RECON STUDY

A POST MARKET OBSERVATIONAL STUDY TO OBTAIN ADDITIONAL INFORMATION ON THE USE OF CORMATRIX® ECM® FOR PERICARDIAL RECONSTRUCTION

STUDY SPONSOR:
CORMATRIX CARDIOVASCULAR, INC.
1100 OLD ELLIS ROAD
ROSWELL, GA 30076

PROTOCOL NUMBER: 14-PR-1095
REVISION: 2.0

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Please Note: Confidential information contained herein is made available to you in your capacity as Investigator, Medical Advisor, or Consultant to CorMatrix Cardiovascular, Inc. ("CorMatrix"). It is provided only for review by you, your staff, IRB/Ethics Committee members, or other regulatory authority. Except as necessary to provide participant with all relevant information, it is expected that there will be no disclosure to other persons.

Investigator Statement of Compliance

I hereby agree to comply with this protocol and applicable regulations governing clinical trials, including local regulations, and Good Clinical Practice / ICH Guidelines.

Investigator Signature: _____

Date: _____

Table of Contents –

CorMatrix Cardiovascular, Inc.

STUDY COORDINATION

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DATA COORDINATION CENTER	**CORMATRIX CARDIOVASCULAR, INC.** 1100 OLD ELLIS ROAD ROSWELL, GA 30076

Study Synopsis

OBJECTIVE	The objective of the study is to actively gather additional information on the use of CorMatrix ECM for pericardial reconstruction.
STUDY POPULATION	Up to 100 clinical sites will enroll subjects who have received CorMatrix ECM for pericardial reconstruction.
INDICATIONS FOR USE	The CorMatrix ECM for Pericardial Closure is intended for the reconstruction and repair of the pericardium.
ENDPOINTS	The endpoint is defined as the proportion of subjects with device related adverse events.
EXAMINATION SCHEDULE	One single post-operative visit following pericardial reconstruction with the CorMatrix ECM.
CLINICAL PARAMETERS	The following clinical data will be collected at a single post-operative visit: • Demographic information • Pre-operative risk factors • Surgical procedure • Blood transfusion information, if applicable • Chest tube placement information • Surgical complications • Use of anticoagulation medication • Cardiac related procedures since surgical procedure • Device related adverse events

1. Introduction and Rationale

Open heart surgery requires opening the pericardium to gain access to the heart structures. Once divided, the pericardium retracts significantly and an inflammatory response starts in the body signaling a change has occurred. Following surgery, the pericardium is difficult to re-approximate and is typically left open to avoid causing undue pressure on underlying grafts and structures. However, the absence of the pericardial barrier often leads to scarring and the formation of adhesions between the heart and the sternum. Moreover, the normal function of the pericardium is compromised. Available synthetic materials have largely been abandoned for pericardial closure because they have been shown to cause more adhesions, calcifications and infections.

The CorMatrix ECM for Pericardial Closure acts as an acellular natural scaffold for repairing the pericardium following cardiac surgery. The acellular ECM scaffold allows the patient's own cells to migrate and attach within the ECM to naturally repair the pericardium.

CorMatrix Cardiovascular, Inc. received FDA 510(k) premarket clearance for the CorMatrix ECM for Pericardial Closure (K051405) on August 31, 2005. This post market observational study will evaluate the safety and effectiveness of CorMatrix ECM for pericardial reconstruction by collecting specific data at the first post-operative visit. Data collected from this study will not be used to support a marketing claim or change in labeling. This study is being performed to gather post-market data only and is not being performed under the direction of the FDA. This study is of minimal risk and involves no procedures for which written consent is usually required.

2. Indication for Use

The CorMatrix ECM for Pericardial Closure is intended for the reconstruction and repair of the pericardium. The entire Instructions for Use (IFU) can be found in Appendix B.

