

		R59	Added Hazard "Release of product not approved for distribution"
		R60	Reworded hazard to "Stored past expiry date"
		R64, R65	Updated Mitigation to "MS5870" (removed Draft status)
		R95	Added Hazard "Exacerbates procedure related adverse event"
		Risk Analysis	Removed Hazard "Adverse surgical event"
		Risk Analysis	Removed Hazard "PerClot applied along suture line"
		Risk Control Verification Table	Updated references and replaced "Documentation Services" with "Document Control"
		Residual Risk Communication Table: R61, R71, R73, R74, R79, R86, R91, R95	Updated residual risk language to be consistent with label modifications
05/2016	012	Throughout	Updated Clinical Trial Protocol reference to PCT1101.011-C (02/15) Amend. 02
		R90	Added Hazard "Use of blood salvage circuits or cell-saver devices"
		Risk Control Verification Table	Updated references
		Residual Risk Communication Table: R92	Updated residual risk language to be consistent with label modifications
06/2016	013	Throughout	Updated Clinical Trial Protocol reference to PCT1101.011-C (02/15) Amend. 03
		Risk Control Verification Table	Updated references
		Residual Risk Communication Table: R83, R92	Updated residual risk language to be consistent with label modifications
01/2017	014	Risk Management File	RMF format updated to be compliant with QA0056.015
		Throughout	Updated Clinical Trial Protocol reference to PCT1101.011-C (02/15) Amend. 06
		R48, R49, R57	Updated sterilization validation mitigation to current report
		R90	Hazard reworded to "Use of blood salvaging systems" to better describe hazard
		Risk Control Verification Table	Updated references
		Residual Risk Communication table: R90, R92	Updated residual risk language to be consistent with IFU modifications

PerClot® Polysaccharide Hemostatic System
Risk Management Plan

Prepared by:

Julissa Piña, Risk Management Associate — Date: 01/30/2017

Reviewed and Approved by:

Regulatory Compliance — Date: 01/30/2017

Quality Assurance/Quality Control — Date: 01/30/2017

Regulatory Affairs — Date: 1/30/2017

Clinical Research — Date: 01/30/2017

Research and Development — Date: 01/30/2017

Operations — Date: 01/31/2017

Marketing — Date: 30 JAN 2017

Medical Relations & Education — Date: 01/30/2017

Quality Management — Date: 30 Jan 2017

PerClot® Polysaccharide Hemostatic System
Risk Management Plan

1. Scope

This Risk Management Plan applies to PerClot® Polysaccharide Hemostatic System (PerClot) and addresses the process of assessing risk throughout the product lifecycle. The risk management activities for PerClot will be conducted in accordance with ISO 14971:2007(E) and BS EN ISO 14971:2012. The objectives of the risk management activities are to identify, assess, and reduce all risks as far as possible. The process, product, and residual risk analyses will be performed using a qualitative model of Risk Management.

This revision to the PerClot Risk Management File was initiated to update the residual risk communication to be consistent with modifications to the Instructions for Use.

2. Device Description (IDE Product)

PerClot® Polysaccharide Hemostatic System (hereinafter referred to as PerClot) is a medical device composed of absorbable polysaccharide granules and delivery applicators. The granules are biocompatible, non-pyrogenic and derived from purified plant starch. The granules do not contain any human or animal components. PerClot granules have a molecular structure that rapidly absorbs water, forming a gelled adhesive matrix that provides a mechanical barrier to further bleeding and results in the accumulation of platelets, red blood cells, and coagulation proteins (thrombin, fibrinogen, etc.). One gram of PerClot absorbs at least 19 mL of water. The gelled adhesive matrix thus promotes the normal, physiological clotting cascade. PerClot granules are enzymatically degraded by alpha-amylase and glucoamylase and by macrophages. Based on preclinical studies, absorption normally requires several days and is dependent on the amount of material applied on the wound and the site of use.

The investigational device product is available in the following configuration:

Table 1: PerClot Product Code

Product Description	Product Code
5 g	PC0005-CR

3. Indications for Use (IDE Product)

The intended use for PerClot in this clinical investigation will be in surgical procedures as an adjunctive hemostatic device when control of capillary, venular, and arteriolar bleeding by pressure, ligature, and other conventional procedures is ineffective or impractical.

4. Life Cycle

PerClot granules, bellows and applicator tip are terminally sterilized by e-beam and are intended for use in a single patient, in a single procedure. PerClot granules are enzymatically degraded by alpha-amylase and glucoamylase and by macrophages. Based on preclinical studies, absorption normally requires several days and is dependent on the amount of material applied on the wound and the site of use. The risk management activities

will consider the risks in the design, process, use, degradation and disposal of the device. Unused PerClot, bellows, cap and applicator tips are potentially biohazardous and disposal should abide by local, state and federal laws/regulations.

5. Verification Plan

Post-production surveillance consists of information collected and reviewed for all phases of the device lifecycle. Post-production surveillance, by way of product complaints, clinical evaluations, nonconformances, etc., are reviewed and evaluated for impact to the Risk Management File.Risks identified in previous revisions of the Risk Management File will be evaluated and the probability and severity will be assessed for appropriateness during this review. New risks or changes to the probability/severity of existing risks identified from post-production surveillance will be included in updates to the Risk Management File as appropriate. A Preliminary Hazard Analysis will not be performed for this revision of the Risk Management File.

6. Allocation of Responsibilities

Risk Management is responsible for managing all activities relative to the construction of the Risk Management File with support from other functional areas with knowledge and experience of the product and its use. The Risk Management File is reviewed and signed by a representative from the following areas: Regulatory Affairs, Research and Development, Operations, Clinical Research, Medical Relations, Quality Management and other pertinent areas as deemed necessary.

7. Criteria for Risk Acceptability

7.1 Product / Process Risk Analyses

The probabilities and severities of risks associated with each hazardous situation will be evaluated and assigned a probability and severity rating. The intent of the probability evaluation is that it includes detectability of the hazard. The severity will be determined using the Common Terminology Criteria for Adverse Events (CTCAE) scale. Table 2 provides the probability/severity ratings for PerClot. After the probability/severity rating has been determined for each risk, a risk rating (chart value) will be assigned. Table 3 provides the risk rating scale for PerClot.

As each hazardous situation is evaluated, the assigned risk ratings will be plotted on a Pre-Mitigation Chart (an example is shown in Figure 1) and then again after mitigation on a Post-Mitigation Chart (an example is shown in Figure 2). The probabilities and severities of risks associated with each hazardous situation will be evaluated and reduced as far as possible by inherently safe design and construction. Post mitigation, the risk-benefit analysis for each individual risk and the overall risk-benefit analysis (weighing all risks combined against the benefit) will be re-evaluated.

Table 2: Probability and Severity Rating

Probability Ratings	**Description**
Low	Unlikely to happen, rare, remote
Medium	Can happen, but not frequently
High	Likely to happen, often, frequent
Severity Ratings	**Description**
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (Activities of Daily Living)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

Table 3: Risk Rating Chart Values

Probability Ratings	Severity Ratings	Chart Value
Low	1	1
Low	2	2
Low	3	3
Low	4	4
Low	5	5
Medium	1	2
Medium	2	4
Medium	3	6
Medium	4	8
Medium	5	10
High	1	3
High	2	6
High	3	9
High	4	12
High	5	15

Figure 1: Example of a Pre-Mitigation Chart

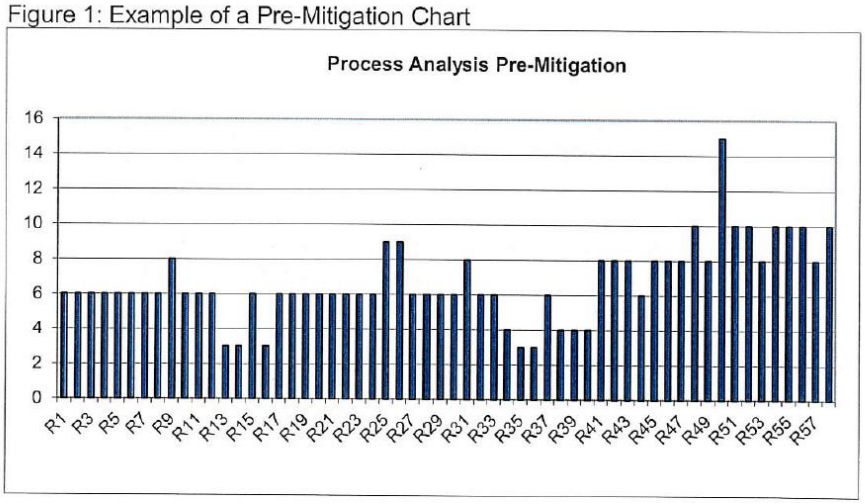
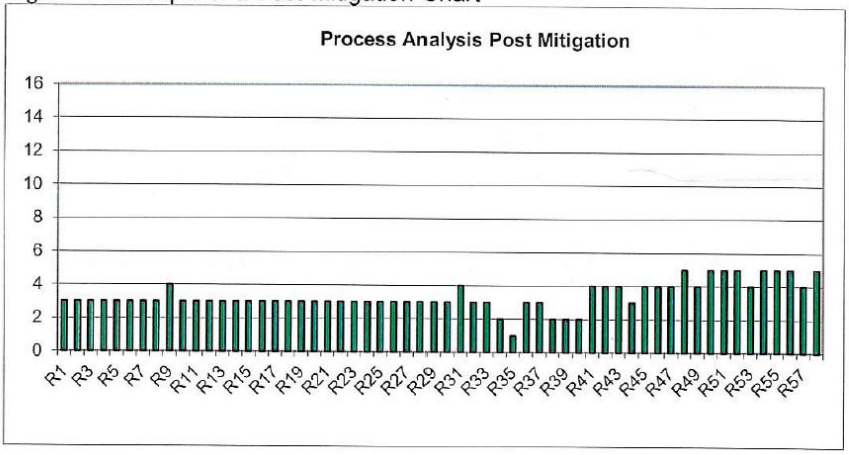


Figure 2: Example of a Post-Mitigation Chart



7.2 Control Measures

All risks will be evaluated and reduced as far as possible by assigning a Mode of Control (Table 4). The mitigations and the resulting impact to the risk score will be documented in the Risk Analysis table. Mitigations will be evaluated to determine whether the mitigation introduced a new risk; each introduced risk will be evaluated and reduced as far as possible. Residual Risk is the risk remaining after the Modes of Control are applied.

Table 4: Control Measures

Mode of Control	Table Key	Description
Design	D	Hazard mitigation or prevention by design.
Protection	P	Hazard minimization by protection. This includes prevention of the hazard by testing prior to shipment (quality testing, quality inspection, validation), procedures, and training.

7.3 Residual Risk

Process, product and residual risk will be disclosed in the Risk Analysis table. Residual risk associated with the post-production phase of the life cycle will be communicated to the user so the device can be used safely and effectively for the intended purpose. Post-production residual risk communication includes, but is not limited to, labels and the Instructions for Use. When symbols are utilized on the product or labeling to convey information essential to the proper use of the product, the symbols will comply with BS EN ISO 15223-1:2016.

8. Overall Statement

As with all products, there are inherent risks and benefits to their use. The individual residual risk and overall residual risk for PerClot will be evaluated to determine if the benefit outweighs the residual risk. The results of the final Risk Analyses will be summarized in the Risk Management Summary.

Attachment B Risk Management Package Development, QA0056.015, Effective 06/13/2016 Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
						PROCESS						
Raw Materials	**R1**	Incorrect raw material- Process Water	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR0222 QA0052	No	L	3	N/A	P
	R2	Incorrect raw material- potato starch	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR0216 QA0052	No	L	3	N/A	P, D
	R3	Incorrect raw material- ethanol	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR4210 QA0052	No	L	3	N/A	P, D
	R4	Incorrect raw material- sodium hydroxide	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR0219 QA0052	No	L	3	N/A	P, D
	R5	Incorrect raw material- monochloroacetic acid	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR0217 QA0052	No	L	3	N/A	P, D
	R6	Incorrect raw material- epichlorohydrin	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR0218 QA0052	No	L	3	N/A	P, D
	R7	Incorrect raw material- sulfuric acid	Unable to formulate product appropriately	Me	3	Incoming inspection Supplier quality audits	MR2063 QA0052	No	L	3	N/A	P, D
	R8	Incorrect raw material- plastics	Product does not perform as designed Irritation Toxicity	Me	4	Incoming inspection Supplier quality audits	MS5877 MS5878 MS5879 MS5923 QA0052	No	L	4	N/A	P, D
	R9	Incorrect raw material- inner pouch	Sterility compromised Loss of moisture barrier	Me	4	Incoming inspection Supplier quality audits	MS5880 QA0052	No	L	4	N/A	P, D
	R10	Incorrect raw material- outer pouch	Sterility compromised	Me	3	Incoming inspection Supplier quality audits	MS5881 QA0052	No	L	3	N/A	P, D
	R11	Incorrect raw material- packaging boxes	Product may not be protected Product damage	Me	3	Incoming inspection Supplier quality audits	MS5882 QA0052	No	L	3	N/A	P, D
Washing of Raw Starch	**R12**	Alcohol solution out of specification (100%)	Unable to formulate product appropriately	Me	3	Starch washing procedure	GI4195	No	L	3	N/A	P, D
	R13	Water wash not performed 3 times	Potentially elevated endotoxin	L	3	Manufacturing process defines washing procedure Training	GI4195	No	L	3	N/A	P, D
	R14	Ethanol wash not performed	Potentially elevated endotoxin Material may not dry	L	3	Manufacturing process defines washing procedure Training	GI4195	No	L	3	N/A	P, D
	R15	Temperature not maintained for drying	Product not dried Shortened shelf-life Starch degradation Bacterial/fungal contamination	Me	3	Manufacturing process defines drying procedure Training	GI4195	No	L	3	N/A	P, D
	R16	Time duration for starch washing step not met	Potentially elevated endotoxin	L	3	Manufacturing process defines time duration Training	GI4195	No	L	3	N/A	P, D

Risk Analysis 1 of 8 PerClot PHS RM-0011.014

Attachment B Risk Management Package Development, QA0056.015, Effective 06/13/2016 Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
						PROCESS						
Modification of starch	**R17**	Alcohol solution out of specification (90-92%)	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R18	Alcohol solution out of specification (80-83%)	Unable to formulate product appropriately Higher residuals	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R19	Incorrect quantity of potato starch	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R20	Incorrect quantity of ethanol	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R21	Incorrect quantity of sodium hydroxide	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R22	Incorrect quantity of monochloroacetic acid	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R23	Incorrect quantity of epichlorohydrin	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R24	Incorrect quantity of sulfuric acid	Unable to formulate product appropriately	Me	3	Modification procedure	GI4196	No	L	3	N/A	P, D
	R25	pH value incorrect following neutralization	Unable to formulate product appropriately	H	3	Modification procedure	GI4196	No	L	3	N/A	P
	R26	Moisture content following drying not ≤10%	Unable to formulate product appropriately	H	3	Modification procedure	GI4196	No	L	3	N/A	P
	R27	38-42°C temperature not maintained for cross-linking steps	Unable to formulate product appropriately	Me	3	Manufacturing process defines appropriate temperature/time duration Training	GI4196	No	L	3	N/A	P, D
	R28	Time duration for alkalization and cross-linking steps not met	Unable to formulate product appropriately	Me	3	Manufacturing process defines time duration Training	GI4196	No	L	3	N/A	P, D
	R29	Temperature not maintained for etherification step	Unable to formulate product appropriately Gelatinization of starch	Me	3	Manufacturing process defines appropriate temperature/ time duration Training	GI4196	No	L	3	N/A	P, D
	R30	Time duration for etherification step not met	Unable to formulate product appropriately	Me	3	Manufacturing process defines time duration Training	GI4196	No	L	3	N/A	P, D
	R31	Inadequate ethanol washes performed	Unable to formulate product appropriately Higher residuals than anticipated Residuals associated with carcinogenic potential	Me	4	Manufacturing process defines number of washes Training	GI4196	No	L	4	N/A	P, D

Risk Analysis 2 of 8 PerClot PHS RM-0011.014

Attachment B Risk Management Package Development, QA0056.015, Effective 06/13/2016 Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
						PROCESS						
Modification of starch cont.	R32	Temperature not maintained for drying of CMS	Unable to formulate product appropriately Gelatinization of starch	Me	3	Manufacturing process defines appropriate temperature duration Training In-process testing	GI4196 MS5870	No	L	3	N/A	P, D
	R33	Time duration for drying of CMS not met	Unable to formulate product appropriately Gelatinization of starch	Me	3	Manufacturing process defines time duration Training In-process testing	GI4196 MS5870	No	L	3	N/A	P, D
	R34	Incorrect size mesh used for sieving of modified starch (prior to granulation)	Granulated powder may not meet specification	Me	2	Manufacturing process defines mesh size Training	GI4202	No	L	2	N/A	P, D
Granulation	R35	Inadequate granulation of CMS	Decreased yield	H	1	Manufacturing inspection Training In-process testing	GI4197 GT0073 MS5870	No	L	1	N/A	P
	R36	Incorrect size mesh used for sieving of modified starch following granulation 60-400 mesh	Product granule size out of specification Inability of product to flow appropriately from applicator tip	L	3	Manufacturing process defines mesh size Training In-process testing	GI4197 GT0073 MS5870	No	L	3	N/A	P, D
Filling	R37	Insufficient product placed in bellows	Insufficient quantity to achieve hemostasis	Me	2	Weight verification during fill process	GI4198	No	L	2	N/A	P, D
	R38	Excess product placed in bellows	Product does not flow properly from bellows	Me	2	Weight verification during fill process	GI4198	No	L	2	N/A	P, D
	R39	Foreign material in filled bellows	Contamination	Me	4	Quality inspections Training	GI4198 GT0073	No	L	4	N/A	P, D
Assembly-Packaging	R40	Improper processing of bellows/cap	Contamination	Me	2	Processing procedures	GI4198 GI4199	No	L	2	N/A	P, D
	R41	Improper processing of standard applicator tip	Contamination	Me	2	Processing procedures	GI4199	No	L	2	N/A	P, D
	R42	Inner pouch not sealed properly	Contamination Loss of sterility	Me	5	Processing procedures In-process testing	GI4199 MS5870	No	L	5	N/A	P
	R43	Outer pouch not sealed properly	Contamination Loss of sterility	Me	5	Processing procedures In-process testing	GI4199 MS5870	No	L	5	N/A	P
	R44	Bioburden level out of specification	Transmission of infectious agents	Me	3	In-process testing	GI4209	No	L	3	N/A	P
	R45	Pouching incorrectly labeled	Misbranding Misuse	Me	4	Processing procedures	GI4199	No	L	4	N/A	P

Risk Analysis 3 of 8 PerClot PHS RM-0011.014

Attachment B Risk Management Package Development, QA0056.015, Effective 06/13/2016 Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
PROCESS												
Assembly-Packaging cont.	R46	Improper packaging of final product	Product damage Inappropriate packaging configuration for sterility Infection	Me	5	Processing procedures	GI4200	No	L	5	N/A	P
	R47	Product not labeled/packaged in appropriate configuration based on product code	Misuse Misbranding Missing components Residual risk not communicated	Me	4	Processing procedures Line clearance	GI4199 GI4200 QA0034	No	L	4	N/A	P
Contract Services - Sterilization	R48	Sterilization process does not provide SAL of 10^{-6}	Device not sterile Infection	Me	5	Supplier quality audits Sterilization validation	QA0052 VP-2015-061-PV	No	L	5	N/A	P
	R49	Failure to demonstrate functionality of process	Unable to claim product sterility Infection	Me	5	Supplier quality audits Sterilization validation	QA0052 VP-2015-061-PV	No	L	5	N/A	P
	R50	Inappropriate segregation of processed and unprocessed goods	Potential mix up between sterilized and unsterilized product Infection	H	5	Supplier quality audits	QA0052	No	L	5	N/A	P, D
	R51	Inconsistent or inadequate dose of sterilizing agent	Device not sterile Infection	Me	5	Supplier quality audits Quality inspections	QA0052 MS5870	No	L	5	N/A	P, D
	R52	Improper equipment used for sterilization process	Device not sterile Infection	Me	5	Supplier quality audits	QA0052	No	L	5	N/A	P, D
	R53	Delays in irradiation cause product to expire	Device not sterile Infection	Me	5	Supplier quality audits Quality inspections	QA0052 MS5870	No	L	5	N/A	P
	R54	Failure of monitoring devices-dosing not accurately measured	Device not sterile Infection	Me	5	Supplier quality audits	QA0052	No	L	5	N/A	P
	R55	Failure of monitoring devices-amount of sterilant applied not accurately measured	Device not sterile Infection	Me	5	Supplier quality audits	QA0052	No	L	5	N/A	P
	R56	Failure of monitoring devices-exposure time not accurately measured	Device not sterile Infection	Me	5	Supplier quality audits	QA0052	No	L	5	N/A	P
	R57	Sterilization process or handling results in product damage	Device compromised/damaged Unable to claim product sterility Infection	Me	5	Supplier quality audits Quality inspections Sterilization validation	QA0052 MS5870 VP-2015-061-PV	No	L	5	N/A	P
	R58	Load outside validated range	Device not sterile Infection	Me	5	Supplier quality audits Quality inspections	QA0052 MS5870	No	L	5	N/A	P
Final Release	R59	Release of product not approved for distribution	Unapproved product released for distribution in clinical trial	Me	5	Quality control review Clinical review	QS4039 CR0004	No	L	5	N/A	P

