A Retrospective Analysis of the Use of Gentrix® Surgical Matrix for Soft Tissue Reinforcement in Ventral Hernia Repair

Short Title: Gentrix Ventral Hernia Repair study

Protocol Number: T-GENVIH-002

National Clinical Trial (NCT) Identified Number: TBD

Version Number: V1.0

11-OCT-2022

Sponsor:
Integra LifeSciences Corporation
1100 Campus Drive, Princeton, New Jersey, 08540
USA
www.integralife.com

Contents

List of Figures

List of Tables

A. ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ADE	Adverse Device Effect
ANCOVA	Analysis of Covariance
ASADE	Anticipated Serious Adverse Device Effect
CDC	Communicable Disease Center
CIP	Clinical Investigational Plan
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CTA	Clinical Trial Agreement
CRF	Case Report Form
DD	Device Deficiency
EDC	Electronic Data Capture
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LOS	Length Of Hospital Stay
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
NCT	National Clinical Trial
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SSO	Surgical Site Occurrence
US	United States
USADE	Unanticipated Serious Adverse Device Event

B. REVISION HISTORY

The table below is intended to capture changes of IRB/EC-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page. Procedures for amending this protocol can be found in the current SOPs.

Version	Date	Description of Change	Brief Rationale

C. AUTHORIZED SIGNATORIES FOR THE SPONSOR

Name, Position/Title	Signature	Date
David Sheleheda Sr Director, Global Clinical Operations	David Sheleheda SignNow e-signature ID: 046f2420ec... 13-Oct-2022 14:39:29 UTC David Sheleheda (Signer)	13-OCT-2022
D. Adam Young , Ph.D. PMP Director, Medical Affairs	D. Adam Young SignNow e-signature ID: 86ca858b49... 13-Oct-2022 14:35:54 UTC Adam Young (Signer)	13-OCT-2022
Hannah Baker, Sr Medical Science Liaison, Clinical Affairs	Hannah Baker SignNow e-signature ID: 7b6091628f... 14-Oct-2022 14:52:31 UTC Hannah Baker (Signer)	14-OCT-2022
Nicole Kotter Sr Manager, Regulatory Affairs	NicoleKotter SignNow e-signature ID: 9b3f3c0081... 13-Oct-2022 14:36:52 UTC Nicole Kotter (Signer)	13-OCT-2022
Habib Nacer-Chérif Clinical Research Manager, Clinical Operations	Habib Nacer-Chérif SignNow e-signature ID: d8ff839580... 13-Oct-2022 14:16:13 UTC Habib Nacer-Chérif (Signer)	13-OCT-2022
Lan Li Data Manager, Global Clinical Affairs	Lan Li SignNow e-signature ID: 0528483c88... 13-Oct-2022 15:14:38 UTC Lan Li (Signer)	13-OCT-2022
Weiwei Xu Senior Biostatistician, Global Clinical Affairs	Weiwei Xu SignNow e-signature ID: 3e3bf6c1b3... 13-Oct-2022 14:31:51 UTC Weiwei Xu (Signer)	13-OCT-2022

D. STUDY INVESTIGATOR AND SITE MEDICAL STAFF

The list of the study investigator and other site medical staff along with their contact information can be found in the Trial Master File.

E. STATEMENT OF COMPLIANCE BY THE INVESTIGATOR

This clinical investigation will be conducted in compliance with the current ISO 14155 guidelines and applicable regulatory requirements, including the Medical Device Regulation (MDR) 2017/745 **[AND/OR]** United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and other applicable national and regional regulatory requirements whichever provides the greater protection of the individual.
This clinical investigation will not be initiated until approval has been obtained from the Ethics Committee(s) (and Regulatory Authority if applicable). Any additional requirements imposed by the Ethics Committee(s) (and Regulatory Authority if applicable) will be followed.
No deviation from the clinical investigation plan will be implemented without the prior review and approval of the Ethics Committee(s) except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the Ethics Committee as soon as possible.

Investigator's Statement

By signing this document, I agree to conduct this clinical **[investigation/study]** in accordance with the design and specific provisions of this clinical investigation plan; modifications to the clinical investigation are only acceptable with a mutually agreed upon clinical investigation plan amendment as approved by the Sponsor and involved Ethics Committee(s).

I agree to await Ethics Committee approval of the clinical investigation plan and informed consent form before initiating the clinical investigation, to obtain consent from subjects prior to their enrolment, to collect and record data as required by the clinical investigation plan and associated case report forms, and to maintain documents related to the clinical investigation for the period of time required.