3. Description

The CorMatrix ECM for Pericardial Closure is an extracellular matrix (ECM) scaffold derived from porcine small intestinal submucosa (SIS). CorMatrix has licensed the technology to implement SIS material for use in cardiac surgery. SIS is a natural collagen construct derived from a select layer of tissue that is recovered from porcine small intestine. During processing, the inner and outer muscle layers of the intestine are removed, leaving an intact, acellular, submucosa with a portion of the tunica propria layer attached to the inner surface. The current CorMatrix ECM application for circumferential pericardial reconstruction and repair has demonstrated the same remodeling characteristics in the pericardium as other tissues in various animal models. After several months, cells infiltrate into the matrix with a lack of inflammation, lay down a neo-mesothelial lining and reconstitute a barrier between the heart and surrounding structures. The SIS slowly remodels and is replaced over time by host tissue. Based on the properties of the SIS material, SIS is

well suited to replace the area left open in the pericardium following open heart surgery. The CorMatrix ECM for Pericardial Closure is supplied in a lyophilized, sterile state and is for single use only. The CorMatrix ECM can be cut to the appropriate size, using aseptic technique, in order to adequately cover the pericardial defect.

4. Prior Clinical Evaluations

CorMatrix ECM has been studied in previous prospective clinical evaluation, and a post-market clinical study is ongoing. The ECM for Pericardial closure has been studied in a randomized, prospective study to evaluate its ability to reduce the incidence of new onset atrial fibrillation; the ECM for Carotid Repair is under evaluation in a post-market study to capture and assess device performance data from subjects undergoing patch angioplasty of the carotid artery following carotid endarterectomy using the product per its FDA-cleared Indications for Use.

4.1. Clinical Evaluation of the ECM Pericardial Closure Device

The CorMatrix ECM Pericardial Closure device was evaluated in a multicenter, prospective, randomized, controlled clinical study, to demonstrate the safety and effectiveness of the device to reduce the incidence of new onset postoperative atrial fibrillation by circumferentially reconstructing the normal pericardial anatomy following isolated, first-time, coronary artery bypass grafting (CABG) procedures as compared to the control group subjects who did not undergo pericardial closure. Safety was to be established by demonstrating that the composite clinical event rate for the ECM group was not worse than the control group. Effectiveness was to be established by demonstrating a reduced incidence of new onset post-operative atrial fibrillation in the ECM group as compared to the control group. 440 patients at 15 U.S. sites were enrolled between December 2010 and November 2012 and randomized in a 1:1 ratio into either the ECM group (pericardial closure) or the control group (no pericardial closure). A blinded, independent core laboratory evaluated all arrhythmia data to determine if subjects met the effectiveness endpoints. A blinded, independent Clinical Events Committee adjudicated all safety endpoint events. Patients were evaluated at hospital discharge, 30 days and 270 days postoperatively. Subjects were adults (at least 18 years of age) with no prior history of atrial fibrillation or history of anti-arrhythmia drug treatment in the past three months and no implantable cardiac devices (i.e., cardiac resynchronization therapy devices with and without defibrillator capabilities [CRT-Ds and CRTs), implantable cardioverter-defibrillators [ICDs] and pacemakers) undergoing isolated, first-time CABG with a median sternotomy approach.

The primary and secondary effectiveness endpoints, superiority of the ECM over no pericardial closure for reduction in the incidence of new onset post-operative atrial fibrillation, were not met. The study results showed that the rate of new onset post-operative atrial fibrillation for the primary effectiveness endpoint was similar between the two groups, with a rate of 38.3% in the ECM group compared with 35.9% in

effectiveness endpoints, the rate of treated or sustained episodes of new onset post-operative atrial fibrillation (defined as a single episode lasting 15 minutes or more), and the rate of treated episodes of new onset post-operative atrial fibrillation, the results were also similar between the two groups (36.8% versus 35.0% and 27.4% versus 22.1%, respectively, for the ECM group compared with the control group).

The composite primary endpoint event rates for the ECM and control group were 3.9% and 3.7%, respectively. Using the protocol specified non-inferiority margin, 7.5%, the ECM was shown to be non-inferior to control for the primary safety endpoint ($p<0.001$). Therefore, the primary safety endpoint for the study was achieved. The composite secondary safety event rate was similar for the two groups (5.8% for the ECM group compared with 3.9% for the control group) demonstrating no significant increase in the rate of bypass graft failure in the ECM group compared with the control group.

