Effectiveness of BoneSeal® on bone hemostats in patients undergoing cardiothoracic surgery

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Study Product: BoneSeal® Bone Wax Hemostats

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List of Abbreviations

CRF	Case Report Form
FDA	Food and Device Administration
GCP	Good Clinical Practice
IRB	Institutional Review Board
HA	Hydroxyapatite
PLA	Poly-lactic acid
PEG	Polyethylene glycol
CABG	Coronary Artery Bypass Grafting
OR	Operating Room

Study Summary

Title	**Effectiveness of BoneSeal® on sternal bone hemostats in patients undergoing cardiothoracic surgery**
Short Title	*Effectiveness of BoneSeal®*
Protocol Number	*Not yet assigned*
Methodology	*Prospective, randomized, open-label, study design*
Study Duration	*Estimated duration for the main protocol (start of screening November 2016) to (last subject processed and finishing the study November 2017)*
Study Center(s)	*Single-center*
Objectives	*To evaluate the effectiveness of BoneSeal® on bone hemostats in patients undergoing cardiothoracic surgery.*
Number of Subjects	*60*
Diagnosis and Main Inclusion Criteria	*Adult patients over 18 years undergoing coronary artery bypass grafting with or without valve replacement or repair ultimately requiring a sternotomy.*
Study Product, Dose, Route, Regimen	*BoneSeal® Bone Wax Hemostats* *Dosage regimen is as follows: 1 to 2 units (2.5 or 3.5 grams) per surgery as determined by the surgeon.*
Reference therapy	*Ostene®*
Statistical Methodology	*Statistical methods for evaluating postoperative bleeding and need for blood transfusions will include a Fisher's exact test (2 groups, 2 outcomes).*

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

During cardiothoracic surgery a sternotomy is used to access the mediastinum. The procedure can often result in significant bleeding from the sternal bone marrow. It has been estimated that sternal bone marrow is responsible for more than 80% of bloodshed in cardiac surgery requiring sternotomy. This leads to increased chance of blood and blood products usage. Blood products transfusions has been shown extensively in the literature to increase both mortality and morbidity. The shortage and exponentially increasing costs adds to this major problem. In order to reduce the possibility of complications resulting from the bleeding, surgeons often use several hemostatic agents on the cut sternal site. Surgical beeswax, an often used substance, is a mixture of sterilized honeybees wax and paraffin wax (1). The resulting hydrophobic bone wax is pliable and easily used to form a physical barrier on the cut spongy bone, occluding the bleeding channels (2). However, the material is not readily absorbed which prevents bone regrowth and possibly leads to infection (3) (4) (5) (6). Other alternative substances have been reported, though the lack wide spread adaptation of these products may be due to the expense of the material and/or the handling properties of the product (7) (8) (9) (10) (11). Ostene®, an alkaline oxide copolymer bone hemostatic material, has been show to achieve immediate hemostasis as compared to bone wax, however, unlike bone wax, the material is water soluble substance had complete dissolved in 3 weeks and bone regrowth was observed (12). While Ostene® is water soluble and thus does not inhibit bone regrowth, it does not appear to promote bone growth (12). Ostene®, can also dissolve within a few minutes and sternal bleeding can continue throughout the case.

1.2 Investigational Agent

BoneSeal® (an FDA cleared product) is an absorbable synthetic, with beeswax consistency, bone hemostatic agent that also contains PLA, PEG and hydroxyapatite which supports bone re-growth. The product is packaged as 5 single use, sterile units (2.5 or 3.5 gram ingot) per carton. One sterile unit contains one ingot. Sterilization is by gamma irradiation. BoneSeal® has FDA 510k clearance (K142348).

1.3 Preclinical Data

In vitro testing has shown that the solubility of hydroxyapatite is enhanced when mixed with a poly-lactic acid oligomer (13). Human studies have shown that reabsorption rates of hydroxyapatite was approximately 20% annually with no adverse reaction seen in the surrounding bone (13). A 6 week porcine bone defect model showed, when compared to bone wax, BoneSeal® had an equally effective hemostastic action. Histomorphometric data showed significantly greater new bone growth as compared to bone wax (14). Furthermore, fibrous tissue was significantly less as compared to bone wax (14).

1.4 Clinical Data to Date

Currently there is no relevant, specific clinical data regarding BoneSeal® at this time. BoneSeal®, is FDA cleared based on the determination that the device is substantially equivalent to currently cleared marketed predicate devices.

1.5 Dose Rationale and Risk/Benefits

Dosage regimen is as follows: 1 to 2 units (2.5 or 3.5 grams) per surgery as determined by the surgeon. This is based on the common amount of the comparable product used and the amount needed to obtain immediate hemostasis during surgery.