Risk Analysis 4 of 8 PerClot PHS RM-0011.014

Attachment B Risk Management Package Development, QA0056.015, Effective 06/13/2016 Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation/ Communication	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
PRODUCT												
Storage	R60	Stored past expiry date	Possible deterioration Product does not perform as designed	Me	4	Expiry date is stated on outer pouch label	L6218	No	Me	4	Yes	N/A
	R61	Stored at incorrect temperatures	Degradation of product Product granule size out of specification Product does not perform as designed	Me	4	Storage requirements on labeling	L6421 L6422 L6423	No	Me	4	Yes	N/A
Handling/ Transport	R62	Package dropped/damaged / sterile barrier punctured/ sterile packaging open	Loss of sterility Product/package damage Infection	Me	5	Labeling states not to use if damaged or opened	L6421 L6422 L6423	No	Me	5	Yes	N/A
	R63	Failure to deliver product on-time and error-free	Incorrect product quantity shipped to site Product shipped to incorrect site Product not received when expected	L	1	Investigational device shipping and storage procedures	CR0004	No	L	1	N/A	P
Bioconta-mination	R64	Bacterial/fungal contamination	Infection Death	Me	5	Terminal sterilization of product and applicators	MS5870	No	L	5	N/A	P
	R65	Pyrogen contamination	Fever Anaphylaxis	Me	5	LAL testing	MS5870 NL0018	No	L	5	N/A	P
Biocomp-atibility	R66	Immune response	Anaphylaxis Death	L	5	Contraindications are identified in labeling	L6421	No	L	5	Yes	N/A
	R67	Systemic toxicity	Toxicity	L	4	Systemic Toxicity evaluated per ISO 10993	T0625_500 T0118_904/S	No	L	4	N/A	P, D
	R68	Cytotoxicity	Toxicity	L	4	Cytotoxicity evaluated per ISO 10993	V0014-130	No	L	4	N/A	P
Misuse	R69	Use by unskilled/untrained personnel	Failure to obtain hemostasis Thromboembolism Improper Use	L	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R70	Device is sterilized by user	Infection Product does not perform as designed	L	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R71	Granule dispenser not connected to applicator in proper fashion	Application to non-target areas	Me	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	2	Yes	N/A

Risk Analysis 5 of 8 PerClot PHS RM-0011.014

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation/ Communication	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
						PRODUCT						
Misuse cont.	**R72**	Excess blood not removed from intended site	Failure to obtain hemostasis	H	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	H	2	Yes	N/A
	R73	Insufficient amount of product applied/wound not thoroughly covered	Failure to obtain hemostasis	Me	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	2	Yes	N/A
	R74	Excess amount of product applied	Toxicity Fever Anaphylaxis	L	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R75	Applicator tip not close enough to source of bleading	Failure to obtain hemostasis Application to non-target areas	Me	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	2	Yes	N/A
	R76	Applicator tip comes in contact with blood	Failure to obtain hemostasis Clogging of applicator tip	Me	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	2	Yes	N/A
	R77	Direct pressure not applied appropriately	Failure to obtain hemostasis	Me	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	2	Yes	N/A
	R78	Pressure dressing adheres to formed blood clot	Failure to obtain hemostasis Disturbance of blood clot	H	2	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	H	2	Yes	N/A
	R79	Excess granules not removed by irrigation and aspiration	Swelling and compression of pressure-sensitive tissues and structures	H	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	H	3	Yes	N/A
	R80	PerClot used on patient with known sensitivity to starch or starch-derived materials	Allergic reaction Anaphylaxis Death	L	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R81	Product administered intravascularly	Thromboembolism Embolism Thrombosis Death	Me	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	5	Yes	N/A
	R82	Product administered into bladder or ureteral lumen	Blockage of the bladder or ureteral lumen	L	4	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	4	Yes	N/A

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation/ Communication	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
PRODUCT												
Misuse cont.	**R83**	Product used as substitute for ligation	Failure to obtain hemostasis Hemorrhage Deep Vein Thrombosis (DVT) Embolism Thrombosis	Me	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	3	Yes	N/A
	R84	Product used in area where infection is suspected	Failure of deep or superficial wound healing	Me	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	3	Yes	N/A
	R85	Product used in combination with other topical hemostatic agents	Product does not perform as designed Failure to obtain hemostasis	Me	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	3	Yes	N/A
	R86	Granules enter the bypass circuit	Blockage of the bypass system	Me	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	5	Yes	N/A
	R87	Product used as primary treatment for coagulation disorders	Failure to obtain hemostasis Hemorrhage	L	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	3	Yes	N/A
	R88	Product comes in contact with fluids prior to application	Product does not perform as designed Failure to obtain hemostasis	H	3	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	H	3	Yes	N/A
	R89	Used on more than one patient	Transmission of infectious agents Death	L	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R90	Use of blood salvaging systems	Thromboembolism if product enters vascular system	Me	5	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	5	Yes	N/A
Patient Selection	**R91**	Application of PerClot in patient with oncologic disease	Cancer recurrence and/or progression	L	5	Clinical protocol Biological Risk Assessment Appropriate use described in IFU	PCT1101.011-C (02/15) Amend. 06 Biological risk assessment PerClot Hemostatic Agent revision 001 L6421	No	L	5	Yes	D

Attachment B — Risk Management Package Development, QA0056.015, Effective 06/13/2016 — Confidential

Risk Category	Risk Item #	Hazard	Effect of Hazard	Risk prior to mitigation		Preventive Action	Mitigation/ Communication	New Hazard Intro.	Risk after mitigation		Res. Risk Communicated	Hazard Control
				Prob.	Severity Grade				Prob.	Severity Grade		
PRODUCT												
Patient Selection cont.	R92	PerClot used on a patient who is not enrolled in or does not meet the acceptance criteria for the clinical trial	Adverse Event Death	L	5	Clinical protocol Appropriate use described in IFU	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	D
	R93	Used where not clinically evaluated	Adverse Event Death	L	5	Clinical protocol Appropriate use described in IFU	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
Side Effects	R94	Adhesions/Fibrosis	Pain Disrupt blood flow Tissue damage	L	3	Clinical protocol Biological Risk Assessment Appropriate use described in IFU	PCT1101.011-C (02/15) Amend. 06 Biological risk assessment PerClot Hemostatic Agent revision 001 L6421	No	L	3	Yes	D
	R95	Activation of Complement C3 to a level sufficient to trigger immune response	Immune response	L	3	Clinical protocol Potential adverse events identified in labeling	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	3	Yes	N/A
	R96	Exacerbates procedure related adverse event	Patient injury	L	5	Clinical protocol Informed Consent Form Potential adverse events identified in labeling	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	5	Yes	N/A
	R97	Peri-operative Hyperglycemia/Glucose Spike	Impaired wound healing Wound infection	Me	3	Clinical protocol Appropriate use described in IFU	PCT1101.011-C (02/15) Amend. 06 L6421	No	Me	3	Yes	N/A
Disposal	R98	Product not properly disposed of after use	Environmental contamination	L	1	Clinical protocol Appropriate use described in IFU Investigator training	PCT1101.011-C (02/15) Amend. 06 L6421	No	L	1	Yes	N/A

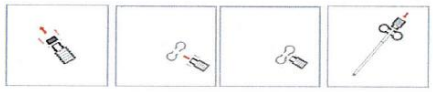
Prepared by: _____ Date: 01/30/2017

Risk Analysis — 8 of 8 — PerClot PHS RM-0011.014

Mitigation/ Communication	Title	Location
CR0004	Clinical Investigation, Investigational Device Shipment, Storage, and Accountability	Document Control
GI4195	Washing Potato Starch in a Chemglass Reactor	Document Control
GI4196	Preparation of Cross-linked Carboxymethyl Starch in a Chemglass Reactor	Document Control
GI4197	Granulation of Cross-linked Carboxymethyl Starch in a VFC Granulator	Document Control
GI4198	Cross-linked Carboxymethyl Starch 5g Fill into Bellow Bottles	Document Control
GI4199	Packaging 5g Cross-Linked Carboxymethyl Starch Filled Bellow Bottles	Document Control
GI4200	Boxing 5g Cross-linked Carboxymethyl Starch Filled Bellow Bottles	Document Control
GI4202	Sub-Assembly, Sieving Cross-Linked Carboxymethyl Starch	Document Control
GI4209	Pouched 5g Filled Bellow - Bioburden and Seal Strength	Document Control
GT0073	PerClot Pilot Employee Training Program	Document Control
L6218	Label, Lot # Add-On	Document Control
L6421	PerClot® Polysaccharide Hemostatic System Instructions for Use	Document Control
L6422	Label, U.S. Clinical, PerClot®(R) Polysaccharide Hemostatic System, Inner Pouch	Document Control
L6423	Label, U.S. Clinical, PerClot®(R) Polysaccharide Hemostatic System, Shelf-Box	Document Control
MR0216	Potato Starch, NF	Document Control
MR0217	Monochloroacetic Acid, ACS Grade	Document Control
MR0218	Epichlorohydrin	Document Control
MR0219	Sodium Hyrdoxide, NF	Document Control
MR0222	Process Water	Document Control
MR2063	Sulfuric Acid	Document Control
MR4210	Ethyl Alcohol, 200 Proof, USP	Document Control
MS5870	Inspection, PerClot®, Investigational Device, 5g	Document Control
MS5877	Bellow, 3g and 5g, PerClot®	Document Control
MS5878	Bellow, Cap, PerClot®	Document Control
MS5879	Applicator Tip, Standard, PerClot®	Document Control
MS5880	Inner Pouch, Standard, PerClot®	Document Control
MS5881	Outer Pouch, Standard, PerClot®	Document Control
MS5882	Shelf Box, Standard, Perclot	Document Control
MS5923	Inspection, Irradiated Packaging Kit	Document Control
NL0018	Testing, LAL, Kinetic Chromogenic	Document Control
QA0034	Procedure, Line Clearance	Document Control
QA0052	Audit Program: Supplier Quality	Document Control
QS4039	PerClot Final Product Release	Document Control
VP-2015-061-PV	Sterilization Process Validation, Sterilization of 5g PerClot Final Assembly, E-Beam, Method VDMAX	Quality Engineering
T0118_904/S	4 Week Systemic Toxicity in Rats Following Subcutaneous Implantation	Clinical Research
T0625_500	ISO Systemic Toxicity Study- Extract	Clinical Research

Mitigation/ Communication	Title	Location
V0014-130	Cytotoxicity Study Using the ISO Elution Method	Clinical Research
PCT1101.011-C (02/15) Amendment 06	Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot®	Clinical Research
N/A	Biological risk assessment PerClot Hemostatic Agent revision 001 (05/08/2013)	Clinical Research

Prepared by: _____ Date: 01/30/2017

Risk Item #	Hazard	Residual Risk Communication	Label
R60	Stored past expiry date	Expiry date is stated on outer pouch label.	L6218
R61	Stored at incorrect temperatures	PerClot should be stored between 0°C and 25°C.	L6421
R62	Package dropped/damaged / sterile barrier punctured/ sterile packaging open	Visually inspect the sealed packages. If either package has been previously opened or damaged, discard and replace with a new package.	L6421
R66	Immune response	Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Anaphylaxis; Fever	L6421
R69	Use by unskilled/untrained personnel	This device should not be used except on the order of a physician.	L6421
R70	Device is sterilized by user	Contents of the PerClot package are supplied sterile for single-patient use only. These contents are sterilized by gamma irradiation and should not be re-sterilized. Discard any unused material from opened or damaged product.	L6421
R71	Granule dispenser not connected to applicator in proper fashion	Connect the bellows firmly to the end of the applicator handle (Fig. 2). The system is now ready for use (Fig. 3). Pump the bellows to deliver granules directly to the site of bleeding (Fig. 4).  Fig.1 Fig.2 Fig.3 Fig.4	L6421
R72	Excess blood not removed from intended site	Remove all excess blood from the intended site by blotting, wiping, or suctioning. Identify and expose the source of bleeding of the wound. Removing excess blood is critical to maximizing the hemostatic performance as it allows the PerClot granules direct contact with the site and source of active bleeding.	L6421
R73	Insufficient amount of product applied/wound not thoroughly covered	Pump the bellows bottle to deliver granules directly to the site of bleeding. Immediately apply a liberal amount of the PerClot granules directly to the source of bleeding. Thoroughly cover the lesion with a layer of granules 3 to 4mm in thickness. Extend the product application to approximately 0.5cm (or 5mm) beyond the edge of the site of bleeding. The amount of application will depend upon the size of the bleeding site, contour of the bleeding site, and severity of bleeding. The amount of PerClot granules applied will increase with increasing size of the bleeding site and severity of bleeding.	L6421

Risk Item #	Hazard	Residual Risk Communication	Label
R74	Excess amount of product applied	Pump the bellows bottle to deliver granules directly to the site of bleeding. Immediately apply a liberal amount of the PerClot granules directly to the source of bleeding. Thoroughly cover the lesion with a layer of granules 3 to 4mm in thickness. Extend the product application to approximately 0.5cm (or 5mm) beyond the edge of the site of bleeding. The amount of application will depend upon the size of the bleeding site, contour of the bleeding site, and severity of bleeding. The amount of PerClot granules applied will increase with increasing size of the bleeding site and severity of bleeding. NOTE: Do not apply more than the entire contents of up to two 5 gram bellows of PerClot implant material per subject. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Fever; Toxicity; Anaphylaxis	L6421
R75	Applicator tip not close enough to source of bleeding	When managing deep wounds, the applicator tip must be as close to the source of the bleeding as possible without contacting blood. NOTE: To optimize the hemostatic performance of PerClot, it is important to ensure that the granules come into the direct contact with the bleeding surface.	L6421
R76	Applicator tip comes in contact with blood	CAUTION: Avoid contacting the applicator tip with blood as this may occlude the applicator. If this occurs, replace applicator tip, if available. If this occurs and a replacement tip is not available, use a stylus to reestablish the delivery pathway by inserting the stylus through the blocked area. Do not attempt to trim the applicator tip.	L6421
R77	Direct pressure not applied appropriately	Appropriate gentle manual pressure can be applied until hemostasis is achieved. Gentle manual pressure will be applied until the first time point (5 minutes), and again between the first and second time points (7 minutes)	L6421
R78	Pressure dressing adheres to formed blood clot	NOTE: Some materials such as standard gauze may adhere to the formed blood clot. Irrigation with saline before carefully removing the gauze is recommended. If standard gauze is adhered to the formed blood clot, the gauze should be fully saturated with saline, then gently and slowly peeled away. The use of a non-adhering substrate to apply pressure is recommended.	L6421

Risk Item #	Hazard	Residual Risk Communication	Label
R79	Excess granules not removed by irrigation and aspiration	Remove excess PerClot granules once hemostasis is achieved. This is particularly important in and around the spinal cord and foramina of the bone since unsaturated granules may swell and compress the surrounding tissues. Once hemostasis is achieved, remove excess granules carefully and completely by gentle saline irrigation and aspiration. Dry, white PerClot should be removed. The possibility of the product interfering with normal function and/or causing compression necrosis of surrounding tissues due to swelling is reduced by removal of excess dry material. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Failure to obtain hemostasis, Swelling and compression of pressure-sensitive tissues and structures. Note: Following the application of PerClot for epicardial bleeding within the pericardial cavity and achievement of hemostasis, the pericardial cavity should be rinsed with up to 70cc of fluid per 1 gram of PerClot applied, which should be removed with suction, in order to ensure removal of excess particles. Observe the pericardial cavity for a minimum of 10 minutes after initial application for product swelling.	L6421
R80	PerClot used on patient with known sensitivity to starch or starch-derived materials	Contraindication: Do not use in patients who have known sensitivity to starch or starch-derived materials	L6421
R81	Product administered intravascularly	Do not inject or place PerClot into blood vessels as potential for embolization and death may exist.	L6421
R82	Product administered into bladder or ureteral lumen	Do not inject into bladder or ureteral lumen. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Blockage of the bladder or ureteral lumen.	L6421
R83	Product used as substitute for ligation	PerClot is not intended as a substitute for good surgical practice, and in particular, the proper use of conventional procedures (such as ligature) for hemostasis. Blood vessels with a diameter of ≥2mm, suture line gaps ≥2mm, and large needle holes ≥2mm must be ligated prior to PerClot application. Perform conventional methods for hemostasis, including, but not limited to, pressure and ligature. Ligate any vessels ≥2mm, suture line gaps ≥2mm, and large needle holes ≥2mm in diameter. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Deep Vein thrombosis (DVT)	L6421
R84	Product used in area where infection is suspected	PerClot should not be used: In subjects with an active or potential infection at the surgical site, defined as wound classification of III or IV based upon the American College of Surgeon's wound classification system. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Failure of deep or superficial wound healing; Infection	L6421
R85	Product used in combination with other topical hemostatic agents	Combined use of PerClot with other topical hemostatic agents has not been studied in controlled clinical trials	L6421

Risk Item #	Hazard	Residual Risk Communication	Label
R86	Granules enter the bypass circuit	Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Blockage of the bypass system; Thromboembolism	L6421
R87	Product used as primary treatment for coagulation disorders	PerClot is not recommended as a primary treatment for coagulation disorders. Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Hemorrhage	L6421
R88	Product comes in contact with fluids prior to application	CAUTION: Avoid contacting the applicator tip with blood as this may occlude the applicator. If this occurs, replace applicator tip, if available. If this occurs and a replacement tip is not available, use a stylus to reestablish the delivery pathway by inserting the stylus through the blocked area. Do not attempt to trim the applicator tip. PerClot is intended to be used in a dry state. Contact with fluids prior to application will result in the loss of hemostatic properties.	L6421
R89	Used on more than one patient	Contents of the PerClot package are supplied sterile for single-patient use only.	L6421
R90	Use of blood salvaging systems	As with other hemostatic agents, do not allow PerClot to enter into cell saver equipment, extracorporeal cardiopulmonary bypass circuits or autologous blood salvage circuits. Granules of PerClot or fragments of gelled PerClot may pass through 40 micron transfusion filters of blood salvaging systems.	L6421
R91	Application of PerClot in patient with oncologic disease	Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Cancer recurrence and/or progression Note: The effects of PerClot on adhesion formation, tumor recurrence, and or progression of malignant disease have not been studied in humans.	L6421
R92	PerClot used on a patient who is not enrolled in or does not meet the acceptance criteria for the clinical trial	PerClot should not be used: • In subjects undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis); • In subjects who have a clinically significant coagulation disorder or disease, defined as a platelet count <100,000 per microliter, an International Normalized Ratio >1.5, or a PTT more than 1.5 times outside the laboratory's normal reference range; • In subjects who used corticosteroids (excluding inhalers, eye-drops, and dermatologic corticosteroids) within 6 weeks prior to surgery; • In subjects who have undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery; • In subjects who have been treated with an investigational product and have not completed the entire follow-up period for that investigational product; • In subjects who are pregnant (as confirmed by a pregnancy test), planning on becoming pregnant during the follow-up period, or actively breast-feeding; • In subjects with poor blood glucose control as per glycosylated hemoglobin > 9%; and • In subjects with an active or potential infection at the surgical site, or whose surgical wound is defined as wound classification of CO (Contaminated) or D (Dirty or Infected) based upon the Centers for Disease Control and Prevention's wound classification system.	L6421

Risk Item #	Hazard	Residual Risk Communication	Label
R93	Used where not clinically evaluated	The safety and effectiveness of PerClot have not been clinically evaluated in pediatric patients, on ophthalmic or neurologic tissues, or in laparoscopic cases.	L6421
R94	Adhesions/Fibrosis	Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Adhesions or fibrosis Note: The effects of PerClot on adhesion formation, tumor recurrence, and or progression of malignant disease have not been studied in humans.	L6421
R95	Activation of Complement C3 to a level sufficient to trigger immune response	PerClot is predicted to activate Complement C3 because of its activity and fluid absorption capacity.	L6421
R96	Exacerbates procedure related adverse event	Possible adverse events that could occur with the use of the investigational device may include, but are not limited to, the following: Exacerbation of procedure related adverse event	L6421
R97	Peri-operative Hyperglycemia/Glucose Spike	Note: Elevated peri-operative blood glucose levels may also be associated with increased rate of wound infection. Elevated blood glucose levels in the immediate post operative period may affect wound healing.	L6421
R98	Product not properly disposed of after use	Discard any unused material from opened or damaged product.	L6421

Prepared By: Julissa Rios Date: 01/30/2017

Appendix D: Draft Pre-Screening and Screening and Enrollment Log

The C.L.O.T Investigation
Pre-Screening Log

Site Name/Site Number: _____

Principal Investigator: _____

Screening Date	Subject Initials	Recruitment/Identification Method (i.e., medical record review, referral)	Subject Eligible to Enroll?	If ineligible,		CRC Initials
				Inclusion Criteria NOT Met	Exclusion Criteria met	
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			
			Y / N			

* Subjects who meet the inclusion criteria and sign the Informed Consent Form will also be listed on the Screening and Enrollment Log.