Confidential

This document contains confidential information belonging to Integra LifeSciences Corporation. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Investigator Name

Investigator Signature Date

1 Protocol Summary

1.1 Protocol Synopsis

Title	A Retrospective Analysis of the Use of Gentrix® Surgical Matrix for Soft Tissue Reinforcement in Ventral Hernia Repair
Short Title	Gentrix Ventral Hernia Repair study
Protocol Number	T-GENVIH-002
Study Description	The purpose of this study is to collect additional safety data and demonstrate the performance of Integra Gentrix® Surgical Matrix for reinforcement of ventral hernia repairs. Retrospective data will be collected and assessed for early post-operative surgical site events and complications in the immediate post-operative period of 90 days.
Pre/Post-Market	Post-Market
Product(s)	Gentrix® Surgical Matrix - (6-layer), - Plus (8-layer), and -Thick **Refer to **Erreur ! Source du renvoi introuvable.** at the end of the protocol for product-specific Stock Keeping Units (SKUs) to be included in this study.*
Indications for Use	Gentrix Surgical Matrix is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia (e.g., hiatal/ diaphragmatic) and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Surgical Matrix minimizes tissue attachment to the device in case of direct contact with viscera.
Study Design	Single-Arm, Retrospective, Single-Center
Study Rationale	This study adds to the available data evaluating the safety and effectiveness of Gentrix® Surgical Matrix in ventral hernia repair, particularly in a real-world population.

Primary Objective	The primary objective of this study is to capture existing clinical performance data to confirm the continued performance of the Gentrix® Surgical Matrix.
Safety Objective	The safety objective is to capture existing Gentrix® Surgical Matrix Complication data in the immediate post-operative period of 90 days. Gentrix® Surgical Matrix Complications are defined but not limited to: • Seroma • Abscess • Dehiscence • Hematoma • Wound necrosis • Ileus • Fistula • Delayed wound healing
Primary Endpoint	1. Incidence of post-operative complications requiring procedural intervention within 90 days post index procedure.
Secondary Endpoints	1. Incidence of early post-operative complications (Surgical Site Occurrences (SSOs)) within 90 days post index procedure (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing). 2. Incidence of Surgical Site Infections (SSIs) within 90 days post index procedure. 3. Incidence of later post-operative complications occurring after 90 days post index procedure. 4. Incidence of hernia recurrence confirmed by clinical assessment. 5. Incidence of reoperation requirement due to index repair.
Tertiary Endpoints	1. Average length of hospital stay (LOS) post index procedure (measured in days). 2. Rate of opioid usage following procedure as determined by % of prescriptions filled and refilled

Description of Study Intervention	The retrospective chart review will include the full consecutive series of patients between 22 years and 80 years old who underwent abdominal wall reconstruction for a hernia with Integra Gentrix® Surgical Matrix during the time period between November 1, 2017, and present (90 days prior). Subjects from that consecutive series will be included in the study based on the defined inclusion and exclusion criteria. Collection of patients' data treated with the Gentrix® Surgical Matrix per routine/standard of care use and in accordance with the Instructions for Use (IFU).
Study Population	Patients between 22 years and 80 years old (inclusive) at time they underwent abdominal wall reconstruction utilizing Gentrix® Surgical Matrix as a reinforcement graft during the time period between November 1, 2017, and present (90 days prior to the start of the data collection).
Inclusion Criteria	1. Patients between 22 years and 80 years old (inclusive) at time they underwent abdominal wall reconstruction utilizing Gentrix® Surgical Matrix as a reinforcement graft during the time period between November 1, 2017, and present (90 days prior to the start of the data collection).. 2. Subject underwent abdominal wall reconstruction for a hernia(s) using Integra® Gentrix® Surgical Matrix.
Exclusion Criteria	1. Subject has known allergy to porcine-derived products. 2. Subject required use of Gentrix® device and a second non-Gentrix surgical mesh in the same plane or in different planes for single hernia e.g., Gentrix sublay and a synthetic device in the onlay position. 3. Subject had active necrotizing fasciitis or any current known uncontrolled systemic infection. 4. Subject had uncontrolled diabetes, defined as Hb1AC value >7% within 12 weeks prior to index procedure. 5. Subject has been diagnosed with cirrhosis and/or ascites.

Description of Sites/Facilities Enrolling Participants	One site located in the United States (US) will participate in this study.
Study Duration	Approximately three months.
Data Collection Duration	Approximately one month from initiation of the site until data delivery.
Study Visits/Schedule of Study Activities	This retrospective study specifically aims to collect data from the day of the index procedure, and post-operatively up to a maximum of one year or shorter as applicable.
Data Collection	Data will be collected via medical records, study worksheets, and entered into electronic data capture system by the site. The following data will be collected: **Patient Data:** • *Basic demographic data* (e.g., gender, year of birth, height, weight, race, ethnicity, nicotine and alcohol use history, clinical presentation, diagnosis, and relevant medical history up to 3 years prior to surgery). **Procedural Data:** • Index Surgery: o Ventral Hernia Details: *Location and size of the ventral hernia(s), CDC Wound Class (the highest one) and complications associated with Hernia(s) repair.* o Surgery Details: *Surgical approach (Robotic, Laparoscopic, Robotic assisted, Laparoscopic assisted, MIS converted to open, Open), Times related to the different steps of the index surgery.* o Type of the Gentrix Surgical Matrix Used. o Intraoperative Details: *Surgical Plane of graft placement, Graft fixation, Component separation, Concomitant procedure, Stoma presence, and Fascial closure.* **Clinical Performance and Safety Evaluation:** 1. Post operative complications

	2. SSI(s) 3. Hernia recurrence 4. Hospital re-admission(s) 5. Reoperation(s) 6. Device Deficiency(ies) 7. Adverse Event(s) 8. Concomitant medications 9. Opioid usage following procedure
Statistical Methods & Analyses	Study outcomes will be summarized using descriptive statistics. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, quartiles, ranges, and numbers of observations. Statistical analysis will be based on data from all evaluable subjects meeting the eligibility criteria. Subgroup analyses may be performed for surgical approach and type of the Gentrix Surgical Matrix Used.