Although the study failed to demonstrate a reduction in the incidence of new onset post-operative atrial fibrillation, the study demonstrated that the CorMatrix ECM for Pericardial Closure continues to be safe for its intended use, with no significant increase in the rate of bypass graft failure or cardiac tamponade compared with no pericardial closure.

4.2 Post-market Clinical Evaluation of the ECM for Carotid Repair

CorMatrix is currently conducting a post-market registry study for the CorMatrix ECM for Carotid Repair (Protocol No. 11-PR-1021). The objective of this registry is to capture and assess device performance data from subjects undergoing patch angioplasty of the carotid artery following carotid endarterectomy using the CorMatrix ECM for Carotid Repair per its commercial Indications for Use. This registry provides an ongoing post-market surveillance mechanism to document clinical outcomes on the use of the CorMatrix ECM for Carotid Repair. This is a multi-center, prospective, single-arm, post-market, observational registry of subjects receiving the CorMatrix ECM for Carotid Repair for patch angioplasty following carotid endarterectomy procedures. This post-market registry may involve up to ten U.S. clinical sites and up to 230 subjects. Data will be collected through the 24-month follow-up.

One-hundred and eighty six patients are enrolled in the study and included in the interim analysis of the CorMatrix ECM for Carotid Repair registry. The data demonstrated that the rate of device related adverse events were consistent with the rates found in the review of the contemporary literature for patch angioplasty. Specifically, no unanticipated events were found and the rate of the events was as anticipated in the risk management plan. Of specific interest in the analysis was the rate of pseudoaneurysm, which was present in 2 (1.08%) of the 186 patients and compared favorably to the rates found in the literature (1.4% to 5%).

The mean carotid stenosis (maximum) at pre-operative was 84.8%. Mean change from baseline values were -56.8%, -57.9%, and -59.6% at the 1 to 3-month, 6-month, and 12-month follow-up evaluations. The mean carotid stenosis (minimum) at pre-operative was 71.7%. Mean change from baseline values were -63.9%, -61.2%, and -63.4% at the 1 to

3-month, 6-month, and 12-month follow-up evaluations. No data are yet available for the 24-month follow-up evaluation, as the first enrollment was on May 24, 2012.

As a result of this analysis and the directed and ongoing risk management activities, the overall residual risk of the CorMatrix ECM for Carotid Repair is determined to be acceptable.

5. Study Objectives

The objective of the study is to actively gather additional information on the use of CorMatrix ECM for pericardial reconstruction.

Endpoint
The endpoint is defined as the proportion of subjects with device related adverse events.

6. Study Design

This is a multi-center post-market observational study. It is anticipated that 100 or more eligible centers will participate. There is no upper limit for the number of enrolled subjects. Eligible candidates will be approached to ascertain interest in study participation at their initial follow up visit. If a subject has had CorMatrix ECM used in their surgery they will be asked to allow their physician to use their medical information from the surgical procedure and the current visit. All elements of the approved informed consent will be provided verbally and the process will be documented in the subject study binder by the research staff. A copy of the consent will be provided to the participant. This study includes a one-time visit at the initial post-operative visit.

7. Study Population

The study population will consist of any subject who has received CorMatrix ECM for pericardial reconstruction. Subjects will be considered enrolled into the study once they have given permission for their medical information to be collected. Before any subject can be enrolled, the IRB for the specific institution must approve the protocol, the informed consent form to be used at that site and a Waiver of Documentation of Consent.

8. Study Methods

Study procedures are standardized to the extent possible and all study-related data will be captured on a standardized Case Report Form. A copy of the Case Report Form is provided in Appendix A.

9. Study Procedures

Patients returning for a post-operative visit following a surgical procedure with pericardial reconstruction with CorMatrix ECM will have the following information collected and documented:

- Documentation of the consent process and verbal approval by subject
- Demographic information
- Pre-operative risk factors
- Surgical procedure
- Blood transfusion information, if applicable
- Chest tube placement information
- Surgical complications
- Use of anticoagulation medication
- Cardiac related procedures since surgical procedure
- Device related adverse events

All study-related data will be captured on a standardized Case Report Form. A copy of the Case Report Forms is provided in Appendix A. Case report forms will be sent to CorMatrix via email or mail. Stamped, self-addressed envelopes will be provided.