PerClot® - The C.L.O.T. Investigation

Draft Screening and Enrollment Log

Site Code: __ __

Subject ID	Screen Date (DD/MMM/YYYY)	Did subject meet all preoperative inclusion/exclusion criteria?		Surgery Date (DD/MMM/YYYY)	Did subject meet the intraoperative eligibility criteria?		Comments*
		Yes	No (Please enter all applicable preoperative exclusion codes)		Yes	No	

* This field is meant to capture any technical failures (i.e., contraindications, misdiagnosis, or intraoperative death prior to treatment, etc.).

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Exclusion Codes

Preoperative Screening Exclusion Codes

Exclusion Code	Criteria
I1	Subject is **not** undergoing one of the following open elective cardiac, general, or urological surgical procedures: • Cardiac procedure (Epicardium) • Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line) • Liver resection • Splenectomy • On-clamp partial nephrectomy • Radical nephrectomy
I2	Subject is **not** willing and able to give prior written informed consent for investigation participation.
I3	Subject is **not** 22 years of age or older.
E1	Subject has known sensitivity to starch or starch-derived materials.
E2	Subject has a clinically significant coagulation disorder or disease, defined as a platelet count <100,000 per microliter, and International Normalized Ratio >1.5, or a PTT more than 1.5 times outside the laboratory's normal reference range.
E3	Subject who used corticosteroids (excluding inhalers, eye-drops, and dermatologic corticosteroids) within 6 weeks prior to surgery
E4	Subject has undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery.
E5	Subject has been treated with an investigational product and has not completed the entire follow-up period for that investigational product.
E6	Subject who is pregnant (as confirmed by a pregnancy test), planning on becoming pregnant during the follow-up period, or actively breast-feeding.
E7	Subject with poor blood glucose control as per glycosylated hemoglobin > 9%.

Intraoperative Screening Exclusion Codes

Exclusion Code	Criteria
I4	Subject who is not undergoing one of the following open elective cardiac, general, or urological surgical procedure without break in sterile technique: • Cardiac procedure (Epicardium) • Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line) • Liver resection • Total Splenectomy • On-clamp partial nephrectomy • Radical nephrectomy
I5	Subject in whom there is **no** bleeding at the specified area for each surgical procedure after any applicable conventional means for hemostasis are attempted as specified by the intraoperative protocol.
I6	Subject in whom the anatomic site is greater than $25cm^2$
I7	Subject in whom the anatomic application site is greater than $47cm^2$.
I8	Subject in whom the bleeding from the identified lesion is ≤ 0.000040 [g/(cm²·s)] or > 0.013 [g/(cm²·s)].
I9	Subject in whom all visible vessels or suture holes greater than or equal to 2mm in diameter have not been ligated.
E8	Subject who has an active or potential infection at the surgical site, or whose surgical wound is defined as a wound classification of CO (Contaminated) or D (Dirty or Infected) based on the Center for Disease Control and Prevention's Wound Classification System.
E9	Subject in whom any major intraoperative bleeding incidences during the surgical procedure occurred (i.e., subject with assignment of an American College of Surgeons Advanced Trauma Life Support Hemorrhage Class of II, III, or IV Hemorrhage).
E10	Subject undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis).

Appendix E: Sample Case Report Forms

A 21 CFR Part 11-compliant electronic database will be used for electronic data capture. The forms in this Appendix are provided for example purposes only; the actual layout of the electronic case report forms may differ.

Subject Screening DRAFT Form
Form 1A

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ /____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 1 Screening

SUBJECT SCREENING

1. Gender: ☐ 0 Male ☐ 1 Female
2. Date of Birth (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐
3. Ethnicity (check one): ☐ 0 Hispanic or Latino ☐ 1 Not Hispanic or Latino
4. Race (Select one or more): ☐ 1 White ☐ 2 Black or African American ☐ 3 American Indian or Alaska Native ☐ 4 Asian ☐ 5 Native Hawaiian or other Pacific Islander ☐ 99 Other, please specify: _____

PREOPERATIVE INCLUSION CRITERIA

5. Subject is undergoing one of the follow open elective general, urological, or cardiac surgical procedures:	Yes	No
a. Cardiac procedure: Epicardium	☐ 1	☐ 0
b. Cardiac procedure: (Aortic Anastomosis or Aortotomy Suture Line)	☐ 1	☐ 0
c. Liver resection	☐ 1	☐ 0
d. Total splenectomy		
e. On-clamp partial nephrectomy	☐ 1	☐ 0
f. Radical nephrectomy	☐ 1	☐ 0

6. Subject is willing and able to give prior written informed consent for investigation participation. ☐ 1 ☐ 0
Must be answered yes to proceed.
Date Informed Consent signed (DD/MMM/YYYY):
☐☐/☐☐☐/☐☐☐☐

7. Subject is ≥ 22 years of age. ☐ 1 ☐ 0

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Subject Screening DRAFT Form
Form 1B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 1 Screening

PREOPERATIVE EXCLUSION CRITERIA

ALL questions regarding EXCLUSION must be answered NO for subject to be eligible for entry into the investigation.

	Yes	No
8. Subject who has known sensitivity to starch or starch-derived materials.	☐ 1	☐ 0
9. Subject who has a clinically significant coagulation disorder or disease, defined as a as a platelet count <100,000 per microliter, an International Normalized Ratio >1.5, or a PTT more than 1.5 times outside the laboratory's normal reference range.	☐ 1	☐ 0
10. Subject used corticosteroids (excluding inhalers, eye-drops, and dermatologic corticosteroids) within 6 weeks prior to surgery.	☐ 1	☐ 0
11. Subject has been treated with an investigational product and has not completed the entire follow-up period for that investigational product.	☐ 1	☐ 0
12. Subject is pregnant (as confirmed by a pregnancy test), planning on becoming pregnant during the follow-up period, or actively breast-feeding.	☐ 1	☐ 0
13. Subject has poor blood glucose control as per glycosylated hemoglobin (HbA1c) > 9%.	☐ 1	☐ 0

Principal Investigator Signature ☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

Preoperative DRAFT Form
Form 2A

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 2 Preoperative

PHYSICAL EXAM

1. Height: ☐☐☐.☐ cm
2. Weight: ☐☐☐.☐ kg
3. Temperature: ☐☐.☐ °C
4. Blood pressure:
   a. Systolic: ☐☐☐ mmHg
   b. Diastolic: ☐☐☐ mmHg

INDICATION FOR SURGERY

5. Indication(s) for surgery (select all that apply):

☐ 1 Benign tumor
☐ 2 Malignant tumor
☐ 3 Metastatic tumor
☐ 4 Cyst
☐ 5 Cardiovascular Disease
☐ 6 Mass (unknown composition)
☐ 7 Other, please specify, including type of implant or graft, if applicable: _____

6. Please list any concomitant procedures: _____ ☐ 0 Not Applicable

7. Has the patient undergone a previous surgery at the same operative site or for the same indication?

☐ 1 Yes, please describe: _____
☐ 0 No

BLOOD MODIFIERS / INSULIN OR BLOOD SUGAR LOWERING MEDICATIONS

8. Use of any blood modifiers, insulin, blood sugar lowering medications, or reversal drugs? (This includes products known to affect bleeding, i.e., NSAIDs, ASA, omega-3 fatty acid supplements, herbal supplements) See Appendix K and Appendix L for detailed list. ☐ 1 Yes ☐ 0 No

If yes, please complete Blood Modifiers Insulin or Blood Sugar Lowering Medications Form.

Note: The physical exam, labs, medical history, and thrombosis risk factor assessment will be taken and recorded no more than 1 month (30 days) prior to surgery date.

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Preoperative DRAFT Form
Form 2B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 2 Preoperative

MEDICAL HISTORY

9. The subject smokes:

- ☐ 1 Never
- ☐ 2 Occassionally or socially
- ☐ 3 Less than half a pack a day
- ☐ 4 Between half a pack and one pack a day
- ☐ 5 More than one pack a day
- ☐ 6 Former smoker, but no longer smokes

10. Is the subject currently on oral contraceptives (females only)? ☐ 1 Yes ☐ 0 No ☐ 2 Not applicable

11. Does the subject have diabetes? ☐ 1 Yes ☐ 0 No

a. If yes, type: ☐ 1 Type I
☐ 0 Type II

12. Does the subject currently have any malignancies?

☐ 1 Yes, please describe: _____

a. If yes, has the subject undergone chemotherapy treatment within the last 6 months? ☐ 1 Yes ☐ 0 No

If yes, date of last treatment: ☐☐/☐☐☐/☐☐☐☐

b. If yes, is the subject undergoing this surgical procedure for this malignancy? ☐ 1 Yes ☐ 0 No

☐ 0 No

Preoperative DRAFT Form
Form 2C

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 2 Preoperative

THROMBOSIS RISK FACTOR ASSESSMENT*

13. Choose all that apply. Each risk factor represents 1 POINT	Yes	No
a. Age 41-60 years	☐ 1	☐ 0
b. Minor surgery planned	☐ 1	☐ 0
c. History of prior major surgery (<1 month)	☐ 1	☐ 0
d. Varicose veins	☐ 1	☐ 0
e. History of inflammatory bowel disease (i.e. Crohn's Disease, ulcerative colitis)	☐ 1	☐ 0
f. Swollen legs (current)	☐ 1	☐ 0
g. Obesity (BMI > 25 kg/m^2)	☐ 1	☐ 0
h. Acute myocardial infarction	☐ 1	☐ 0
i. Congestive Heart Failure (<1 month)	☐ 1	☐ 0
j. Sepsis (<1 month)	☐ 1	☐ 0
k. Serious lung disease including pneumonia (<1 month)	☐ 1	☐ 0
i. Abnormal pulmonary function (COPD)	☐ 1	☐ 0
j. Medical patient currently at bed rest	☐ 1	☐ 0
k. Other risk factors: ☐	☐ 1	☐ 0
l. Oral contraceptives or hormone replacement therapy	☐ 1	☐ 0
m. Pregnancy or Postpartum (<1 month)	☐ 1	☐ 0
n. History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant	☐ 1	☐ 0

14. Subtotal ☐ *(Total number "yes" to Question #13) x* ***1 point***

*Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell Jr. DA, Caprini JA. "A Validation Study of a Retrospective Venous Thromboembolism Risk Scoring Method". Annals of Surgery 2009. http://www.venousdisease.com/documents/Annals_of_Surgery_VTE_Risk_Score_Validation.pdf

Ŧ http://www.med.umich.edu/clinical/images/VTE-Risk-Assessment.pdf

Preoperative DRAFT Form
Form 2D

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 2 Preoperative

THROMBOSIS RISK FACTOR ASSESSMENT*₸ (Continued)

15. Choose all that apply. Each risk factor represents 2 POINTS	Yes	No
a. Age 61-74 years	☐ 1	☐ 0
b. Arthroscopic surgery	☐ 1	☐ 0
c. Malignancy (present or previous)	☐ 1	☐ 0
d. Major surgery (>45 minutes)	☐ 1	☐ 0
e. Laparoscopic surgery (>45 minutes)	☐ 1	☐ 0
f. Patient confined to bed (> 72 hours)	☐ 1	☐ 0
g. Immobilizing plaster cast (< 1 month)	☐ 1	☐ 0
h. Central venous access	☐ 1	☐ 0

16. Subtotal ☐ *(Total number "yes" to Question #15) x* ***2 points***

17. Choose all that apply. Each risk factor represents 3 POINTS	Yes	No
a. Age 75 years or older	☐ 1	☐ 0
b. History of DVT/PE	☐ 1	☐ 0
c. Family history of thrombosis	☐ 1	☐ 0
d. Positive Factor V Leiden	☐ 1	☐ 0
e. Positive Prothrombin 20210A	☐ 1	☐ 0
f. Elevated serum homocysteine	☐ 1	☐ 0
g. Positive lupus anticoagulant	☐ 1	☐ 0
h. Elevated anticardiolipin antibodies	☐ 1	☐ 0
i. Heparin-induced thrombocytopenia (HIT) (Do not use heparin or any low molecular weight heparin)	☐ 1	☐ 0
j. Other congenital or acquired thrombophilia If yes: Type ☐	☐ 1	☐ 0

18. Subtotal ☐ *(Total number "yes" to Question #17) x* ***3 points***

*Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell Jr. DA, Caprini JA. "A Validation Study of a Retrospective Venous Thromboembolism Risk Scoring Method". Annals of Surgery 2009. http://www.venousdisease.com/documents/Annals_of_Surgery_VTE_Risk_Score_Validation.pdf

₸ http://www.med.umich.edu/clinical/images/VTE-Risk-Assessment.pdf

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Preoperative DRAFT Form
Form 2E

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 2 Preoperative

THROMBOSIS RISK FACTOR ASSESSMENT*Ŧ (Continued)

19. Choose all that apply. Each risk factor represents 5 POINTS	Yes	No
a. Elective major lower extremity arthroplasty	☐ 1	☐ 0
b. Hip, pelvis, or leg fracture (<1 month)	☐ 1	☐ 0
c. Stroke (<1 month)	☐ 1	☐ 0
d. Multiple trauma (<1 month)	☐ 1	☐ 0
e. Acute spinal cord injury (paralysis) (<1 month)	☐ 1	☐ 0

20. Subtotal ☐ *(Total number "yes" to Question #19) x* ***5 points***

21. Total Risk Factor Score ☐ *(Sum of reported values from Questions 14, 16, 18, and 20)*

*Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell Jr. DA, Caprini JA. "A Validation Study of a Retrospective Venous Thromboembolism Risk Scoring Method". Annals of Surgery 2009. http://www.venousdisease.com/documents/Annals_of_Surgery_VTE_Risk_Score_Validation.pdf

Ŧ http://www.med.umich.edu/clinical/images/VTE-Risk-Assessment.pdf

Please perform a Complete Blood Count and assessment of coagulation status (platelet count, PTT, INR, and fibrinogen) and a Complement C3 test will be evaluated preoperatively within 30 days of surgery. Document lab results on the Laboratory Form.

☐ Principal Investigator Signature

☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Operative DRAFT Form
Form 3A

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Surgery Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 3 Intraoperative

SURGICAL PROCEDURE INFORMATION

1. Surgeon Name:

2. Description of Surgical procedure:

- ☐ 1 Coronary Artery Bypass Graft (CABG)
- ☐ 2 Re-do CABG
- ☐ 3 Aortic Valve Repair
- ☐ 4 Re-do Aortic Valve Repair
- ☐ 5 Mitral Valve Repair
- ☐ 6 Re-do Mitral Valve Repair
- ☐ 7 Liver Resection
- ☐ 8 Total Splenectomy
- ☐ 9 On-clamp Partial Nephrectomy
- ☐ 10 Radical Nephrectomy
- ☐ 11 Other, please specify, including type of implant or graft, if applicable:

3. Was aspirin use discontinued prior to surgery? ☐ 1 Yes ☐ 0 No ☐ N/A
if yes, how far in advance of surgery was aspirin use discontinued?

4. Please describe any concomitant procedures, if applicable:

BLEEDING SITE INFORMATION

5. Bleeding site to be evaluated (please select one):

- ☐ 1 Cardiac procedure: epicardium
- ☐ 2 Liver resection: resected liver surface
- ☐ 3 Total splenectomy: retroperitoneal surface
- ☐ 4 On-clamp partial nephrectomy: kidney bed
- ☐ 5 Radical nephrectomy: retroperitoneal cavity
- ☐ 6 Cardiac procedure: aortic anastomosis or aortotomy suture line

6. Conventional means for hemostasis performed before assessment of bleeding (select all that apply):

- ☐ 1 Suture
- ☐ 2 Clips
- ☐ 3 Electrocautery
- ☐ 4 Argon beam coagulator
- ☐ 5 Reversal of coagulopathy
- ☐ 6 Staples
- ☐ 7 Other, please specify all:

Operative DRAFT Form
Form 3B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ [3] Intraoperative

BLEEDING SEVERITY ASSESSMENT

7. Mass (g) of packaged, sterile gauze: ☐☐.☐☐☐

8. Mass (g) of 2 packaged 5g bellows – PERCLOT: ☐☐.☐☐☐

9. Mass (g) of 2 packaged 5g bellows – ARISTA: ☐☐.☐☐☐

10. Mass (g) of unused gauze, gauze packaging, and blood-stained gauze: ☐☐.☐☐☐

11. Blood mass (g) collected: ☐☐.☐☐☐ *[(Value from Question #9) – (Value from Question #6)]*

12. Time gauze held (seconds): ☐☐

13. Bleeding Site length[Ŧ] (cm): ☐☐.☐

14. Bleeding Site width[Ŧ] (cm): ☐☐.☐

15. Anatomic Site (cm^2): ☐☐.☐ *[Bleeding site length[Ŧ] (cm) x Bleeding site width[Ŧ](cm)]*
Not to exceed 25 cm^2

16. Calculate Bleeding Flux $\left(\frac{g}{cm^2 \cdot s}\right)$: ☐.☐☐☐☐☐☐☐

$$Bleeding\ Flux\ \left(\frac{g}{(cm^2 \cdot s)}\right) = \frac{[Blood\ Mass\ Collected\ (g)]}{[Anatomic\ Site\ (cm^2) \cdot Time\ Gauze\ held(s)]}$$

17. Anatomic Application Site (cm^2): ☐☐.☐ *[(Bleeding site length[Ŧ] (cm) +1 cm) x (Bleeding site width[Ŧ](cm)+1 cm)]*
See responses to Questions 12 and 13 to calculate.
Not to exceed 47 cm^2

18. Verbal description of each site on the bleeding severity scale: ☐ (a-f) See Below Descriptors.

a. A score of 0 denotes no active bleeding. The surgical field is completely dry with no blood or the surgical field is stained with blood, but this blood is completely stagnant.
b. A score of 1 denotes oozing. The rate of bleeding is slow. This is what one may expect from capillary, venular, or arteriolar bleeding.
c. A score of 2 denotes slight bleeding. The rate of bleeding is slightly faster than oozing. There is no pulsatile flow present. This is what one may expect from capillary, venular, or arteriolar bleeding.
d. A score of 3 denotes moderate bleeding. There may be a weak pulsatile flow present. If there is a pulsatile flow, the rate of blood flow is similar to the rate of flow for a score of 2. If there is no pulsatile flow, the rate of blood flow is faster than slight bleeding.
e. A score of 4 denotes severe bleeding. For the most part, pulsatile flow is present. If there is no pulsatile flow, then the rate of blood flow is extremely rapid.
f. A score of 5 denotes life-threatening bleeding. A strong pulsatile flow is always present and the rate of blood flow is extremely rapid.