2 Study Objectives

A prospective randomized open-label study that will evaluate the effectiveness of the pliable and absorbable bone hemostats (BoneSeal®) composed of synthetic materials and hydroxyapatite on the reduction of bleeding from the sternal bone marrow in patients undergoing Coronary Artery Bypass Grafting, with or without valve replacement or repair. This product will be compared to the similar, currently used product, Ostene®. Bleeding will be evaluated qualitatively by the surgeon as well as quantitatively by comparing pre- and post-operative hemoglobin levels, intra-operative and post-operative blood product usage, and post-operative chest tube output. A 30 day follow-up will be conducted to evaluate the patient's tolerance of the product, possible complications, or infection. Additionally, surgeons will be asked to comment on the ease of use of the product.

3 Study Design

3.1 General Design

- Design: Prospective randomized trial
- Qualitative hemostatic action during application and quantitative evaluation of post-operative hemoglobin, intra- and post-operative blood product usage, and post-operative chest-tube output.
- Duration of subject participation: 30 days post procedure

3.2 Primary Study Endpoints

1) Qualitative determination of bleeding and hemostatic action during application graded by the surgeon using the mild, moderate, and severe for bleeding and complete, moderate, minimal, and failure for hemostatic action.

2) Occurrence of re-bleeding during the operation will be noted. Reapplication of product will not occur.
3) Postoperative hemoglobin as compared to baseline preoperative readings.
4) Post-operative chest tube output.
5) Intra-operative and post-operative blood product transfusion quantities.
6) Sternal wound infection or other complications within 30 days post procedure.

3.3 Secondary Study Endpoints

1) Ease of use of BoneSeal® compared to Ostene® – graded by primary surgeon using a Likert-scale (ranging from 1 [very easy] to 5 [very difficult]).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

Inclusion criteria include patients with the following:

1) Consent given by patient prior to surgery
2) Adult patients over 45 years
3) Subjects requiring elective, prescheduled or urgent open heart surgery requiring a sternotomy including, but not limited to CABG, valve repair, valve replacement

4.2 Exclusion Criteria

Exclusion criteria include patients with the following:

1) An immune system disorder
2) Known hypersensitivity to components in BoneSeal® or Ostene®
3) Patients undergoing emergency surgery
4) Patients undergoing aortic dissection
5) No consent given

4.3 Subject Recruitment and Screening

Subjects will be recruited for the study from the International Heart Institute's clinic, referring physicians. The principal investigator and study physicians will screen the patients based on their ability to meet inclusion criteria and a medical chart review.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients will be withdrawn from the study prior to their expected completion if they meet one of the exclusion item criteria's after their primary surgery, if the investigator believes they should be withdrawn due to safety reasons or failure of subjects to adhere to protocol requirements (such as a need for emergency surgery).

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consents to participate in the study, attempts will be made to obtain permission to record survival data. Subjects considered lost to follow-up require at least 3 phone calls to the subject.

5 Study Device

5.1 Description

BoneSeal® is an absorbable synthetic bone hemostats that also contains of PLA, PEG and hydroxyapatite which supports bone re-growth. The product is packaged as 5 single use, sterile units (2.5-3.5 gram ingot) per carton. One sterile unit contains one ingot. Sterilization is by gamma irradiation. BoneSeal® has FDA approval (K142348).

5.2 Treatment Regimen

BoneSeal® is applied to the cut surfaces of the sternum under the direction of a licensed healthcare provider. The material forms a mechanical barrier that occludes the vascular openings on the spongy bone of the sternum. It is left on the site and ultimately reabsorbed by the body with no expected adverse effects.

5.3 Method for Assigning Subjects to Treatment Groups

Subjects will be randomized on the day of surgery. A number will be assigned to each package – study device and control. This number will be printed on a page and a page sealed that is then sealed in an envelope. On the day of surgery, an envelope will be pulled and opened by the OR Coordinator and confirmed by the investigator. The corresponding number will be selected from the labeled packages. The printed number will be labeled with the subject's information filed as a source document. The number and corresponding assignment (study device or control) will be noted in the patient's record.

5.4 Packaging and Administration of Study Device

The device comes ready packaged and sterile for use. Each unit is a 2.5-3.5 gram ingot that can be molded as needed by the surgeon and applied to the cut site of the sternum. The control comes similarly packaged. Each dosage of either the study device or the control should be individually separated and numbered. Individual envelops with printouts of the corresponding numbers will be used for randomization.

5.5 Receiving, Storage, Dispensing and Return

5.5.1 Receipt of Device Supplies

Upon receipt of the of the study treatment supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study device in a given shipment (study device or comparator) will

be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.5.2 Storage

The device and the control will be stored in a locked file cabinet with the OR Coordinator.