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10. Adverse Event Reporting

10.1 Definitions

Adverse Event (AE)
An adverse event ("AE") will be defined as any undesirable clinical occurrence in a subject whether it is considered to be device related or not, that includes a clinical sign, symptom, or condition and/or an observation of an unintended technical performance or performance outcome of the device. Causality is defined as not-related, possibly-related, and probably-related to the device. This post market clinical study will collect only events that relate to the use of the CorMatrix ECM as well as any pericardial reconstruction clinical findings.

Serious Adverse Event (SAE)
A serious adverse event ("SAE") will be defined as an event that: 1) threatens life, 2) results in permanent impairment of a body function or permanent damage to a body

structure, 3) necessitates medical or surgical intervention to preclude such impairment, 4) requires or prolongs hospitalization, or 5) is fatal (death).

Adverse Device Event
An Adverse Device Event will be defined as a clinical sign, symptom, or condition that is causally related to the device procedure, the presence of the device, or the performance of the device. Due to the temporal proximity of the AE to product administration, there is a reasonable possibility that the product may have caused the AE or may have contributed to the severity or duration of an event caused by other means.

10.2 Assessing and Recording Adverse Events

Each AE recorded must be documented on the Case Report Form. All serious and device related events must be reported immediately to CorMatrix via telephone or email within 24 hours of the Investigator becoming aware of the event. The case report form will be submitted to CorMatrix. The site will be contacted by CorMatrix for additional information including, but not limited to:

- Description of the event and underlying cause (diagnosis), coexisting disease, or other.
- Date of onset and date of resolution. If the event is present at the single post-operative visit it will be marked as unresolved.
- Intensity of the event: mild, moderate, or severe.
- Frequency of the event: single episode, intermittent, or continuous.
- Action taken: none, medication, procedure, medication and procedure, or other.
- Relationship to the procedure/surgery: not-related, possibly-related, or probably-related.

The Investigator must ensure that the details of the event are documented in the medical notes including full details of the outcome, in addition to recording the event on the appropriate case report form.

Serious adverse events and/or device related events contact information at CorMatrix:

Dawn Flanders
Quality Systems Manager, CorMatrix
(470) 514-4029
RECON@cormatrix.com

10.3 Possible Adverse Events

Potential risks are the same as those associated with any thoracic surgery procedure, including bleeding, MI, stroke, death, and scarring from the incision. There is also a risk of infection and/or wound healing complications, but an increase in these

complications over standard thoracic surgery has not been observed in other pericardial closure/reconstruction. This study will capture events reported at the first (initial) postoperative follow up as reported by the PI and/or subject and from a review of medical records.

11. Data Analysis

Since this is a post-market study, analyses will consist of tabulated data and descriptive statistics. Subject data listings and tabular and graphical presentations of the summary and statistical results will be provided. Additional quantitative and qualitative comparisons will be made to contemporary literature and similar studies

12. Ethical Considerations

12.1 Code of Conduct

The Investigator will ensure that the clinical study is conducted in accordance with good clinical practice and all regulatory and institutional requirements, including those for subject privacy, informed consent, Institutional Review Board or Ethics Committee approval, and record retention. (Appendix D: Investigator Qualifications and Responsibilities)

12.2 Ethics Committee / Institutional Review Board Approval and Oversight

The Investigator must obtain appropriate Ethics Committee ("EC") or Institutional Review Board ("IRB") approval before the study can be initiated. A copy of the written approval from the EC/IRB and a copy of the approved Informed Consent Form (approved Waiver of Documentation of Consent, if applicable) should be sent to CorMatrix. Appropriate study progress reports will be prepared for the EC/IRB by the Principal Investigator. Any changes to the protocol must be discussed and approved by CorMatrix in writing unless the change is made to assure the safety of the subject. In the non-emergent setting, after agreement on the changes has been reached, an amendment to the protocol will be provided by CorMatrix for submission to the EC/IRB for review and approval prior to initiation of the change. Any change made emergently must be documented in the subject's medical record. The Investigator must immediately forward to the EC/IRB any written safety reports or updates from CorMatrix.