[Ŧ] Greatest perpendicular measurements (cm)

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Operative DRAFT Form

Form 3C

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____

Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

CONFIRMATION OF INTRAOPERATIVE ELIGIBILITY CRITERIA

The following questions regarding INCLUSION must be answered YES for subject to be eligible for entry into the investigation.

19. Subject in whom there is bleeding at the specified area for each surgical procedure after any applicable conventional means for hemostasis are attempted as specified by the intraoperative protocol.	☐ 1 Yes	☐ 0 No
20. Subject in whom all visible vessels or suture holes ≥ 2mm in diameter, suture line gaps ≥ 2mm, and large needle holes ≥ 2mm have been ligated prior to application.	☐ 1 Yes	☐ 0 No
21. Subject in whom the bleeding flux from the identified bleeding site is > 0.000040 g/cm^2*s and ≤ 0.013 g/s*cm^2. ***See Question 15.***	☐ 1 Yes	☐ 0 No
22. Subject in whom the Anatomic Site is ≤ 25 cm^2. ***See Question 14.***	☐ 1 Yes	☐ 0 No
23. Subject in whom the Anatomic Application Site is ≤ 47 cm^2. ***See Question 16.***	☐ 1 Yes	☐ 0 No
24. Subject is undergoing one of the following open elective cardiac, general, or urological surgical procedures: Cardiac procedure (Epicardium); Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line); Liver resection; Total splenectomy; On-clamp partial nephrectomy; or Radical nephrectomy.	☐ 1 Yes	☐ 0 No

The following questions regarding EXCLUSION must be answered NO for subject to be eligible for entry into the investigation.

25. Subject in whom any major intraoperative bleeding incidences during the surgical procedure occurred (i.e. subject with assignment of an American College of Surgeons Advanced Trauma Life Support Hemorrhage Class of II, III, or IV Hemorrhage).*	☐ 1 Yes	☐ 0 No
26. Subject who has an active or potential infection at the surgical site, or whose surgical wound is defined as a wound classification of CO (Contaminated) or D (Dirty or Infected) based upon the Center of Disease Control and Prevention's wound classification system. **	☐ 1 Yes	☐ 0 No
27. Subject who has undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery.	☐ 1 Yes	☐ 0 No
28. Subject undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis).	☐ 1 Yes	☐ 0 No

***Class I Hemorrhage** involves up to 15% of blood volume. There is typically no change in vital signs and fluid resuscitation is not usualyl necessary. **Class II Hemorrhage** involves 15-30% of total blood volume. A patient is often tachycardic (rapid heart beat) 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. The patient may exhibit slight changes in behavior. Volume resuscitation with crystalloids (saline solution or Lactated Ringer's solution) is all that is typically required. Blood transfusion is not typically required. **Class III Hemorrhage** involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral perfusion (shock), such as capillary refill worsens, and the mental status worsens. Fluid resuscitation with crystalloid and blood transfusion are usually necessary. **Class IV Hemorrhage** 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.

****Class I/Clean (C):** An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria. ***Class II/Clean-Contaminated (CC):*** An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered. ***Class III/Contaminated (CO):*** Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category. ***Class IV/ Dirty-Infected* (D):** Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation. (http://www.cdc.gov/hicpac/SSI/table7-8-9-10-SSI.html)

‡ Patients undergoing Cardiac procedures only.

Operative DRAFT Form
Form 3D

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

ENROLLMENT & RANDOMIZATION

29. Did the subject meet all intraoperative eligibility criteria? ☐ 1 Yes ☐ 0 No

Must be answered YES for the subject to be enrolled and randomized.

30. Subject randomized to:

☐ 1 PerClot

☐ 2 Arista

31. Device Identifier Number: _____

32. Note any technical failures (check all that apply):

☐ 1 Contraindication

☐ 2 Misdiagnosis

☐ 3 Intraoperative death prior to treatment

☐ 4 Other, please specify: _____

☐ 0 Not applicable

AFTER RANDOMIZATION AND BEFORE HEMOSTATIC AGENT APPLICATION

33. Blood pressure:

a. Diastolic: _____ mmHg

b. Systolic: _____ mmHg

34. Pulse: _____ beats/min

35. Core body temperature: ☐☐☐.☐ °C

36. Blood Glucose: _____ mg/dL

37. Use of any blood modifiers, insulin, or blood sugar lowering medications?

☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form.
Refer to Appendices L & K For Complete List.

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Operative DRAFT Form

Form 3E

CryoLife®

Form completed by: _____

Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

TOTAL HEMOSTATIC PRODUCT APPLIED

38. Number of bellows used: 1 ☐ 1 2 ☐ 2

39. Verify mass of 2 packaged 5g bellows before application – RANDOMIZED: ☐☐.☐☐ grams

40. Mass of packaging: ☐☐.☐☐ grams

41. Mass of bellows and applicator tips after application: ☐☐.☐☐ grams

42. Mass of hemostat applied: ☐☐.☐☐ grams

[(Value from Question #41) – (Value from Question #42) – (Value from Question #43)]

43. Time of Application:
HH:MM:SS (24-hour clock) ☐☐:☐☐:☐☐ ☐ 0 N/A

5 MINUTE ASSESSMENT OF HEMOSTASIS

44. Has hemostasis been achieved?

☐ 1 Yes ☐ 0 No

45. Time of Assessment
HH:MM:SS (24-hour clock)

☐☐:☐☐:☐☐

46. Was the study device dislodged during gauze removal?

☐ 1 Yes ☐ 0 No

47. Was dislodgement perceived to be the sole reason for hemostatic failure?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

Operative DRAFT Form
Form 3F

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

7 MINUTE ASSESSMENT OF HEMOSTASIS

48. Has hemostasis been achieved?

☐ 1 Yes ☐ 0 No

49. Time of Assessment
HH:MM:SS (24-hour clock)

☐☐ : ☐☐ : ☐☐

50. Was the study device dislodged during gauze removal?

☐ 1 Yes ☐ 0 No

51. Was dislodgement perceived to be the sole reason for hemostatic failure?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

If hemostasis is confirmed at 7 minutes, observe site for an additional 5 minutes.

ADDITIONAL 5 MINUTE OBSERVATION FOR MAINTENANCE OF HEMOSTASIS

52. Was hemostasis maintained for the additional 5 minute observation period (12 minutes post-application)?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

53. Time of Assessment:
HH:MM:SS (24-hour clock) ☐☐ : ☐☐ : ☐☐ ☐ 0 N/A

If breakthrough bleeding occurs during additional 5 minute observation, document that time as the Time of Assessment.

ADDITIONAL HEMOSTATIC MEASURES

54. If hemostasis was not achieved at 7 minutes, or if hemostasis was achieved at 7 minutes but not maintained through the additional 5 minute observation (12 minutes post-application), what alternative means of achieving hemostasis were used (check all that apply):

☐ a. Stitches
If checked, specify # of stitches: _____

☐ b. Manual pressure applied
If checked, specify time (minutes): _____

☐ c. Other hemostatic device
If checked, specify: _____

☐ d. Other
If checked, specify: _____

☐ e. No additional actions were taken or products used ☐ Not applicable

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Operative DRAFT Form
Form 3G

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

POST HEMOSTASIS ASSESSMENTS (Prior to Closure)

55. Volume of fluid used to rinse away excess Study Device: ☐☐☐ mL

56. After saline irrigation and aspiration , estimate the amount of hemostatic material remaining in this subject in relation to the original amount applied and document the amount of saline irrigation used:

- ☐ 1 Approximately 0% - almost all or all of the material was removed
- ☐ 2 Approximately 25% - about 75% of the material was removed
- ☐ 3 Approximately 50% - about 50% of the material was removed
- ☐ 4 Approximately 75% - about 25% of the material was removed
- ☐ 5 Approximately 100% - very little or none of the material was removed

57. Blood pressure:
   a. Diastolic: ☐☐☐ mmHg
   b. Systolic: ☐☐☐ mmHg

58. Pulse: ☐☐☐ beats/min

59. Core body temperature: ☐☐.☐ °C

60. Use of any blood modifiers, insulin, or blood sugar lowering medications? ☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form. Refer to Appendices K & L For Complete List.

61. Placement of Drain: ☐ 1 Yes ☐ 0 No *If yes, time of drain placement (24-hour clock) (HH:MM) :* ☐☐ : ☐☐

62. Prior to closure asses if the treated bleeding site maintained hemostasis ☐ 1 Yes ☐ 0 No

ADDITIONAL HEMOSTATIC MEASURES

63. If hemostasis has not maintained prior to closure, what alternative means of achieving hemostasis were used (check all that apply):

- ☐ a. Stitches
  If checked, specify # of stitches: _____
- ☐ b. Manual pressure applied
  If checked, specify time (minutes): _____
- ☐ c. Other hemostatic device
  If checked, specify: _____
- ☐ d. Other
  If checked, specify: _____
- ☐ e. No additional actions were taken or products used ☐ Not applicable

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Operative DRAFT Form

Form 3H

CryoLife®

Form completed by: _____

Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ Intraoperative

AFTER COMPLETION OF OPERATIVE PROCEDURE

64. Total operative time (skin incision to skin closure): ☐☐☐ minutes

65. Estimated total blood loss: ☐ mL

66. Other Hemodilution:

a. Colloids: ☐ mL

b. Crystalloids: ☐ mL

c. Urine output: ☐ mL

d. Other, please specify: ☐ ☐ mL

67. Intraoperative blood products:

Red Blood Cells ☐☐ Units Fresh Frozen Plasma ☐☐ Units

Platelets ☐☐ Units Cryoprecipitate ☐☐ Units

68. Use of any blood modifiers, insulin, or blood sugar lowering medications? ☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers/ Insulin or Blood Sugar Lowering Medications Form. Refer to Appendices L & K for Complete List.

69. Please list any other topical hemostatic agents used during procedure: ☐ 0 No other topical hemostatic agents used

☐

Record Blood Glucose (mg/dL) within one hour following device application on Laboratory Form.
Note: Blood glucose measurement should be evaluated by a venous blood draw or Nova StatStrip blood glucose meter.

Operative DRAFT Form
Form 3I

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / ____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

CALCULATION OF NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE (NNIS)*‡

70. The patient's procedure is classified as (select one):

- ☐ 0 Clean
- ☐ 1 Clean-Contaminated
- ☐ 2 Contaminated
- ☐ 3 Dirty

71. ASA score (select one): See Table 1.

- ☐ 1 Class I
- ☐ 2 Class II
- ☐ 3 Class III
- ☐ 4 Class IV
- ☐ 5 Class V

Table 1. Physical Status Classification for Surgical Patients *‡

Class I	A normally healthy patient
Class II	A patient with mild systemic disease
Class III	A patient with severe systemic disease
Class IV	A patient with severe systemic disease that is a constant threat to life
Class V	A moribund patient not expected to survive without the operation

72. T Point (hours) for procedure (select one): See Table 2.

- ☐ 1 1
- ☐ 2 2
- ☐ 3 3
- ☐ 4 4
- ☐ 5 5
- ☐ 6 Other, please specify: _____

Table 2. The T Point for Common Surgical Procedures*

Operation	T Point (hours)
Coronary artery bypass graft	5
Bile duct, liver, or pancreatic surgery	4
Nephrectomy	4
Splenectomy	3
Colonic surgery	3
Vascular surgery	3
Abdominal or vaginal hysterectomy	2
Ventricular shunt	2
Herniorrhaphy	2
Appendectomy	1

73. Select all that apply:

This simplified risk index has a range from 0 to 3 points. A point is added to the patient's risk index for each of the following 3 variables:

a. **1 point** - The patient has an operation that is classified as either contaminated or dirty. ☐ *See Operative Form Question 70.*

b. **1 point** - The patient has an American Society of Anesthesiologists (ASA) preoperative assessment score of III, IV, or V (Table 1) ☐ *See Operative Form Question 71.*

c. **1 point** - The duration of the operation exceeds the 75th percentile where a standard T point (75% percentile) was determined from the NNIS database (Table 2); the T point is defined as the length of time in hours that represents the 75th percentile of procedures reported in the NNIS survey ☐ *See Operative Form Question 64 and Question 72.*

Checked boxes from (73a + 73b + 73c) = ☐ **NNIS Risk Index**

* "National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004" http://www.cdc.gov/nhsn/PDFs/dataStat/NNIS_2004.pdf

‡ http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf

Operative DRAFT Form
Form 3J

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

DEVICE MALFUNCTIONS*

74. Incidence of any of the following device malfunctions (please check all that apply)?*

a. Blockage within device or device component (FDA Source Code 1065)	☐ 1 Yes	☐ 0 No
b. Break - undesired damage or breakage of device or device component (FDA Source Code 1069)	☐ 1 Yes	☐ 0 No
c. Clumping - granules are aggregated into irregular masses (FDA Source Code 1095)	☐ 1 Yes	☐ 0 No
d. Coagulation in device or device component - clogging of applicator tip (FDA Source Code 1096)	☐ 1 Yes	☐ 0 No
e. Device component missing (FDA Source Code 2306)	☐ 1 Yes	☐ 0 No
f. Detachment of device or device component (FDA Source Code 2907)	☐ 1 Yes	☐ 0 No
g. Device clogged (FDA Source Code 1094)	☐ 1 Yes	☐ 0 No
h. Device damaged prior to use (FDA Source Code 2284)	☐ 1 Yes	☐ 0 No
i. Inability to irrigate (FDA Source Code 1337)	☐ 1 Yes	☐ 0 No
j. Inaccurate delivery (FDA Source Code 2339)	☐ 1 Yes	☐ 0 No
k. Occlusion (obstruction or blockage) within device or device component (FDA Source Code 2423)	☐ 1 Yes	☐ 0 No

l. Other, please specify:
Please include FDA Source Code

*Device malfunctions will be reported using nomenclature specific to devices per the FDA Center for Devices and Radiological Health Event Reporting webpage: http://www.fda.gov.MedicalDevices/Safety/ReportaProblem/EvenProblemCodes/ucm/134751.htm.

INTRAOPERATIVE ADVERSE EVENTS

75. Did any complications/adverse events occur intraoperatively?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

76. Please list any known intraoperative deviations to the protocol: ☐ 0 Not applicable

77. Additional comments: ☐ 0 Not applicable

Principal Investigator Signature

☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Postoperative DRAFT Form
Form 4A

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 4 Postoperative

POSTOPERATIVE ASSESSMENT

1. Does the subject have clinical signs or symptoms of bleeding?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*
☐ 0 No

2. Did the subject undergo a reoperation?

☐ 1 Yes *If yes, please complete the Reoperation Form.*
☐ 0 No

3. Blood products administered postoperatively:

☐ 1 None

Blood Product	Units
Red Blood Cells	☐☐
Platelets	☐☐
Fresh Frozen Plasma	☐☐
Cryoprecipitate	☐☐

4. Use of any blood modifiers or reversal drugs? (This includes products known to affect bleeding, i.e., NSAIDs, ASA, omega-3 fatty acid supplements, herbal supplements.) *A list of blood modifiers can be found in the protocol Appendix L.*

☐ 1 Yes *If yes, please complete the Blood Modifiers / Insulin Blood Sugar Lowering Medications form.*
☐ 0 No

5. Use or administration of insulin or blood-sugar lowering medication? *A list of blood-sugar lowering medications can be found in the protocol Appendix K.*

☐ 1 Yes *If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications form.*
☐ 0 No

6. Drainage: ☐ Not applicable

a. Drainage volume within 24 hours postoperatively: ☐☐☐☐ mL

b. Time of drainage volume measurement (24-hour clock, hh:mm): ☐☐:☐☐

7. Has the subject had any complications or adverse events since surgery?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*
☐ 0 No

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Postoperative DRAFT Form
Form 4B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____

Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

CLINICAL SIGNS OR SYMPTOMS OF THROMBOEMBOLISM

8. Does the subject have clinical signs, symptoms, or events that may be associated with thromboembolism? ***Check all that apply.***

A. Leg pain	☐ 1 Yes	☐ 0 No
B. Leg swelling	☐ 1 Yes	☐ 0 No
C. Chest pain	☐ 1 Yes	☐ 0 No
D. Shortness of breath	☐ 1 Yes	☐ 0 No
E. Transient orthostatic hypotension	☐ 1 Yes	☐ 0 No
F. Decreased level of consciousness presumed to be narcotic excess	☐ 1 Yes	☐ 0 No
G. Fainting spell	☐ 1 Yes	☐ 0 No
H. Hypoxia	☐ 1 Yes	☐ 0 No
I. Sudden death	☐ 1 Yes	☐ 0 No
J. Death without autopsy	☐ 1 Yes	☐ 0 No
K. Postoperative stroke due to patent foramen ovale	☐ 1 Yes	☐ 0 No
L. Suspected myocardial infarction	☐ 1 Yes	☐ 0 No
M. Failure to thrive, sinking spell, or "the dwindles"	☐ 1 Yes	☐ 0 No
N. Post-thrombotic syndrome during physical examination of the legs (standing)	☐ 1 Yes	☐ 0 No
O. Post-operative pneumonia	☐ 1 Yes	☐ 0 No
P. Follow-up of patient for re-admission or death prior to last study evaluation	☐ 1 Yes	☐ 0 No

If yes to any subpart of Question 8, please complete the Adverse Event form.

Discharge DRAFT Form
Form 5A

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Discharge Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 5 Discharge

DISCHARGE ASSESSMENT

1. Does the subject have clinical signs or symptoms of bleeding?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

2. Has the subject undergone a reoperation?

☐ 1 Yes *If yes, please complete the Reoperation Form.*

☐ 0 No

3. Use of any blood modifiers or reversal drugs? (This includes products known to affect bleeding, i.e., NSAIDs, ASA, omega-3 fatty acid supplements, herbal supplements.) *A list of blood modifiers can be found in the protocol Appendix L.*

☐ 1 Yes *If yes, please complete the Blood Modifiers/Blood Sugar Lowering Medications Form.*

☐ 0 No

4. Use or administration of insulin or blood-sugar lowering medication? *A list of blood-sugar lowering medications can be found in the protocol Appendix K.*

☐ 1 Yes *If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form.*

☐ 0 No

5. Total hospitalization time:

☐☐ days

6. Has the subject had any complications or adverse events since surgery?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

7. Drainage: ☐ Not applicable

a. Drainage volume: ☐☐☐☐ mL

b. Time of drainage volume measurement (hh:mm): ☐☐:☐☐

c. Time of drainage removal (24-hour clock, HH:MM): ☐☐:☐☐

Note: Discharge evaluations will occur at hospital discharge or between 24 hours and 14 days postoperatively.