5.5.3 Dispensing of Study Device

Once randomization has occurred the study investigators will be notified of the study patient's treatment allocation and the printout kept with the study patient's source documents. The study patient's charts will be labeled in order for them to easily be recognized as a study patient. The morning of the planned surgery, the Nurse Manager in the operating room will be notified that the patient is a study patient and that they will receive BoneSeal or Ostene during the surgery. The study investigator will obtain the product prior to the start of surgery. The study device will be kept with the OR Coordinator in a locked file cabinet in order for the study device to remain separate and in a temperature controlled environment. Regular study device reconciliation will be performed to document treatment assigned, treatment consumed, and treatment remaining. This reconciliation will be logged on the device reconciliation form, and signed and dated by the Principal Investigator.

5.5.4 Return or Destruction of Study Device

At the completion of the study, there will be a final reconciliation of device shipped, device consumed, and device remaining. This reconciliation will be logged on the device reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study device. Device destroyed on site will be documented in the study files.

6 Study Procedures

6.1 Study Data Point 1

Hemostasis during surgery will be determined by surgeon's qualitative evaluation. Notation of re-bleed will be made. Re-application of product will not occur.

6.2 Study Data Point 2

Postoperative bleeding will be evaluated by documentation surgical site drainage and the use of blood products.

6.3 Study Data Point 3

30 day post-op follow-up to all for sufficient time to heal and evaluate for possible post-operative infection or complications. This evaluation can be conducted either in person or by phone.

6.4 Schedule of Events

Pre-Operative	Study Data Point 1 – Intra-Operative Hemostasis Evaluation	Study Data Points 2 – Post-Operative 24 hours	Study Data Point 3 – Post-Operative 30 Day Follow-up by phone
Inclusion/Exclusion	Notation of severity of osteoporosis	Hemoglobin Levels	Survival Documentation
Informed Consent	Qualitative evaluation osteoporosis during surgery	Notation of post-operative blood product usage	Notation of any visits for infection of complications.
Hemoglobin levels	Qualitative evaluation of bleeding of the cut sternum during the surgery	6 hours Post-op Surgical Site Drainage	
	Qualitative evaluating of the ease of use of the product	12 hours Post-op Surgical Site Drainage	
	Notation of in-operative blood product usage	18 hours Post-op Surgical Site Drainage	
	Notation of a re-bleed occurrence	24 hours Post-op Surgical Site Drainage	

7 Statistical Plan

7.1 Sample Size Determination

The power of 60 patients was not determined statistically. The number was determined at the request of the sponsor based on their minimum requirements. In order to compensate for the lack of statistical sample size determination, an increase in alpha and adding an ANCOVA to explain any differences found will be utilized.

7.2 Statistical Methods

Descriptive statistics for mean homeostasis scores, the length of operation time, the surgical drainage output, and the ease of BoneSeal® application.

7.3 Subject Population(s) for Analysis

- All-randomized population: Any subject randomized into the study, regardless of whether they received study device

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, device overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the 30 day follow-up.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the device, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to:

Hemostasis, LLC
5000 Township Parkway
Saint Paul, MN 55110
Fax : 651-855-1465

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the LLU IRB

This section describes the requirements for safety reporting by investigators who are Loma Linda University faculty, affiliated with a Loma Linda University research site, or otherwise responsible for safety reporting to the Loma Linda University IRB. Loma Linda University IRB requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Loma Linda University IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Loma Linda University IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths: more rapid reporting requirements

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Loma Linda University IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Loma Linda University IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:

For clinical trials, the following events are also reportable to the Loma Linda University IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of device exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality

- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4 Stopping Rules

The following practical reasons for terminating the study early will be applied:

- Treatment is found to be convincingly different
- Treatment is found to be convincingly not different
- Side effects or toxicity are too severe to continue treatment, relative to the potential benefits
- The data are of poor quality
- Accrual is too slow to complete the study in a timely fashion
- Definitive information becomes available from an outside study, making the present study unnecessary or unethical
- The scientific questions are no longer important due to other developments
- Adherence to the protocol is unacceptably poor
- Resources to perform the study become no longer available
- The study integrity becomes undermined by fraud or misconduct

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment by the sponsor, of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 3 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Patient safety will be monitored by the sponsor.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment ___ for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from Hemostasis, LLC.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Loma Linda University Medical Center investigators will follow the University conflict of interest policy.

12.3 Disclosure

Let it be disclosed that Dr. Nahidh Hasaniya served as a medical expert in the production of the study device. He did not receive payment for his expertise, nor is he on any patents related to the product.

12.4 Subject Stipends or Payments

Subjects will not paid for participation.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

Once consent from the sponsor has taken place, the Investigator plans to submit the study for publication into any of the following journals:

1) Annals of Thoracic Surgery
2) Journal of Thoracic & Cardiovascular Surgery
3) Circulation

14 References

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15 Attachments

Sample Consent Form