12.3 Informed Consent Documentation and Subject Confidentiality

The investigator will be responsible for submitting the clinical study protocol and Informed Consent/Waiver of Documentation of Consent to their EC/IRB or centralized EC/IRB. The Informed Consent/Waiver of Documentation of Consent and protocol must be approved by the local/centralized EC/IRB before the study is initiated and subjects enrolled. Prior to obtaining any study specific information approved informed consent will be reviewed with the subject and the subject must provide verbal approval. Documentation of the consent process must be completed by the research personnel. The

investigator shall provide a copy of the Informed Consent to the subject. Completed documentation of the consent process will be available for auditing by CorMatrix or their representative, as applicable.

CorMatrix will maintain the confidentiality of the identity of subjects enrolled in the study and the information contained in their study records. CorMatrix will also instruct the study investigators in the importance of maintaining the confidentiality of study records. Any publication of any data collected as part of this trial will only use de-identified data, so that identification of any individual subject will not be possible. The records will be made available as required for review by the FDA, or other applicable regulatory agency and a reviewing EC/IRB; however to the extent possible, the subject's identity will not be disclosed. The Case Report Forms will use a subject identification number, with the patient name and address NOT appearing anywhere on the study form to be submitted to the sponsor (Appendix C: Sponsor's Commitments).

13. Bibliography

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Appendix A

Case Report Form

To be provided as a separate document

Appendix B

Instructions for Use

To be provided as a separate document

Appendix C

Sponsor Commitments

SPONSOR'S COMMITMENTS

CorMatrix is committed to:

1. Complying with the Declaration of Helsinki and all applicable health authority regulations governing the conduct of clinical research studies.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing the clinical investigators of any new information about the study which may affect the health, safety, or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical investigators with the study protocol and Case Report Form on which to document the study evaluation variables for each subject entered into the study.
5. Providing the clinical investigators and study staff training on the protocol and completion of the Case Report Form.
6. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
7. Certifying that EC/IRB approval of the protocol and Investigators Agreement will be completed prior to treatment at a clinical site.

Appendix D

Investigator Qualifications and Responsibilities

INVESTIGATOR QUALIFICATIONS AND RESPONSIBILITIES

Each investigator must be a licensed physician who has received training for using the CorMatrix ECM for the reconstruction and repair of the pericardium. The investigators have the following responsibilities:

1. **Subject Selection**

   The investigator is responsible for assuring that all subjects entering the study are eligible to participate.

2. **Informed Consent**

   The investigator is responsible for fully reviewing the nature of the study. The investigator is responsible for documenting the Informed Consent process in compliance with applicable regulations for each patient, prior to enrollment in the trial. A copy of the Informed Consent Form and documentation of the consent process will be maintained in the patient's medical record.

3. **Ethics Committee (EC)/Institutional Review Board (IRB) Approval**

   The investigator must obtain approval for his participation in this protocol from an EC/IRB prior to entering any patients in the study. The Informed Consent document and Waiver of Documentation of Consent to be used will also be submitted by the Investigator to the EC/IRB for approval prior to initiation of the study. Assurance that the EC/IRB approval of the study protocol and Informed Consent/Waiver of Documentation of Consent has been obtained will be provided to the Sponsor prior to initiation of the study.

4. **Subject Evaluation and Data Reporting**

   The investigator is responsible for performing the patient evaluations as described in the study protocol. All information generated by the patient evaluation will be recorded on the Subject Case Report Form provided by the Sponsor. The Case Report Form will be filled out in black ink. Any corrections will be made by lining out with a single line, providing the date of corrections and initials of person making the correction. Correction fluid will not be used. The person completing the form will date and initial each form upon its completion and will send the form via mail, email or fax to CorMatrix. Copies of all Case Report Forms will be retained in the Investigator's office.

5. **Record Retention**

   The Investigator must retain all subject records for at least 2 years, or longer, if required by local regulations.