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Discharge DRAFT Form
Form 5B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / ____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Discharge Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 5 Discharge

DVT PROPHYLAXIS

8. Deep Venous Thrombosis (DVT) prophylactic methods employed (*check all that apply*): ☐ 0 Not applicable

	Start Date (DD/MMM/YYYY):	End Date (DD/MMM/YYYY):
☐ 1 Unfractionated heparin (low dose UH)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 2 Low molecular weigh heparin (LMWH)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 3 Pneumatic compression device(s) (PCD)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 4 IVC filters	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 5 Compression stockings	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 6 Coumadin	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 7 Other, please specify all and duration:		

Principal Investigator Signature ☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Follow-Up DRAFT Form
Form 6A

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

Visit Type: ☐ 6 6-week follow-up ☐ 6 Unscheduled

FOLLOW-UP ASSESSMENT

1. Does the subject have clinical signs or symptoms of bleeding?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

2. Has the subject undergone a reoperation?

☐ 1 Yes *If yes, please complete the Reoperation Form.*

☐ 0 No

3. Has the subject been re-hospitalized?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

4. Use of any blood modifiers or reversal drugs? (This includes products known to affect bleeding, i.e., NSAIDs, ASA, omega-3 fatty acid supplements, herbal supplements.) *A list of blood modifiers can be found in the protocol Appendix L.*

☐ 1 Yes *If yes, please complete the Blood Modifiers/Blood Sugar Lowering Medications Form.*

☐ 0 No

5. Use or administration of insulin or blood-sugar lowering medication? *A list of blood-sugar lowering medications can be found in the protocol Appendix K.*

☐ 1 Yes *If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form.*

☐ 0 No

6. Has the patient had any complications or adverse events since surgery?

☐ 1 Yes *If yes, please complete the Adverse Event Form.*

☐ 0 No

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Follow-Up DRAFT Form
Form 6B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

CLINICAL SIGNS OR SYMPTOMS OF THROMBOEMBOLISM

7. Does the subject have clinical signs, symptoms, or events that may be associated with thromboembolism? ***Check all that apply.***

A. Leg pain	☐ 1 Yes	☐ 0 No
B. Leg swelling	☐ 1 Yes	☐ 0 No
C. Chest pain	☐ 1 Yes	☐ 0 No
D. Shortness of breath	☐ 1 Yes	☐ 0 No
E. Transient orthostatic hypotension	☐ 1 Yes	☐ 0 No
F. Decreased level of consciousness presumed to be narcotic excess	☐ 1 Yes	☐ 0 No
G. Fainting spell	☐ 1 Yes	☐ 0 No
H. Hypoxia	☐ 1 Yes	☐ 0 No
I. Sudden death	☐ 1 Yes	☐ 0 No
J. Death without autopsy	☐ 1 Yes	☐ 0 No
K. Postoperative stroke due to patent foramen ovale	☐ 1 Yes	☐ 0 No
L. Suspected myocardial infarction	☐ 1 Yes	☐ 0 No
M. Failure to thrive, sinking spell, or "the dwindles"	☐ 1 Yes	☐ 0 No
N. Post-thrombotic syndrome during physical examination of the legs (standing)	☐ 1 Yes	☐ 0 No
O. Post-operative pneumonia	☐ 1 Yes	☐ 0 No
P. Follow-up of patient for re-admission or death prior to last study evaluation	☐ 1 Yes	☐ 0 No
Q. Other	☐ 1 Yes	☐ 0 No

Please describe: _____

If yes to any subpart of Question 7, please complete the Adverse Event form.

Follow-Up DRAFT Form
Form 6C

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

DVT PROPHYLAXIS

10. Deep Venous Thrombosis (DVT) prophylactic methods employed (*check all that apply*): ☐ 0 Not applicable

	Start Date (DD/MMM/YYYY):	End Date (DD/MMM/YYYY):
☐ 1 Unfractionated heparin (low dose UH)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 2 Low molecular weigh heparin (LMWH)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 3 Pneumatic compression device(s) (PCD)	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 4 IVC filters	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 5 Compression stockings	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 6 Coumadin	☐☐/☐☐☐/☐☐☐☐	☐☐/☐☐☐/☐☐☐☐
☐ 7 Other, please specify all and duration:		

Principal Investigator Signature ☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Follow-Up DRAFT Form
Form 7

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

Visit Type: ☐ 6 24-month follow-up – oncology patients only

FOLLOW-UP ASSESSMENT

1. Is the subject alive?

☐ 1 Yes
☐ 0 No *If No, please complete the Adverse Event Form.*
☐ Unknown *If unknown, check all method of contact that apply.*

2. Confirmation methods utilized:

☐ 1 Medical Record Review
☐ 2 Confirmation of Death via Obituary
☐ 3 Email/Letter
☐ 4 Phone Call
☐ 5 Lost to Follow up

The Subject is considered lost to follow up after three failed attempts to contact the subject by phone, letter, and/or email.

☐ 6 Other:_____

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Blood Modifiers / Insulin or Blood Sugar Lowering Medications DRAFT Form
Form 8

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / ____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

Visit Type: ☐ 2 Preoperative ☐ 3 Operative ☐ 4 Postoperative ☐ 5 Discharge ☐ 6 6 week follow-up
☐ 6 Unscheduled

BLOOD MODIFIERS / INSULIN OR BLOOD SUGAR LOWERING MEDICATIONS / REVERSAL DRUGS

Record only relevant blood modifiers, i.e., Protamine, Aprotinin, etc. A list of blood modifiers and a list of blood sugar lowering medications can be found in the Protocol Appendices K & L.

☐ 1 None

	Generic/Brand Name	Dose (with units)	Frequency*	Route of Admin**	Indication	Start Date and Time DD/MMM/YYYY; HH:MM (24-hour clock)	Stop Date and Time DD/MMM/YYYY; HH:MM (24-hour clock)	or Continuing
1.						☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐ 1
2.						☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐ 1
3.						☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐ 1
4.						☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐ 1
5.						☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐☐/☐☐☐/☐☐☐☐ ☐☐:☐☐	☐ 1

*Frequency: QOD = every other day; QD = every day; BID = twice daily; TID = three times daily; QID = four times daily; QHS = every night; Q6H = every 6 hours; ONCE; PRN = as needed
**Routes of Administration: 1 = IV; 2 = PO; 3 = SL; 4 = IM; 5 = SQ; 6 = PR; 7 = topical; 8 = inhaled; 9 = intra-arterial

Principal Investigator Signature ☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Laboratory DRAFT Form

Form 9

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____

Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Date of Blood Draw (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Time of Blood Draw (HH:MM, 24-Hour clock): ☐☐:☐☐

Visit Type: ☐ 2 Preoperative ☐ 4 Post-operative ☐ 6 Unscheduled

COMPLETE BLOOD COUNT AND COAGULATION STATUS

Lab Test	Value		Not Applicable	Result within normal range?		If not within normal range, is the lab value clinically significant?	
1. Hemoglobin		g/dL	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
2. Hematocrit		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
3. RBC		$x10^9/L$	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
4. WBC		$x10^9/L$	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
5. Neutrophils		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
6. Lymphocytes		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
7. Monocytes		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
8. Eosinophils		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
9. Basophils		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
10. Platelet count		$x10^9/L$	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
11. PTT		seconds	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
12. Fibrinogen		mg/dL	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
13. INR			☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
14. Albumin		g/dL	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
15. HbA1c		%	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
16. C3		mg/dL	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No
17. Blood Glucose[†]		mg/dL	☐ 1	☐ 1 Yes	☐ 0 No	☐ 1 Yes*	☐ 0 No

Note: Blood glucose measurement should be evaluated by a venous blood draw or Nova StatStrip blood glucose meter.

Preoperative Lab work will occur no more than 1 month (30 days) prior to surgery.

**Please complete the Adverse Event Form after device application only.*

[†]*Blood glucose levels should be collected within 1hr (±30 minutes) after device application, 6 hours (±30 minutes), 12 hours (±30 minutes), 24 hours (±30 minutes).*

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Reoperation DRAFT Form
Form 10

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / ____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Surgery Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

Visit Type: ☒ 9 Reoperation

PROCEDURE INFORMATION

1. Reason for reoperation: _____

2. Procedure(s) performed: a. _____
   b. _____
   c. _____

3. Was this reoperation for hemostatic agent application site bleeding?

   ☐ 1 Yes
   ☐ 0 No

   a. If yes, methods used to attempt to obtain hemostasis (check all that apply):

      ☐ 1 Not applicable
      ☐ 2 Make-up stitches (# of stitches: ☐☐)
      ☐ 3 Other, please specify: _____

4. Was the hemostatic device visually apparent?

   ☐ 1 Yes, please comment: _____
   ☐ 0 No

Please complete the Adverse Event Form for all Reoperations.

_____ ☐☐/☐☐☐/☐☐☐☐
Principal Investigator Signature Date (DD/MMM/YYYY)

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Adverse Event DRAFT Form
Form 11A

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

ADVERSE EVENT

1. Description of adverse event:

2. CTCAE-2009* short name for adverse event:

3. Date of onset (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

4. Severity of adverse event (per CTCAE-2009* grade):

- ☐ 1 Grade 1 - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- ☐ 2 Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- ☐ 3 Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
- ☐ 4 Grade 4 - Life-threatening consequences; urgent intervention indicated
- ☐ 5 Grade 5 - Death related to adverse event

5. Outcome of adverse event (check only one):

- ☐ 1 Resolved, date of resolution (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐
- ☐ 2 Resolved with sequelae, please specify:
  Date of resolution (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐
- ☐ 3 Ongoing
- ☐ 4 Caused or prolonged hospitalization
- ☐ 5 Death due to adverse event
- ☐ 6 Death due to other cause, please specify:

6. Expected or unexpected? ☐ 1 Expected ☐ 0 Unexpected

*CTCAE-2009: Common Toxicity Criteria for Adverse Events (2009)
http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

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Adverse Event DRAFT Form
Form 11B

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / ____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

ADVERSE EVENT

7. Relationship to hemostatic device (check only one):

☐ 1 Not related - The adverse event is due to the underlying disease state or is due to concomitant medication or therapy not related to the use of the hemostatic device

☐ 2 Possibly related - The adverse event had a reasonable temporal relationship to the hemostatic device and alternative etiology is equally or more likely compared to the potential relationship with the hemostatic device

☐ 3 Probably related - The adverse event had a strong temporal relationship to the hemostatic device and alternative etiology is less likely compared to the hemostatic device

☐ 4 Definitely related - The adverse event follows a strong temporal relationship to the hemostatic device, follows a known response pattern to the hemostatic device, and cannot reasonbly be explained by known characteristic of the subject's clinical state or other therapies

8. Action taken (check all that apply):

☐ 1 None
☐ 2 Medication, please specify: _____
☐ 3 Laboratory/other tests, please specify: _____
☐ 4 Hospitalization or prolongation of hospitalization
☐ 5 Reoperation*
☐ 6 Observation
☐ 7 Other, please specify: _____

**Please complete the Reoperation Form.*

9. Was this a Serious Adverse Event (SAE)?

☐ 0 No
☐ 1 Yes *If yes, please describe the event by choosing all that apply:*

- ☐ 1 Results in death
- ☐ 2 Results in a life-threatening adverse event
- ☐ 3 Results in inpatient hospitalization or prolongation of existing hospitalization
- ☐ 4 Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- ☐ 5 Results in a congenital anomaly or birth defect
- ☐ 6 Requires intervention to prevent permanent impairment or damage
- ☐ 7 Other Serious, please describe: _____

_____ ☐☐/☐☐☐/☐☐☐☐
Principal Investigator Signature Date (DD/MMM/YYYY)

Completion/Discontinuation
DRAFT Form
Form 12

CryoLife®

Form completed by: _____

Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

DETERMINATION

1. Date subject last evaluated (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

2. Did subject complete the study as planned?

☐ 1 Yes *Please complete the Completion section below (Questions 3 and 4).*

☐ 0 No *Please complete the Discontinuation section below (Question 5)*

COMPLETION

3. Is patient contact information current? ☐ 1 Yes ☐ 0 No* **Please request updated information*

4. For an oncologic patient and/or subject enrolled for a cardiac procedure, has patient been reminded of extended follow-up studies? ☐ 1 Yes ☐ 0 No ☐ 0 Not applicable

DISCONTINUATION

5. Specify reason for discontinuation (check one only):

☐ 1 Subject voluntarily withdrew from the study

☐ 2 Subject non-compliant, please describe: _____

☐ 3 Subject required reoperation, reason: _____

Please complete the Reoperation Form.

☐ 4 Subject experienced a complication/AE resulting in removal from study

Please complete the Adverse Event Form.

☐ 5 Subject experienced irreversible morbidity

☐ 6 Subject lost to follow-up

☐ 7 Subject expired

a. Date of death (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

b. If death occurred within 24 hours of investigational device use, provide time of death (24-hr clock): ☐☐:☐☐

c. Probable cause of death: _____

d. Was an autopsy performed? ☐ 1 Yes ☐ 0 No

If yes, autopsy report is: ☐ 1 Attached ☐ 0 Not available*

e. Was pathological analysis performed? ☐ 1 Yes ☐ 0 No

If yes, pathology report is: ☐ 1 Attached ☐ 0 Not available*

f. Death occurred: ☐ 1 During surgery ☐ 2 After surgery, but prior to discharge ☐ 3 After discharge

☐ 8 Other reason, please specify: _____

**Please provide report via fax to (770) 590-3749 when available.*

_____ ☐☐/☐☐☐/☐☐☐☐

Principal Investigator Signature Date (DD/MMM/YYYY)

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Protocol Deviation DRAFT Form
Form 13

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

PROTOCOL DEVIATION

1. Protocol Deviation:

2. Date of deviation (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐

3. Type of deviation (select one):

- ☐ 1 Informed Consent Procedures
- ☐ 2 Inclusion/Exclusion Criteria
- ☐ 3 Study Procedures
- ☐ 4 Laboratory Procedures
- ☐ 5 Visit schedules
- ☐ 6 Randomization
- ☐ 7 Other, please specify:

4. Status / Action Taken:

Principal Investigator Signature ☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

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Equipment Calibration DRAFT Form
Form 14

CryoLife®

Form completed by: _____

Date form completed: ___ / ___ / ____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Surgery Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 3 Intraoperative

MASS BALANCE CALIBRATION

1. Equipment Number: ☐

2. Mass of Check Weight: ☐☐☐.☐☐☐ grams

3. Does recorded mass meet predefined range of acceptability? ☐ 1 Yes ☐ 0 No

Must be answered YES to proceed with the remainder of the Intraoperative Protocol.

If answered NO, calibrate the scale according to the Calibration Plan.

Perform Check Weight mass measurements until mass displayed is 50.000 ± 0.001 g.

4. Performed by: ☐

5. Verified by: ☐

☐ ☐
Coordinator Initials & Date (dd/mm/yyyy)

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Appendix F: Operative Worksheet

The Operative Worksheet is designed to assist in the collection of study-specific data in the operating room. This Operative Worksheet is provided as an example and may be subject to change, dependent upon the data that will need to be collected intraoperatively.

Operative Worksheets
Page 1

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐

Surgery Date (DD/MMM/YYYY): ☐☐/☐☐☐/☐☐☐☐ Visit Type: ☒ 3 Intraoperative

SURGICAL PROCEDURE INFORMATION

1. Surgeon Name: ☐

2. Description of Surgical procedure:

- ☐ 1 Coronary Artery Bypass Graft (CABG)
- ☐ 2 Re-do CABG
- ☐ 3 Aortic Valve Repair
- ☐ 4 Re-do Aortic Valve Repair
- ☐ 5 Mitral Valve Repair
- ☐ 6 Re-do Mitral Valve Repair
- ☐ 7 Liver Resection
- ☐ 8 Total Splenectomy
- ☐ 9 On-clamp Partial Nephrectomy
- ☐ 10 Radical Nephrectomy
- ☐ 11 Other, please specify, including type of implant or graft, if applicable: ☐

3. Was aspirin use discontinued prior to surgery? ☐ 1 Yes ☐ 0 No ☐ N/A
if yes, how far in advance of surgery was aspirin use discontinued? ☐

4. Please describe any concomitant procedures, if applicable: ☐

BLEEDING SITE INFORMATION

5. Bleeding site to be evaluated (please select one):

- ☐ 1 Cardiac procedure: epicardium
- ☐ 2 Liver resection: resected liver surface
- ☐ 3 Total splenectomy: retroperitoneal surface
- ☐ 4 On-clamp partial nephrectomy: kidney bed
- ☐ 5 Radical nephrectomy: retroperitoneal cavity
- ☐ 6 Cardiac procedure: aortic anastomosis or aortotomy suture line

6. Conventional means for hemostasis performed before assessment of bleeding (select all that apply):

- ☐ 1 Suture
- ☐ 2 Clips
- ☐ 3 Electrocautery
- ☐ 4 Argon beam coagulator
- ☐ 5 Reversal of coagulopathy
- ☐ 6 Staples
- ☐ 7 Other, please specify all: ☐

Operative Worksheets
Page 2

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ [3] Intraoperative

BLEEDING SEVERITY ASSESSMENT

7. Mass (g) of packaged, sterile gauze: ☐☐.☐☐☐

8. Mass (g) of 2 packaged 5g bellows – PERCLOT: ☐☐.☐☐☐

9. Mass (g) of 2 packaged 5g bellows – ARISTA: ☐☐.☐☐☐

10. Mass (g) of unused gauze, gauze packaging, and blood-stained gauze: ☐☐.☐☐☐

11. Blood mass (g) collected: ☐☐.☐☐☐ *[(Value from Question #9) – (Value from Question #6)]*

12. Time gauze held (seconds): ☐☐

13. Bleeding Site length[Ŧ] (cm): ☐☐.☐

14. Bleeding Site width[Ŧ] (cm): ☐☐.☐

15. Anatomic Site (cm^2): ☐☐.☐ *[Bleeding site length[Ŧ] (cm) x Bleeding site width[Ŧ](cm)]*
Not to exceed 25 cm^2

16. Calculate Bleeding Flux $\left(\frac{g}{cm^2 \cdot s}\right)$: ☐.☐☐☐☐☐☐

$$Bleeding\ Flux\ \left(\frac{g}{(cm^2 \cdot s)}\right) = \frac{[Blood\ Mass\ Collected\ (g)]}{[Anatomic\ Site\ (cm^2) \cdot Time\ Gauze\ held(s)]}$$

17. Anatomic Application Site (cm^2): ☐☐.☐ *[(Bleeding site length[Ŧ] (cm) +1 cm) x (Bleeding site width[Ŧ](cm)+1 cm)]*
See responses to Questions 12 and 13 to calculate.
Not to exceed 47 cm^2

18. Verbal description of each site on the bleeding severity scale: ☐ (a-f) See Below Descriptors.

a. A score of 0 denotes no active bleeding. The surgical field is completely dry with no blood or the surgical field is stained with blood, but this blood is completely stagnant.
b. A score of 1 denotes oozing. The rate of bleeding is slow. This is what one may expect from capillary, venular, or arteriolar bleeding.
c. A score of 2 denotes slight bleeding. The rate of bleeding is slightly faster than oozing. There is no pulsatile flow present. This is what one may expect from capillary, venular, or arteriolar bleeding.
d. A score of 3 denotes moderate bleeding. There may be a weak pulsatile flow present. If there is a pulsatile flow, the rate of blood flow is similar to the rate of flow for a score of 2. If there is no pulsatile flow, the rate of blood flow is faster than slight bleeding.
e. A score of 4 denotes severe bleeding. For the most part, pulsatile flow is present. If there is no pulsatile flow, then the rate of blood flow is extremely rapid.
f. A score of 5 denotes life-threatening bleeding. A strong pulsatile flow is always present and the rate of blood flow is extremely rapid.

[Ŧ] Greatest perpendicular measurements (cm)

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Operative Worksheets

Page 3

CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____

Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

CONFIRMATION OF INTRAOPERATIVE ELIGIBILITY CRITERIA

The following questions regarding INCLUSION must be answered YES for subject to be eligible for entry into the investigation.

19. Subject in whom there is bleeding at the specified area for each surgical procedure after any applicable conventional means for hemostasis are attempted as specified by the intraoperative protocol. ☐ Yes 1 ☐ No 0

20. Subject in whom all visible vessels or suture holes ≥ 2mm in diameter, suture line gaps ≥ 2mm, and large needle holes ≥ 2mm have been ligated prior to application. ☐ Yes 1 ☐ No 0

21. Subject in whom the bleeding flux from the identified bleeding site is > 0.000040 g/cm^2*s and ≤ 0.013 g/s*cm^2. ***See Question 15.*** ☐ Yes 1 ☐ No 0

22. Subject in whom the Anatomic Site is ≤ 25 cm^2. ***See Question 14.*** ☐ Yes 1 ☐ No 0

23. Subject in whom the Anatomic Application Site is ≤ 47 cm^2. ***See Question 16.*** ☐ Yes 1 ☐ No 0

24. Subject is undergoing one of the following open elective cardiac, general, or urological surgical procedures: ☐ Yes 1 ☐ No 0

    Cardiac procedure (Epicardium);
    Cardiac procedure (Aortic Anastomosis or Aortotomy Suture Line);
    Liver resection;
    Total splenectomy;
    On-clamp partial nephrectomy; or
    Radical nephrectomy.

The following questions regarding EXCLUSION must be answered NO for subject to be eligible for entry into the investigation.

25. Subject in whom any major intraoperative bleeding incidences during the surgical procedure occurred (i.e. subject with assignment of an American College of Surgeons Advanced Trauma Life Support Hemorrhage Class of II, III, or IV Hemorrhage).* ☐ Yes 1 ☐ No 0

26. Subject who has an active or potential infection at the surgical site, or whose surgical wound is defined as a wound classification of CO (Contaminated) or D (Dirty or Infected) based upon the Center for Disease Control and Prevention wound classification system. ** ☐ Yes 1 ☐ No 0

27. Subject who has undergone platelet receptor GP IIb/IIIa antagonist therapy less than 48 hours prior to surgery. ☐ Yes 1 ☐ No 0

28. Subject undergoing a cardiac procedure in which there is no aortic anastomosis or aortotomy suture line to evaluate using the bleeding severity scale (i.e., not for treatment at the distal coronary artery bypass graft anastomosis). ☐ Yes 1 ☐ No 0

***Class I Hemorrhage** involves up to 15% of blood volume. There is typically no change in vital signs and fluid resuscitation is not usualyl necessary. **Class II Hemorrhage** involves 15-30% of total blood volume. A patient is often tachycardic (rapid heart beat) 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. The patient may exhibit slight changes in behavior. Volume resuscitation with crystalloids (saline solution or Lactated Ringer's solution) is all that is typically required. Blood transfusion is not typically required. **Class III Hemorrhage** involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral perfusion (shock), such as capillary refill worsens, and the mental status worsens. Fluid resuscitation with crystalloid and blood transfusion are usually necessary. **Class IV Hemorrhage** 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.

****Class I/Clean (C):*** An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria. ***Class II/Clean-Contaminated (CC):*** An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered. ***Class III/Contaminated (CO):*** Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category. ***Class IV/ Dirty-Infected*** **(D):** Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation. (http://www.cdc.gov/hicpac/SSI/table7-8-9-10-SSI.html)

‡ Patients undergoing Cardiac procedures only.

Operative Worksheets
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CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

ENROLLMENT & RANDOMIZATION

29. Did the subject meet all intraoperative eligibility criteria? ☐ 1 Yes ☐ 0 No

Must be answered YES for the subject to be enrolled and randomized.

30. Subject randomized to:

☐ 1 PerClot

☐ 2 Arista

31. Device Identifier Number: _____

32. Note any technical failures (check all that apply):

☐ 1 Contraindication

☐ 2 Misdiagnosis

☐ 3 Intraoperative death prior to treatment

☐ 4 Other, please specify: _____

☐ 0 Not applicable

AFTER RANDOMIZATION AND BEFORE HEMOSTATIC AGENT APPLICATION

33. Blood pressure:

a. Diastolic: _____ mmHg

b. Systolic: _____ mmHg

34. Pulse: _____ beats/min

35. Core body temperature: ☐☐☐.☐ °C

36. Blood Glucose: _____ mg/dL

37. Use of any blood modifiers, insulin, or blood sugar lowering medications?

☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form.
Refer to Appendices L & K For Complete List.

Operative Worksheets
Page 5

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / ____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

TOTAL HEMOSTATIC PRODUCT APPLIED

38. Number of bellows used: 1 ☐ 1 2 ☐ 2

39. Verify mass of 2 packaged 5g bellows before application – RANDOMIZED: ☐☐.☐☐ grams

40. Mass of packaging: ☐☐.☐☐ grams

41. Mass of bellows and applicator tips after application: ☐☐.☐☐ grams

42. Mass of hemostat applied: ☐☐.☐☐ grams

[(Value from Question #41) – (Value from Question #42) – (Value from Question #43)]

43. Time of Application:
HH:MM:SS (24-hour clock) ☐☐:☐☐:☐☐ ☐ 0 N/A

5 MINUTE ASSESSMENT OF HEMOSTASIS

44. Has hemostasis been achieved?

☐ 1 Yes ☐ 0 No

45. Time of Assessment
HH:MM:SS (24-hour clock)

☐☐:☐☐:☐☐

46. Was the study device dislodged during gauze removal?

☐ 1 Yes ☐ 0 No

47. Was dislodgement perceived to be the sole reason for hemostatic failure?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

Operative Worksheets
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CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

7 MINUTE ASSESSMENT OF HEMOSTASIS

48. Has hemostasis been achieved?

☐ 1 Yes ☐ 0 No

49. Time of Assessment
HH:MM:SS (24-hour clock)

☐☐ : ☐☐ : ☐☐

50. Was the study device dislodged during gauze removal?

☐ 1 Yes ☐ 0 No

51. Was dislodgement perceived to be the sole reason for hemostatic failure?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

If hemostasis is confirmed at 7 minutes, observe site for an additional 5 minutes.

ADDITIONAL 5 MINUTE OBSERVATION FOR MAINTENANCE OF HEMOSTASIS

52. Was hemostasis maintained for the additional 5 minute observation period (12 minutes post-application)?

☐ 1 Yes ☐ 2 No ☐ 0 N/A

53. Time of Assessment:
HH:MM:SS (24-hour clock) ☐☐ : ☐☐ : ☐☐ ☐ 0 N/A

If breakthrough bleeding occurs during additional 5 minute observation, document that time as the Time of Assessment.

ADDITIONAL HEMOSTATIC MEASURES

54. If hemostasis was not achieved at 7 minutes, or if hemostasis was achieved at 7 minutes but not maintained through the additional 5 minute observation (12 minutes post-application), what alternative means of achieving hemostasis were used (check all that apply):

☐ a. Stitches
If checked, specify # of stitches: _____

☐ b. Manual pressure applied
If checked, specify time (minutes): _____

☐ c. Other hemostatic device
If checked, specify: _____

☐ d. Other
If checked, specify: _____

☐ e. No additional actions were taken or products used ☐ Not applicable

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CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

POST HEMOSTASIS ASSESSMENTS (Prior to Closure)

55. Volume of fluid used to rinse away excess Study Device: ☐☐☐ mL

56. After saline irrigation and aspiration , estimate the amount of hemostatic material remaining in this subject in relation to the original amount applied and document the amount of saline irrigation used:

- ☐ 1 Approximately 0% - almost all or all of the material was removed
- ☐ 2 Approximately 25% - about 75% of the material was removed
- ☐ 3 Approximately 50% - about 50% of the material was removed
- ☐ 4 Approximately 75% - about 25% of the material was removed
- ☐ 5 Approximately 100% - very little or none of the material was removed

57. Blood pressure:
   a. Diastolic: ☐☐☐ mmHg
   b. Systolic: ☐☐☐ mmHg

59. Core body temperature: ☐☐.☐ °C

58. Pulse: ☐☐☐ beats/min

60. Use of any blood modifiers, insulin, or blood sugar lowering medications? ☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers / Insulin or Blood Sugar Lowering Medications Form. Refer to Appendices K & L For Complete List.

61. Placement of Drain: ☐ 1 Yes ☐ 0 No *If yes, time of drain placement (24-hour clock) (HH:MM) :* ☐☐ : ☐☐

62. Prior to closure asses if the treated bleeding site maintained hemostasis ☐ 1 Yes ☐ 0 No

ADDITIONAL HEMOSTATIC MEASURES

63. If hemostasis has not maintained prior to closure, what alternative means of achieving hemostasis were used (check all that apply):

- ☐ a. Stitches
  If checked, specify # of stitches: _____
- ☐ b. Manual pressure applied
  If checked, specify time (minutes): _____
- ☐ c. Other hemostatic device
  If checked, specify: _____
- ☐ d. Other
  If checked, specify: _____
- ☐ e. No additional actions were taken or products used ☐ Not applicable

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CryoLife®

PerClot® - The C.L.O.T. Investigation

Form completed by: _____
Date form completed: ___ / ___ / _____

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒

AFTER COMPLETION OF OPERATIVE PROCEDURE

64. Total operative time (skin incision to skin closure): ☐☐☐ minutes

65. **Estimated total blood loss:** ☐ **mL**

66. Other Hemodilution:

a. Colloids: mL

b. Crystalloids: mL

c. Urine output: mL

d. Other, please specify: ☐ mL

67. Intraoperative blood products:

Red Blood Cells	☐☐	Units	Fresh Frozen Plasma	☐☐	Units
Platelets	☐☐	Units	Cryoprecipitate	☐☐	Units

68. Use of any blood modifiers, insulin, or blood sugar lowering medications? ☐ 1 Yes ☐ 0 No

If yes, please complete the Blood Modifiers/ Insulin or Blood Sugar Lowering Medications Form. Refer to Appendices L & K for Complete List.

69. Please list any other topical hemostatic agents used during procedure: ☐ 0 No other topical hemostatic agents used

☐

Record Blood Glucose (mg/dL) within one hour following device application on Laboratory Form.
Note: Blood glucose measurement should be evaluated by a venous blood draw or Nova StatStrip blood glucose meter.

Operative Worksheets
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CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

CALCULATION OF NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE (NNIS)*‡

70. The patient's procedure is classified as (select one):

- ☐ 0 Clean
- ☐ 1 Clean-Contaminated
- ☐ 2 Contaminated
- ☐ 3 Dirty

71. ASA score (select one): See Table 1.

- ☐ 1 Class I
- ☐ 2 Class II
- ☐ 3 Class III
- ☐ 4 Class IV
- ☐ 5 Class V

Table 1. Physical Status Classification for Surgical Patients *‡

Class I	A normally healthy patient
Class II	A patient with mild systemic disease
Class III	A patient with severe systemic disease
Class IV	A patient with severe systemic disease that is a constant threat to life
Class V	A moribund patient not expected to survive without the operation

72. T Point (hours) for procedure (select one): See Table 2.

- ☐ 1 1
- ☐ 2 2
- ☐ 3 3
- ☐ 4 4
- ☐ 5 5
- ☐ 6 Other, please specify: _____

Table 2. The T Point for Common Surgical Procedures*

Operation	T Point (hours)
Coronary artery bypass graft	5
Bile duct, liver, or pancreatic surgery	4
Nephrectomy	4
Splenectomy	3
Colonic surgery	3
Vascular surgery	3
Abdominal or vaginal hysterectomy	2
Ventricular shunt	2
Herniorrhaphy	2
Appendectomy	1

73. Select all that apply:

This simplified risk index has a range from 0 to 3 points. A point is added to the patient's risk index for each of the following 3 variables:

a. **1 point** - The patient has an operation that is classified as either contaminated or dirty. ☐ *See Operative Form Question 70.*

b. **1 point** - The patient has an American Society of Anesthesiologists (ASA) preoperative assessment score of III, IV, or V (Table 1) ☐ *See Operative Form Question 71.*

c. **1 point** - The duration of the operation exceeds the 75th percentile where a standard T point (75% percentile) was determined from the NNIS database (Table 2); the T point is defined as the length of time in hours that represents the 75th percentile of procedures reported in the NNIS survey ☐ *See Operative Form Question 64 and Question 72.*

Checked boxes from (73a + 73b + 73c) = ☐ **NNIS Risk Index**

* "National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004" http://www.cdc.gov/nhsn/PDFs/dataStat/NNIS_2004.pdf

‡ http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf

Operative Worksheets
Page 10

CryoLife®

Form completed by: _____
Date form completed: ___ / ___ / _____

PerClot® - The C.L.O.T. Investigation

Subject Initials: ☐☐☐ Subject Number: ☐☐☐☐ Visit Type: ☒ 3 Intraoperative

DEVICE MALFUNCTIONS*

74. Incidence of any of the following device malfunctions (please check all that apply)?*

a. Blockage within device or device component (FDA Source Code 1065)	☐ 1 Yes	☐ 0 No
b. Break - undesired damage or breakage of device or device component (FDA Source Code 1069)	☐ 1 Yes	☐ 0 No
c. Clumping - granules are aggregated into irregular masses (FDA Source Code 1095)	☐ 1 Yes	☐ 0 No
d. Coagulation in device or device component - clogging of applicator tip (FDA Source Code 1096)	☐ 1 Yes	☐ 0 No
e. Device component missing (FDA Source Code 2306)	☐ 1 Yes	☐ 0 No
f. Detachment of device or device component (FDA Source Code 2907)	☐ 1 Yes	☐ 0 No
g. Device clogged (FDA Source Code 1094)	☐ 1 Yes	☐ 0 No
h. Device damaged prior to use (FDA Source Code 2284)	☐ 1 Yes	☐ 0 No
i. Inability to irrigate (FDA Source Code 1337)	☐ 1 Yes	☐ 0 No
j. Inaccurate delivery (FDA Source Code 2339)	☐ 1 Yes	☐ 0 No
k. Occlusion (obstruction or blockage) within device or device component (FDA Source Code 2423)	☐ 1 Yes	☐ 0 No

l. Other, please specify:
Please include FDA Source Code

*Device malfunctions will be reported using nomenclature specific to devices per the FDA Center for Devices and Radiological Health Event Reporting webpage: http://www.fda.gov.MedicalDevices/Safety/ReportaProblem/EvenProblemCodes/ucm/134751.htm.

INTRAOPERATIVE ADVERSE EVENTS

75. Did any complications/adverse events occur intraoperatively?

☐ 1 Yes ***If yes, please complete the Adverse Event Form.***

☐ 0 No

76. Please list any known intraoperative deviations to the protocol: ☐ 0 Not applicable

77. Additional comments: ☐ 0 Not applicable

Principal Investigator Signature

☐☐/☐☐☐/☐☐☐☐ Date (DD/MMM/YYYY)

Appendix G: Protocol Signature Page

PerClot® Polysaccharide Hemostatic System
Protocol Signature Page

Clinical Investigation Title: Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System (The C.L.O.T. Investigation)

Protocol Number: PCT1101.011-C (02/15) Amendment 09

IDE Number: G110072

I acknowledge that I have received a copy of the above titled protocol and understand my responsibilities associated with its execution.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

Appendix H: Sample Principal Investigator Agreement

Sample Principal Investigator Agreement

Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System

The C.L.O.T. Investigation

CLINICAL PRINCIPAL INVESTIGATOR: _____

CLINICAL SITE: _____

I hereby agree to participate in a clinical evaluation of PerClot® Polysaccharide Hemostatic System (PerClot) Sponsored by the manufacturer, CryoLife, Inc. ("Sponsor"). I understand that the purpose of this clinical investigation (the "Investigation") is to collect clinical data concerning the safety and efficacy of PerClot versus another hemostatic device (the control) in multiple surgical disciplines when used as an adjunct to conservative measures of achieving hemostasis such as pressure or ligature. I will conduct the Investigation as outlined in the clinical Investigation protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB, in accordance with the following Food and Drug Administration (FDA) regulations: 21 CFR Part 812, Investigational Device Exemptions (IDE); 21 CFR Part 50, Protection of Human Subjects; 21 CFR Part 54, Financial Disclosure by Clinical Investigators; 21 CFR Part 56, Institutional Review Boards, in accordance with the International Conference on Harmonization E6 (Good Clinical Practices),as recognized by FDA. Furthermore,

1. I assure that:

   a. I have read and understand the (i) Clinical Research Agreement entered into by Sponsor, the Institution acting as the Investigation site and me as Principal Investigator (the "Research Agreement") dated _____, and (ii) clinical Investigation protocol and associated evaluation documents ("Protocol") and agree with the Protocol's acceptability.

   b. I have adequate time and subject base to complete the Investigation described in the Protocol, given the magnitude of concurrent studies.

   c. I have the appropriate, relevant qualifications to conduct and oversee the conduct of the Investigation in accordance with the Protocol as described by the following *(check one of the following statements)*:

      ___ My relevant qualifications, including dates, location, extend, and type of experience, are listed in my most recent curriculum vitae (CV), which is attached to this Agreement.

      ___ My CV, which is attached to this Agreement, does not reflect my relevant qualifications; therefore, in addition to a copy of my most recent CV is a statement of my relevant experience including dates, locations, extent, and type of experience.

d. There are no reasons to question my ability to oversee the appropriate conduct of the Investigation described in the Protocol. *(Check one of the following statements)*

___ I have never participated in an investigation or other research activity which was terminated by FDA, the IRB (or equivalent), or a sponsor of an investigation due to a non-compliance issue.

___ I have participated in an investigation or other research activity which was terminated by FDA, the IRB (or equivalent), or sponsor due to a non-compliance issue. The specific circumstances leading to this termination and my role in the respective problems or issues and the resolution of these problems or issues are summarized in an attachment to this Agreement.

I further certify that I have not been debarred under the Generic Drug Enforcement Act of 1992, 21 USC §§ 335a and 335b. In the event that I become debarred or receive notice of an action or threat of an action with respect to my debarment during the term of this Agreement, I agree to immediately notify the Sponsor and the authorized IRB for the Investigation.

e. The answer to each question contained in paragraphs 6a, 6b, and 6c below is negative unless I have specified otherwise on an attached financial disclosure.

2. I agree:

a. To obtain and maintain Institutional Review Board (IRB) approval of all individual Investigators participating in this Protocol as required in 21 CFR Part 56. I will submit the certification of IRB approval and any conditions of this approval to the Sponsor.

b. To obtain and maintain IRB approval of the Protocol and associated INFORMED CONSENT material prior to contacting potential subjects or implementing the Protocol.

c. To obtain IRB approval of any changes to the Protocol and associated INFORMED CONSENT material prior to implementing such changes. Any changes to the INFORMED CONSENT must be approved by the Sponsor prior to use.

d. To respond promptly and fully to IRB inquiries and notify the Sponsor, in writing, of any IRB inquiries.

e. To comply with IRB requirements and applicable federal, state and institutional regulations concerning periodic review of the evaluation by the IRB and submission of reports to the IRB.

3. I agree:

a. To conduct the Investigation in strict compliance with the Protocol, with applicable institutional and IDE regulations, applicable regulations of the FDA and other applicable laws, rules and regulations ("Applicable Laws"), the International Conference on Harmonization E6 (Good Clinical Practices), as recognized by FDA, any conditions of approval imposed by my reviewing IRB and/or the FDA, and the responsibilities of Investigators addressed under 21 CFR Part 812, Subpart E and Subpart G (collectively the "Requirements"). Any deviation must be reported immediately to the Sponsor.

b. To obtain written INFORMED CONSENT in accordance with the requirements found in 21 CFR Part 50, and ICH E6 (Good Clinical Practices), as recognized by FDA, prior to enrolling any subject into the Investigation and to fully inform any subject of all risks and benefits. I further agree to ensure that a signed copy of the INFORMED CONSENT is available to the Sponsor, Sponsor's monitor and any affiliated entity of the Sponsor. The Sponsor must be notified immediately of any failure to obtain written INFORMED CONSENT prior to use of the device.

c. To use diligent efforts to complete enrollment of the appropriate number of subjects as set forth in the Protocol.

d. To supervise all Investigation use of PerClot on human subjects and allow only those physician Sub-Investigators who have signed a Sub-Investigator Agreement to administer the Investigation Device and/or perform follow-up medical evaluations on the Investigation Device.

e. To be responsible for accountability of PerClot delivered to or received by my Investigation site and to return all unused PerClot to the Sponsor or otherwise follow the instructions of the Sponsor for disposal of the unused devices.

f. To terminate the evaluation of an individual subject whenever the subject so requests, or the Sponsor so directs.

g. To terminate the entire evaluation if the IRB or the Sponsor so directs.

h. To immediately notify Sponsor of any adverse events as defined in the Protocol.

i. To keep Sponsor informed as to current enrollment and changes in enrollment.

j. To cease enrolling subjects upon notice by Sponsor.

4. I agree:

a. To keep, maintain, and retain subject records and other records as required by the Research Agreement, Protocol, the Requirements, Applicable Lawson and applicable institutional and IDE regulations.

b. To accurately prepare, promptly submit, and retain copies of case report forms provided by the Sponsor, a final report, and special reports as required by the Research Agreement, Protocol, or by applicable institutional regulations.

c. To permit the Sponsor, Sponsor's monitor and any affiliated entity of the Sponsor reasonable access to me or to any Sub-Investigator, facilities used and to the records kept, maintained, and retained in connection with this evaluation per Applicable Laws.

d. To permit reasonable access to authorized FDA employees at reasonable times and in a reasonable manner to me or to any Sub-Investigator, all records, and facilities as required by Applicable Laws.

e. To respond in writing to Sponsor's data resolution queries within 5 days of receipt.

5. I have read and understand the Research Agreement and agree to comply with all of its provision (except those relating exclusively to the Institution), including but not limited to the Research Agreement provisions relating to (i) Adverse Event Reporting, (ii) Debarment, (iii) Non-Exclusion Warranty, (iv) Confidential and Proprietary Information, (v) Intellectual Property, (vi) Use and Publication of Information, (vii) Indemnification, and (viii) Health Insurance Portability and Accountability Act.

6. As required by 21 CFR Part 54, Financial Disclosure by Clinical Investigators, I agree to disclose sufficient and accurate financial information to the SPONSOR in the financial disclosure document supplied specifying the following information for me and each sub-Investigator:

   a. Whether I or any sub-Investigator's compensation from the SPONSOR is affected by the outcome of the PROTOCOL. In addition, whether my or any sub-Investigator's compensation, including an equity interest in the SPONSOR or compensation tied to the sale of PerClot (*e.g.,* a royalty interest) could be higher for a favorable outcome than for an unfavorable outcome.

   b. Whether I or any sub-Investigator have acquired an ownership interest, stock option, or other financial interest that exceeds $50,000 in the SPONSOR during the evaluation period and for one (1) year following completion of the investigation.

   c. Whether I or any sub-Investigator have a proprietary interest in PerClot or a property or other financial interest in PerClot including, but not limited to: a subject, trademark, copyright, or license agreement.

   I further agree to notify the SPONSOR if my disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the investigation.

7. I acknowledge that I am an independent contractor and not an agent, joint venturer or partner of Sponsor which means that among other things I cannot bind Sponsor to any action or agree to do anything for a third party's benefit in the name of Sponsor.

8. Neither party shall use the names of the other in connection with any products, promotion or advertising without the prior written permission of the other party. I understand that Sponsor may request my permission to state my name or the Site's name, and location of the Investigation in order to identify it and as required by Applicable Laws. Such a request shall not be unreasonably denied.

9. During the term hereof, I shall disclose to (i) any committee of which I am a member that develops clinical guidelines, or (ii) any entity of which I am an employee that provides health care services (i) that I am a paid investigator to Sponsor, and (ii) generally, and without disclosing any confidential and Proprietary Information (as defined in the Research Agreement), the type of services provided by me to Sponsor. Finally, I acknowledge that pursuant to legislation titled "The Physician Payment Sunshine Act" as may be amended form time to time, Sponsor (or its affiliates) may disclose payments and other expenditures made hereunder to the United States government and pursuant to other legislation in certain states.

10. Notices and communications, other than services of process, shall be submitted to the addresses listed below and shall be deemed made two days after the date of mailing if delivered by U.S. mail by registered or certified envelope, postage pre-paid or if delivered by overnight service or hand delivered, when received, or to such other address as may be hereinafter designated by notice in writing and as otherwise provided by law:

    If to Sponsor:

    Scott B. Capps
    Vice President, Clinical Research
    CryoLife, Inc.
    1655 Roberts Blvd., NW
    Kennesaw, GA 30144

    If to Principal Investigator:

    _____

    _____

    _____

11. The terms of this Agreement represent the complete agreement of the parties related to the subject matter herein. If any provision of this Agreement conflicts with any provision of the Protocol, this Agreement shall take precedent.

    Thus I hereby state that I will comply with this Agreement, the Protocol and any Applicable Laws regarding the execution of the Investigation. I fully understand my responsibilities as an Investigator and protector of the rights of human subjects.

_____ _____
Principal Investigator Signature Date

_____
NPI No.

_____ _____
CryoLife Representative Signature Date

Appendix I: Sample Sub-Investigator Agreement

Sample Sub-Investigator Agreement

Prospective, Multicenter, Multidisciplinary, Controlled Clinical Investigation Evaluating the Safety and Efficacy of PerClot® Polysaccharide Hemostatic System

The C.L.O.T. Investigation

CLINICAL SUB-INVESTIGATOR: _____

CLINICAL SITE: _____

I hereby agree to participate in a clinical evaluation of PerClot® Polysaccharide Hemostatic System (PerClot) Sponsored by the manufacturer, CryoLife, Inc. ("Sponsor"). I understand that the purpose of this clinical investigation (the "Investigation") is to collect clinical data concerning the safety and efficacy of PerClot versus other hemostatic devices (the control) in multiple surgical disciplines when used as an adjunct to conservative measures of achieving hemostasis such as pressure or ligature. I will conduct the Investigation as outlined in the clinical Investigation protocol agreed to by the Sponsor and given approval/favorable opinion by the IRB, in the following Food and Drug Administration (FDA) regulations: 21 CFR Part 812, Investigational Device Exemptions (IDE); 21 CFR Part 50, Protection of Human Subjects; 21 CFR Part 54, Financial Disclosure by Clinical Investigators; 21 CFR Part 56, Institutional Review Boards; in accordance with the International Conference on Harmonization E6 (Good Clinical Practices), as recognized by FDA. Furthermore,

1. I assure that:

   a. I have read and understand the (i) Clinical Research Agreement entered into by the Sponsor, Principal Investigator, and the Institution acting as the Investigation Site (the "Research Agreement") dated _____, and (ii) clinical Investigation protocol and associated evaluation documents ("Protocol") and agree with the Protocol's acceptability.

   b. I have adequate time and subject base to complete the investigation described in the Protocol, given the magnitude of concurrent studies.

   c. I have the appropriate, relevant qualifications to conduct and oversee the conduct of the Investigation in accordance with the Protocol as described by the following *(check one of the following statements)*:

      ___ My relevant qualifications, including dates, location, extend, and type of experience, are listed in my most recent curriculum vitae (CV), which is attached to this Agreement.

      ___ My CV, which is attached to this Agreement, does not reflect my relevant qualifications; therefore, in addition to a copy of my most recent CV is a statement of my relevant experience including dates, locations, extent, and type of experience.

d. There are no reasons to question my ability to conduct the Investigation described in the Protocol. (Check one of the following statements)

___ I have never participated in an investigation or other research activity which was terminated by FDA, the IRB (or equivalent), or Sponsor of an investigation due to a non-compliance issue.

___ I have participated in an investigation or other research activity which was terminated by FDA, the IRB (or equivalent), or a Sponsor due to a non-compliance issue. The specific circumstances leading to this termination and my role in the respective problems or issues and the resolution of these problems or issues are summarized in an attachment to this Agreement.

I further certify that I have not been debarred under the Generic Drug Enforcement Act of 1992, 21 USC §§ 335a and 335b. In the event that I become debarred or receive notice of an action or threat of an action with respect to my debarment during the term of this Agreement, I agree to immediately notify the Sponsor and the authorized IRB for my Investigation site.

e. The answer to each question contained in paragraphs 5a, 5b, and 5c below is negative unless I have specified otherwise on an attached financial disclosure.

2. I agree:

a. To conduct the Investigation in strict compliance with the Protocol, with applicable institutional and IDE regulations, other applicable regulations of the FDA and other applicable laws, rules and regulations ("Applicable Laws"), the International Conference on Harmonization E6 (Good Clinical Practices), as recognized by FDA, any conditions of approval imposed by my reviewing IRB and/or the FDA and the applicable responsibilities of Investigators addressed under 21 CFR Part 812, Subpart E and Subpart G (collectively the "Requirements"). Any deviation must be reported immediately to the Sponsor.

b. To obtain written INFORMED CONSENT in accordance with the requirements found in 21 CFR Part 50, ICH E6 (Good Clinical Practices), as recognized by FDA prior to enrolling any subject into the Investigation and to fully inform any subject of all risks and benefits. I further agree to ensure that a signed copy of the INFORMED CONSENT is available to the Sponsor, Sponsor's monitor and any affiliated entity of the Sponsor. The Sponsor must be notified immediately of any failure to obtain written INFORMED CONSENT prior to use of the device.

c. To use diligent efforts to complete enrollment of the appropriate number of subjects as set forth in the Protocol.

d. To terminate the evaluation of an individual subject whenever the subject so requests, or the Sponsor so directs.

e. To cease enrolling subjects upon notice by Sponsor.

3. I agree:

a. To keep, maintain, and retain subject records and other records as required by the Protocol, the Requirements, Applicable Laws and applicable institutional and IDE regulations.

b. To accurately prepare, promptly submit, and retain copies of case report forms provided by the Sponsor, a final report, and special reports as required by the Research Agreement, Protocol or by applicable institutional regulations.

c. To permit the Sponsor, Sponsor's monitor and any affiliated entity of the Sponsor reasonable access to me, facilities used and to the records kept, maintained, and retained in connection with this evaluation and Applicable Laws.

4. I have read and understand the Research Agreement and agree to comply with all of its provision (except those relating exclusive to the Institution or the Principal Investigator), including but not limited to the Clinical Agreement provisions relating to (i) Adverse Event Reporting, (ii) Debarment, (iii) Non-Exclusion Warranty, (iv) Confidential and Proprietary Information, (v) Intellectual Property, (vi) Use and Publication of Information, (vii) Indemnification, and (viii) Health Insurance Portability and Accountability Act.

5. As required by 21 CFR Part 54, Financial Disclosure by Clinical Investigators, I agree to disclose sufficient and accurate financial information to the Sponsor in the financial disclosure document supplied specifying the following information for me:

   a. Whether my compensation from the Sponsor is affected by the outcome of the Protocol. In addition, whether my compensation, including an equity interest in the Sponsor or compensation tied to the sale of PerClot (*e.g.,* a royalty interest) could be higher for a favorable outcome than for an unfavorable outcome.

   b. Whether I have acquired an ownership interest, stock option, or other financial interest that exceeds $50,000 in the Sponsor during the evaluation period and for one (1) year following completion of the investigation.

   c. Whether I have a proprietary interest in PerClot or a property or other financial interest in PerClot including, but not limited to: a subject, trademark, copyright, or license agreement.

   I further agree to notify the Sponsor if my disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the investigation.

6. I acknowledge that I am an independent contractor and not an agent, joint venturer or partner of Sponsor which means that among other things I cannot bind Sponsor to any action or agree to do anything for a third party's benefit in the name of Sponsor.

7. During the term hereof, I shall disclose to (i) any committee of which I am a member that develop clinical guidelines, or (ii) any entity of which I am an employee that provides health care services (i) that I am a paid investigator to Sponsor, and (ii) generally, and without disclosing any Confidential and Proprietary Information (as defined in the Research Agreement), the type of services provided by me to Sponsor. Finally, I acknowledge that pursuant to legislation titled "The Physician Payment Sunshine Act" as may be amended from time to time, Sponsor (or its affiliates) may disclose payments and other expenditures made hereunder to the United State government and pursuant to other legislation in certain states.

8. Neither party shall use the names of the other in connection with any products, promotion or advertising without the prior written permission of the other party. I understand that Sponsor may request my permission to state my name or the Site's name, and location of the

Investigation in order to identify it and as required by applicable law. Such a request shall not be unreasonably denied.

9. Notices and communications, other than services of process, shall be submitted to the addresses listed below and shall be deemed made two days after the date of mailing if delivered by U.S. mail by registered or certified envelope, postage pre-paid or if delivered by overnight service or hand delivered, when received, or to such other address as may be hereinafter designated by notice in writing and as otherwise provided by law:

   If to Sponsor:

   Scott B. Capps
   Vice President, Clinical Research
   CryoLife, Inc.
   1655 Roberts Blvd., NW
   Kennesaw, GA 30144

   If to Sub-Investigator:

   _____

   _____

   _____

10. The terms of this Agreement represent the complete agreement of the parties related to the subject matter herein. If any provision of this Agreement conflicts with any provision of the Protocol, this Agreement shall take precedent.

    Thus I hereby state that I will comply with this Agreement, the Protocol and any Applicable Laws regarding the execution of the Investigation. I fully understand my responsibilities as an Investigator and protector of the rights of human subjects.

_____ _____
Sub-Investigator Date

_____
NPI No.

_____ _____
CryoLife Representative Date

Appendix J: Labeling

Labeling

Please refer to Appendix A of the protocol for a product Instructions for Use (IFU). Sample investigational labeling is included below (Figures 1 & 2).

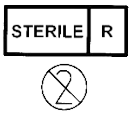
Figure 1. PC0005-CR Pouch Label

PerClot® Polysaccharide Hemostatic System

5g Dispenser and Applicator

Contents:

- One sterile, single patient use applicator tip and dispenser (bellows) containing absorbable modified polymer granules derived from purified plant starch



Contents sterile if inner pouch is not opened or damaged.

For single patient use only. Do not resterilize contents.

Store between 0°C and 25°C.

See Instructions for Use.

"CAUTION – Investigational Device. Limited by Federal (or United States)

law to investigational use."

CryoLife, Inc., 1655 Roberts Boulevard, NW, Kennesaw, GA 30144 USA

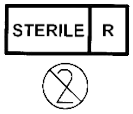
Figure 2. PC0005-CR Box Label

PerClot® Polysaccharide Hemostatic System

5 x 5g Units – Product Code No. PC0005-CR

Contents:

- Instructions for Use
- Five, individually pouched, sterile, single patient use applicator tips and dispensers (bellows) containing absorbable modified polymer granules derived from purified plant starch



Contents sterile if inner pouches are not opened or damaged.

For single patient use only. Do not resterilize contents.

Store between 0°C and 25°C.

See Instructions for Use.

"CAUTION – Investigational Device. Limited by Federal (or United States)

law to investigational use."

CryoLife, Inc., 1655 Roberts Boulevard, NW, Kennesaw, GA 30144 USA

L6423.002

Appendix K: Insulin or Blood Sugar Lowering Medications

Insulin or Blood Sugar Lowering Medications

Name	Commercial Name
Acebutolol	(Sectral®)
Acetohexamide	(Dymelor®)
Alcohol	Alcohol
Aloe	Oral Herbal Supplement, especially if taken with other agents such as glyburide, glipizide, nateglinide, repaglinide, glimepiride, or insulin.
Amphotericin B	(Ambisome®, Amphocin®, Fungizone Intravenous® Amphotec®, Abelcet®)
Amphotericin B lipid formulations	(Abelcet®, AmBisome®)
Asian Ginseng	(Ginseng; Panax ginseng)
Aspirin	(Numerous tradenames; check label.)
Aspirin + dipyridamole	(Aggrenox®)
Atenolol	Tenormin®, Tenoretic® containing atenolol & chlorthalidone)
Betaxolol	(Betoptic®, Betoptic S® {eyedrops}, Kerlone® {oral})
Bisoprolol	(Zebeta®)
Bisoprolol + hydrochlorothiazide	(Ziac®)
Bromocriptine	(Cycloset®)
Chloramphenicol	(Chloromycetin®)
Chlorpropamide	(Diabinese®)
Choline salicylate	(Acuprin 81®, Amigesic®, Anacin Caplets®, Anacin Maximum Strength®, Anacin Tablets®, Anaflex 750® Arthritis Pain, Ascriptin® Arthritis Pain)
Choline salicylate + magnesium salicylate C	(MT®, Tricosal®, Trilisate®)
Chromium	(Various tradenames; check label)
Clarithromycin B	(Biaxin® Filmtab®, Biaxin® Granules, Biaxin® XL Filmtab, Biaxin® XL Pac, Prevpac®)
Diazoxide	(Proglycem®)
Dicumarol	(Coumadin®, Miradon®)
Diltiazem	(Cardizem®, Tiazac®)
Disopyramide	(Norpace®, Norpace® CR)
Dorzolamide + timolol	(Cosopt®)
Exenatide	(Byetta®)
Fluoxetine	(Prozac®, Sarafem®)
Fosphenytoin	(Cerebyx®, Dilantin®, Dilantin-125®, Dilantin Infatabs®, Dilantin Kapseals®, Mesantoin®, Peganone®, Phenytek®)
Glimepiride	(Amaryl®)
Glimepiride and Rosiglitazone	(Avandaryl®)
Glipizide	(Glucotrol®, Glucotrol XL®)
Glipizide and Metformin	(Metaglip®)

Name	Commercial Name
Glyburide	(Diabeta®, Glynase®, Micronase®, Glycron®)
Glyburide + metformin	(Glucovance®)
Horse chestnut	(Aesculus hippocastanum)
Hydrochlorothiazide + metoprolol	(Lopressor HCT®)
Insulin	(Lantus®, Levemir®, NPH®, Humulin®, Novolin®, Apidra®, Novolog®, Humalog®)
Interferon beta-1b	(Betaseron®)
Levofloxacin	(Levaquin®, Levaquin® in Dextrose Injection Premix, Quixin®)
Liraglutide	(Victoza®)
Magnesium salicylate	(Bayer Select® Backache Pain Formula, Doans® Pills, Mobidin®, Nuprin® Backache Caplet)
Metformin	(Fortamet®, Glucophage®, Glucophage XR®, Glumetza®, Riomet®)
Metoprolol	(Lopressor®, Lopressor® HCT, Toprol XL®)
Morphine	(Kadian®, MS Contin®, MSIR®, Roxanol®)
Nadolol	(Corgard®)
Nateglinide	(Starlix®)
Nifedipine	(Adalat CC®, Procardia®, Afeditab® CR)
Octreotide	(Sandostatin®, Sandostatin LAR® Depot)
Paloperidone	(Invega®)
Penicillamine	(Cuprimine®, Depen®)
Pentamidine	(Nebupent®, Pentam 300®)
Phenelzine	(Nardil®)
Phenytoin	(Dilantin®, Dilantin-125®, Dilantin Infatabs®, Dilantin Kapseals®, Phenytek®)
Pindolol	(Visken®)
Pioglitazone	(Actos®) –(hypoglycemia usually only when in combination with other diabetic drugs such as sulfonylureas or insulin)
Pioglitazone and Glimepiride	(Duetact®)
Pioglitazone and Metformin	(Actoplus Met®, ActoPlus Met XR®)
Pramlintide	(Symlin®) (with insulin-induced hypoglycemia)
Probenecid	(Benemid®, Probalan®)
Quinine	(Quinamm®, Quindan®, Quiphile®, Q-vel®, Strema®)
Quinupristin + dalfopristin	(Synercid®)
Repaglinide	(Prandin®)
Repaglinide and Metformin	(PrandiMet®)
Ritodrine	(Yutopar®)
Rituximab	(Rituxan®)
Rosiglitazone	(Avandia®)
Rosiglitazone and Metformin	(Avandamet®)
Rotigotine	(Neupro®)

Name	Commercial Name
Salicylates	(Numerous tradenames of aspirin formulations; check label)
Salsalate	(Argesic®-SA, Disalcid®, Mono-Gesic®, Salflex®, Salsitab®)
Saxagliptin	(Onglyza®)
Selegiline	(Eldepryl®)
Sitagliptin	(Januvia®)
Sitagliptin and Metformin HCL	(Janumet®)
Sodium ferric gluconate complex	(Ferrlecit®)
Somatropin	(Genotropin®, Genotropin Miniquick®, Humatrope®, Norditropin cartridges®, Norditropin NordiFlex®, Nutropin, Nutropin AQ®, Saizen®, Serostim®, Zorbtive®)
Sotalol	(Betapace®, Betapace AF®, Sorine®)
Streptozocin	(Zanosar®)
Sulfadiazine	(Microsulfon®)
Tacrolimus P	(Prograf®, Protopic®)
Tetracaine	(Altacaine®, Tetcaine®, Pontocaine®)
Theophylline	(Theo-24®, Theo-Dur®, TheoCap®)
Timolol	(Timoptic®, Timoptic-XE®)
Tolazamide	(Tolinase®)
Tolbutamide	(Orinase®)
Tranylcypromine	(Parnate®)
Varenicline	(Chantix®)
Verapamil	(Calan®, Calan SR®, Isoptin SR®, Verelan®)

Appendix L: Blood Modifiers

Blood Modifiers

Name	Description
Abbokinase® (urokinase)	Thrombolytic agent obtained from human neonatal kidney cells grown in tissue culture
Advil®	Ibuprofen
Acriptin®	Aspirin buffered with Maalox
Activase (alteplase)	A tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids
Actron®	Ketoprofen
Advate Antihemophilic Factor (recombinant)	Purified glycoprotein
Aggrastat (tirofiban hydrochloride)	Non-peptide antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor
Aggrenox® (aspirin/ extended-release dipyridamole)	Combination antiplatelet agent
Agrylin® (anagrelide hydrochloride)	Reduces blood platelet count
Aleve®	Naproxen sodium
Amicar (aminocaproic acid)	6-aminohexanoic acid, acts is an inhibitor of fibrinolysis
Anacin®	Aspirin and caffeine
Anadrol®-50 (oxymetholone)	Anabolic and androgenic drug
Angiomax® (bivalirudin)	Specific and reversible direct thrombin inhibitor
Ansaid	Flurbiprofen
Apixaban	Eliquis
Aquamephyton (phytonadione)	Vitamin
Argatroban	Synthetic direct thrombin inhibitor derived from L-arginine
Aranesp®	Erythropoiesis stimulating protein
Arixtra®	Sterile solution containing fondaparinux sodium
Arthritab	Magnesium salicylate
Arthropan	Choline salicylate
Arthrotec	Diclofenac sodium with misoprostol
Bayer®	Aspirin
Bayer Select	Magnesium salicylate
Benefix®	Coagulation Factor IX (Recombinant)
Buminate 25%	Albumin (Human), 25% Solution is a sterile, nonpyrogenic preparation of albumin in a single dosage form for intravenous administration
Buminate 5%	Albumin (Human), 5% Solution, is a sterile, nonpyrogenic preparation of albumin in a single dosage form for intravenous administration
Cataflam	Diclofenac potassium
Cathflo® Activase® (alteplase)	Plasminogen activator (t-PA) produced by recombinant DNA technology
Celebrex®	Celecoxib
Coumadin® (warfarin sodium)	Anticoagulant which acts by inhibiting vitamin K-dependent

Name	Description
	coagulation factors
Cyklokapron®	Tranexamic acid
Dabigatran	Pradaxa
DDAVP®	Desmopressin acetate is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin
Dolobid	Diflunisal
Ecotrin (aspirin)	Enteric coated aspirin (acetylsalicylic acid)
Epogen® (erythropoietin)	A glycoprotein which stimulates red blood cell production
Excedrin®	Acetaminophen, aspirin, and caffeine
Feiba VH (anti-inhibitor coagulant complex)	Freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity
Ferrlecit® (sodium ferric gluconate complex in sucroseinjection)	Stable macromolecular complex with anapparent molecular weight on gel chromatography of 289,000-440,000 daltons
Feverfew (*tanacetum parthenium*)	Herbal medicine used for migraines, and can inhibit platelet activity and increase bleeding
Flolan® (epoprostenol sodium)	Sterile sodium salt for intravenous administration
Fragmin	Dalteparin sodium injection is a sterile, low molecular weight heparin
Gammaplex	Sterile solution of polyclonal human Immunoglobulin G for IV administration
Garlic (*allium sativum*)	Clove garlic, may potentiate warfarin, may see increased INR (PT)
Ginger (*zingiber officinale*)	Potent inhibitor of thromboxane synthetase, may increase bleeding time; may cause excessive bleeding when used with warfarin
Ginkgo (*ginkgo biloba*)	Used as a circulatory stimulant and may enhance bleeding in patients on anticoagulant or antithrombotic therapy
Hemofil M	Antihemophilic Factor (Human) (AHF), Method M, Monoclonal Purified, is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (Factor VIII, Factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 22 AHF International Units/mg of total protein
Heparin	Anticoagulant
Indocin, Indocin SR	Indomethacin
INFeD (iron dextran injection, USP)	Dark brown, slightly viscous sterile liquid complex of ferric hydroxide and dextran for intravenous or intramuscular use
Integrilin (Eptifibatide)	Eptifibatide is a cyclic heptapeptide containing six amino acids and one mercaptopropionyl (des-amino cysteinyl) residue
Jantoven™	An anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors
Kinlytic™ (urokinase for injection)	Thrombolytic agent obtained from human neonatal kidney cells grown in tissue culture
Koate-DVI (antihemophilic factor)	Sterile, stable, purified, dried concentrate of human Antihemophilic Factor (AHF, factor VIII, AHG)
Leukine® (sargramostim)	Recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF) produced by recombinant DNA technology in a yeast *(S. cerevisiae)* expression system

Name	Description
Lodine, Lodine XL	Etodolac
Lovenox (enoxaparin sodium)	A sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin
Meclomen	Meclofenamate sodium
Mephyton® (phytonadione)	MEPHYTON tablets possess the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X).
Mobic	Meloxicam
Mononine®	Coagulation Factor IX (Human), is a sterile, stable, lyophilized concentrate of Factor IX prepared from pooled human plasma
Motrin, Motrin IB	Ibuprofen
Mozobil (plerixafor injection)	Hematopoietic stem cell mobilizer
Nalfon	Fenoprofen calcium
Naprosen	Naproxen
Nascobal® (cyanocobalamin nasal)	Cyanocobalamin is a synthetic form of vitamin B_{12} with equivalent vitamin B_{12} activity.
Neulasta® (pegfilgrastim)	Covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monomethoxypolyethylene glycol
Neumega (IL-11)	Interleukin eleven (IL-11) is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production
NovoSeven®	Recombinant human coagulation Factor VIIa (rFVIIa),
Nplate (romiplostim subcutaneous)	Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways leading to increased platelet production via the TPO receptor
Nuprin®	Ibuprofen
Orudis, Orudis KT	Ketoprofen
Oruvail	Ketoprofen
Pentoxil®	Pentoxifylline extended-release tablets
Persantine® (dipyridamole USP)	Platelet inhibitor
Plasmanate (plasma protein fraction)	Plasma proteins buffered with sodium carbonate and stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan
Plavix (clopidogrel bisulfate)	Inhibitor of ADP-induced platelet aggregation
Pletal (cilostazol)	Quinolinone derivative that inhibits cellular phosphodiesterase
Ponstel	Mefenamic acid
Promacta (eltrombopag)	Eltrombopag olamine, a small molecule thrombopoietin (TPO) receptor agonist for oral administration
Protamine	Arginine-rich, nuclear proteins that replace histones; used to neutralize anticoagulant effects of heparin
Prothrombin complex concentrates	Used to reverse anticoagulant effects of warfarin
Refludan (lepirudin (rDNA) for injection)	A highly specific direct inhibitor of thrombin
Relafen	Nabumetone

Name	Description
ReoPro® (abciximab)	Fab fragment of the chimeric human-murine monoclonal antibody 7E3. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ((alpha)$_v$(beta)$_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells
RiaSTAP™	Lyophilized fibrinogen (coagulation factor I) powder made from pooled human plasma
Rivaroxaban	Xarelto
Thrombate III® (antithrombin III)	Sterile, nonpyrogenic, stable, lyophilized, preparation of purified human antithrombin III
Thrombin-JMI	Substance produced through a conversion reaction in which prothrombin of bovine origin is activated by tissue thromboplastin of bovine origin in the presence of calcium chloride
Ticlid® (ticlopidine hydrochloride)	Platelet aggregation inhibitor
Trasylol® (aprotinin)	Natural proteinase inhibitor obtained from bovine lung
Tricosal	Choline and magnesium trisalicytes
Trilisate	Choline and magnesium trisalicytes
Tnkase (tenecteplase)	Tissue plasminogen activator (tPA) produced by recombinant DNA technology
Vitamin E	May increase bleeding, particularly in conjunction with other anticoagulant and antithrombotic drugs
Vitamin K	Used for reversal of anticoagulation
Voltaren, Voltaren XR	Diclofenac sodium
Xigris®	Drotrecogin alfa (activated) is a recombinant form of human Activated Protein C

Appendix M: NNIS Instructions

NNIS Instructions

Calculation of National Nosocomial Infections Surveillance (NNIS) Risk Index.[1-2]This simplified risk index has a range of 0 to 3 points. A point is added to the patient's risk index for each of the following 3 variables:

- 1 point: The patient has an operation that is classified as either contaminated or dirty
- 1 point: The patient has an American Society of Anesthesiologists (ASA) preoperative assessment score of III, IV, or V (Table 1)
- 1 point: The duration of the operation exceeds the 75th percentile where a standard T point (75% percentile) was determined for the NNIS database (Table 2); the T point is defined as the length of time in hours that represents the 75th percentile of procedures reported on the NNIS survey

The point total results in the NNIS Risk Index.

Table 1. Physical Status Classification for Surgical Patients[1-2]	
Class I	A normally healthy patient
Class II	A patient with mild systemic disease
Class III	A patient with severe systemic disease
Class IV	A patient with severe systemic disease that is a constant threat to life
Class V	A moribund patient not expected to survive without the operation

Table 2. The T Point for Common Surgical Procedures[1,3]	
Coronary artery bypass graft	5
Bile duct, liver, or pancreatic surgery	4
Nephrectomy[3]	4
Craniotomy	4
Head and Neck surgery	4
Splenectomy[3]	3
Colonic surgery	3
Joint prosthesis surgery	3
Vascular surgery	3
Abdominal or vaginal hysterectomy	2
Ventricular shunt	2
Herniorrhapy	2
Appendectomy	1
Limb amputation	1
Cesarean section	1

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Appendix N: Operative Steps

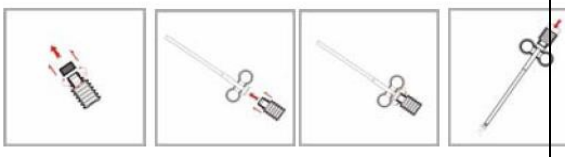
Operative Steps

	Investigator	Coordinator/Surgical Associate
1		a. Assure all necessary equipment are present and ready for use, including: □ Writing utensil with indelible ink; □ Calibrated mass balance (readability and repeatability in milligrams, 0.001 g); □ Timing device (precision in seconds); □ Millimeter incremented tool; □ Study Devices (2 packaged 5g bellows of PerClot and 2 packaged 5g bellows of Arista) □ Calculator or device with calculator function; □ Sterile bowl; □ Paper copy of Operative Worksheets; □ 2 packages Covidien™ Vistec™ X-ray Detectable Sponges, 16-Ply, 4"x4" (hereinafter referred to as gauze) □ 1 liter of warm saline; and □ Envelopes for randomization. b. Tare calibrated scale. c. Pre-weigh packaged, sterile gauze in grams to 3 decimal places (0.001 g increments) and record. d. In a manner that will not compromise sterility, introduce pre-weighed and non-weighed sterile gauze to the sterile field until ready for use. e. Visually inspect the sealed packages of devices. If either package has been previously opened or damaged, discard and replace with a new package. f. Pre-weigh packaged Study Devices in grams to 3 decimal places (0.0001 g increments) and record.
2	a. Perform conventional methods for hemostasis, including but not limited to, pressure and ligature. b. Blot bleeding site with clean non-weighed gauze and gentle pressure to remove blood and any other fluid from the study site. c. Ligate any remaining vessels or suture holes >/= 2 mm diameter.	

	Investigator	Coordinator/Surgical Associate
3	a. Inspect the bleeding site. Determine whether additional hemostatic measures need to be performed by application of a topical hemostat agent.	
4	a. Using a millimeter-incremented tool, measure the 2 longest perpendicular distances (cm) of the bleeding site.	a. Record the 2 longest perpendicular distances of the bleeding site. b. Multiply those two values to calculate the **Anatomic Site**. c. Add 1cm to each of the 2 recorded longest perpendicular distances of the bleeding site and multiply those two values to calculate **Anatomic Application Site**. d. Verify eligibility of Anatomic Site and Anatomic Application Site based on calculated surface areas with intraoperative inclusion/exclusion criteria before proceeding.
5	a. Blot bleeding site with clean non-weighed gauze and hold gentle pressure for 10 seconds to remove blood and any other fluid from the study site. b. Have at hand, a stack of two gauze from pre-weighed packaged gauze (herein referred to as pre-weighed gauze).	
6	a. Immediately place two pre-weighed, gauze onto the bleeding site and hold them in place with gentle uniform pressure (enough to capture all the blood without deforming the gauze or the tissue) until blood is seen on top layer or for 10 seconds whichever occurs first using the timing device.	a. Start Timing device (seconds) when pre-weighed gauze contacts the bleeding site. b. Stop timing device and remove gauze from bleeding site at 10 seconds or when surgeon sees blood on the top layer of the gauze, whichever occurs first.
7		a. Tare pre-calibrated scale. Weigh unused gauze, gauze packaging, and blood-stained gauze (in grams, to 3 decimal places) and record.

<table>
<tr><th></th><th>Investigator</th><th>Coordinator/Surgical Associate</th></tr>
<tr><td>8</td><td>a. Identify verbal description of bleeding site (a-f).

a. A score of 0 denotes no active bleeding. The surgical field is completely dry with no blood or the surgical field is stained with blood, but this blood is completely stagnant.
b. A score of 1 denotes oozing. The rate of bleeding is slow. This is what one may expect from capillary, venous, or arteriolar bleeding.
c. A score of 2 denotes slight bleeding. The rate of bleeding is slightly faster than oozing. There is no pulsatile flow present. This is what one may expect from capillary, venous, or arteriolar bleeding.
d. A score of 3 denotes moderate bleeding. There may be a weak pulsatile flow present. If there is a pulsatile flow, the rate of blood flow is similar to the rate of flow for a score of 2. If there is no pulsatile flow, the rate of blood flow is faster than slight bleeding.
e. A score of 4 denotes severe bleeding. For the most part, pulsatile flow is present. If there is no pulsatile flow, then the rate of blood flow is extremely rapid.
f. A score of 5 denotes life-threatening bleeding. A strong pulsatile flow is always present and the rate of blood flow is extremely rapid.</td><td>b. Calculate (2 significant digits after the decimal) Bleeding Flux [g/(cm²·s)]= [(blood mass collected(g))]/ [Anatomic Site (cm²) · time gauze held (s)], record on Operative Worksheet 2.
If bleeding flux is > 0.000040[g/(cm²·s)] and ≤ 0.013[g/(cm²·s)] enroll measured bleeding area; if bleeding flux is <0.000040 or > 0.013[g/(cm²·s)], exclude bleeding site.

<table><tr><th>Bleeding Severity Score</th><th>Bleeding Flux [g/(cm²·s)]</th></tr><tr><td>0=No Bleeding</td><td>0-0.000040</td></tr><tr><td>1=Ooze</td><td>>0.000040-0.0056</td></tr><tr><td>2=Slight Bleeding</td><td>>0.0056-0.013</td></tr><tr><td>3=Moderate Bleeding</td><td>>0.013-0.041</td></tr><tr><td>4=Severe Bleeding</td><td>>0.041-0.063</td></tr><tr><td>5=Life-Threatening Bleeding</td><td>>0.063</td></tr></table></td></tr>
<tr><td>9</td><td>a. Confirm all Intraoperative eligibility criteria. If subject is eligible, continue to Randomization.</td><td>a. Record confirmation of intraoperative eligibility.</td></tr>
<tr><td>10</td><td></td><td>Prepare RSD Accordingly
PerClot Preparation
1. Remove the applicator from the package. Remove the granule dispenser (bellows) from its package. Remove the cap using a counter-clockwise turning motion (Fig.1).
Connect the bellows firmly to the end of the applicator handle (Fig. 2). The system is now ready for use (Fig. 3). (Fig. 4).
 
Fig.1 Fig.2 Fig.3 Fig.4

Arista Preparation
1. Remove the applicator cap using a bending and twisting motion.</td></tr>
<tr><td>12</td><td></td><td>a. Record Randomized Study Device (RSD) identifier number.</td></tr>
<tr><td>13</td><td></td><td>a. Introduce RSD (two 5g bellows) to sterile field.</td></tr>
</table>

	Investigator	Coordinator/Surgical Associate
14	a. Before applying the RSD, have at hand: (1) a stack of two sterile non-weighed gauze and (2) warm sterile saline. b. Apply RSD, according to respective instructions for use.	a. Prepare 700 cc of warm saline for irrigation
Device-Specific Application Instructions (INVESTIGATOR USE ONLY)		
	PerClot	**Arista**
15	a. Remove all excess blood from the intended site by blotting, wiping, or suctioning. Identify and expose the source of bleeding of the wound. Ensure surface to which hemostat is being applied is dry and free from blood/fluid prior to application. Removing excess blood is critical to maximizing the hemostatic performance as it allows the granules direct contact with the site and source of active bleeding. b. Pump the granule dispenser/bellows to deliver granules directly to the site of bleeding. Immediately apply a liberal amount of PerClot granules directly to the source of bleeding. Thoroughly cover the lesion with a layer of granules 3-4 mm in thickness. Extend the product application to approximately 0.5cm (or 5mm) beyond the edge of the site of bleeding. The amount of application will depend upon the size of the bleeding site, contour of the bleeding site, and severity of bleeding. The amount of PerClot granules applied will increase with increasing size of the bleeding site and severity of bleeding. 1. The PerClot granules will help identify the source(s) of active bleeding; granules over source(s) of active bleeding will stain with blood. Additional granules should be applied to these area(s). 2. When managing deep wounds, the applicator tip must be as close to the source of the bleeding as possible without contacting blood.	a. Blot, wipe, or suction the bleeding tissue. It is important to remove excess blood so that Arista may be applied immediately and directly to the site of active bleeding. b. Immediately apply a liberal amount of Arista at the site of bleeding within the wound, as close to the source of bleeding as possible, completely covering the wound. Deep wounds may require equally deep application of Arista. To minimize occlusion of the tip, pressure should be applied to deliver as the applicator enters the wound. **Do not apply more than the entire contents of up two 5 gram bellows of Arista per subject.**

	Investigator	Coordinator/Surgical Associate
	CAUTION: Avoid contacting the applicator tip with blood as this may occlude the applicator. If this occurs, replace applicator tip, if available. If this occurs, and a replacement tip is not available, use a stylus to reestablish the delivery pathway by inserting the stylus through the blocked area. Do not attempt to trim the applicator tip. **Do not apply more than the entire contents of up to two 5 gram bellows of PerClot per subject.**	
Discontinue Device-Specific Instructions. Continue with the remaining Operative Steps for both PerClot and Arista.		
16	a. Immediately following application, cover treated site with two clean, sterile, non-weighed gauze. Hold and apply gentle uniform pressure to gauze pads until 5 minutes and 0 seconds.	a. Start Timing Device. b. Weigh RSD packaging on a calibrated scale and record. c. Weigh used RSD bellow(s) and applicator tip(s) on a calibrated scale and record. d. Calculate weight of hemostat applied by subtracting the mass measured in steps 16b and 16c from the mass of the pre-weighed packaged study device to which the subject was randomized.
17	a. At 5 minutes, gently remove gauze by fully saturating gauze with saline and slowly peeling them off as not to dislodge hemostat mass.	a. Record actual time at 5 minute assessment.
18	a. Assess for hemostasis (complete cessation of bleeding). b. Assess for dislodgement of RSD and if primary reason for any observed bleeding.	a. Record 5 minute assessment. b. Record if dislodgement of RSD was observed and if primary reason for any observed bleeding.
19	a. Cover treated site with two clean, sterile, non-weighed gauze. Hold and apply gentle uniform pressure to gauze until 7 minutes and 0 seconds.	
20	a. At 7 Minutes, gently remove gauze by fully saturating gauze with saline and slowly peeling them off as not to dislodge hemostatic mass.	a. Record actual time at 7 minute assessment.
21	a. Assess for hemostasis (complete cessation of bleeding). b. Assess for dislodgement of RSD and if primary reason for any observed bleeding.	a. Record 7 minute assessment. b. Record if dislodgement of RSD was observed and if primary reason for any observed bleeding.

	Investigator	Coordinator/Surgical Associate
22	a. If hemostasis was achieved at 7 minutes observe site until 12 minutes to assess maintenance of hemostasis. After the 12 minute observation period, remove excess RSD carefully by gentle saline irrigation and aspiration. ***Cardiac patients who have received PerClot only:*** Following the application of PerClot for epicardial bleeding within the pericardial cavity and achievement of hemostasis, the pericardial cavity should be rinsed with up to70cc of fluid per 1 gram of PerClot in order to ensure removal of excess particles. b. If hemostasis was not achieved at 7 minutes or if hemostasis was not maintained at any point during the additional 5 minute observation period or beyond (12 minute post-application), the surgeon may employ alternative means of achieving hemostasis.	a. If applicable, record actual time at additional 5 minute assessment (12 minutes post-application). If breakthrough occurs, record actual time of breakthrough. b. Record any alternative means for achieving hemostasis. c. Record the volume of fluid used to rinse away excess RSD and the estimated amount of study device remaining following irrigation.
23	a. Estimate the amount of RSD left in the patient in relation to the original amount applied (percentage) after careful and complete saline irrigation and aspiration of excess material, if applicable.	
24		a. Return not assigned RSD to investigational drug pharmacy or accountability center and any remaining assigned RSD/packaging. Used RSD packaging is to be kept throughout patient study duration.
25	a. Prior to surgical closure, verify hemostasis maintenance. If hemostasis is not maintained, the surgeon may employ alternative means of achieving hemostasis.	a. Record verification of hemostasis maintenance. b. Record any alternative means for achieving hemostasis, if applicable.

RESUME all Post-Operative Safety and Data Instructions.

Appendix O:
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