1.2 Schedule of Data Collection Activities

Table 1: Scheduled of Data Collection Activities

Retrospective Data Collection	Screening	Index Surgery	Discharge	Follow-up Visit
Eligibility	X			
Demographics	X			
Medical history	X			
Ventral hernia details (location, size)		X		
CDC Wound Class *(highest applicable class)*		X		
Complications associated with Hernia(s) repair		X		
Surgery details *(surgical approach, Time into procedure room, Time skin cut, Time skin closed, and Time out of procedure room)*		X		
Gentrix Surgical Matrix Used *(type)*		X		
Intraoperative Details *(Surgical Plane of Graft Placement, Graft fixation, Component Separation, Concomitant Procedure, Stoma presence (if applicable), Fascial closure)*		X		
Adverse events		X	X	X
Device deficiencies		X		
Concomitant medication		X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

2 Introduction

2.1 Background

Ventral hernias are a type of abdominal hernias that can occur at any location along the vertical abdominal wall. Typically, these defects are acquired resulting from complications of a prior surgery, trauma or natively weak points of the abdominal wall in some individuals. Obesity may contribute in large part to the weak points due to cyclic patterns of weight gain and loss. One in 8 patients will develop an incisional hernia after abdominal surgery[1].

Ventral hernia repair is one of the most common surgical procedures performed in the United States. Every year there are approximately 350,000 repairs performed in the US with an estimated cost of $3.2 billion.[2] Different patient populations require different solutions in order to make a repair as cost-effective and risk-averse as possible.

Clinical evidence has shown that primary suture repair of a ventral hernia alone results in high recurrence rates (>50%), and that all incisional hernia repairs should be reinforced with surgical mesh.[3,4] Despite this consensus, due to the large variety of surgical meshes available currently, there is a lack of consensus on the ideal material for each repair. Ventral hernia treatment decisions are typically tied to patient operative risk, symptomatic concerns and potential clinical complications of the repair.

Permanent synthetic mesh has been the standard of care in the reinforcement of simple, clean hernias due to its minimal cost and history of low recurrence.[5,6] However, due to the inherent permanence, long-term complications such as product migration, contraction, erosion, and infection are common.[5-8] In the complex hernia setting, synthetic materials may not be ideal due to the increased risks of surgical site occurrences (SSOs) and resulting recurrences.[5-8] These complications can prove costly with each hernia recurrence and wound event estimated to cost an additional $44,000 and $85,000 respectively.[9,10] Specifically, a mesh infection can cost up to $140,000 and may require explanation of the mesh altogether.[10]

Biologically-derived materials, such as acellular dermal matrices, were developed for use in complex hernia repair to mitigate some of the risks seen with synthetic materials. However, long-term study of these materials demonstrated a 31.8% recurrence rate and 36.6% wound infection rate at 18.2 months follow-up.[11]

Approximately 74% of inpatient ventral hernia repairs are completed as open procedures. While this number is slightly lower for outpatient ventral hernia repairs (64%), this remains the predominant surgical approach[12] likely for more complex cases.

Currently available biologically derived mesh options for reinforced repairs include a class of non-dermal products including Gentrix Surgical Matrix devices.

This post-market clinical study is being conducted to characterize the performance and safety of Gentrix® Surgical Matrix -(6-layer), -Plus (8-layer) and -Thick devices in the repair of ventral hernias in patients between 22 years and 80 years old (inclusive) at time they underwent abdominal wall reconstruction utilizing Gentrix Surgical Matrix as a reinforcement graft during the time period between November 1, 2017, and present (90 days prior).

2.2 Investigational Product Overview

Gentrix Surgical Matrix is intended for implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery.

Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following open or laparoscopic procedures: hernia (e.g., hiatal/diaphragmatic) and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair. Gentrix Surgical Matrix minimizes tissue attachment to the device in case of direct contact with viscera.

The Gentrix Surgical Matrix Device configuration includes the Gentrix Surgical Matrix (6-layer), Gentrix Surgical Matrix Plus (8-layer), and the Gentrix Surgical Matrix Thick.

2.2.1 Gentrix Surgical Matrix (6-layer):

Gentrix™ Surgical Matrix (6-layer) is composed of a porcine-derived extracellular matrix, also known as urinary bladder matrix. The device is supplied in a multilayer sheet configuration in sizes up to 10 cm x 15 cm and packaged in double peel-open pouches. The device is terminally sterilized using electron beam irradiation.

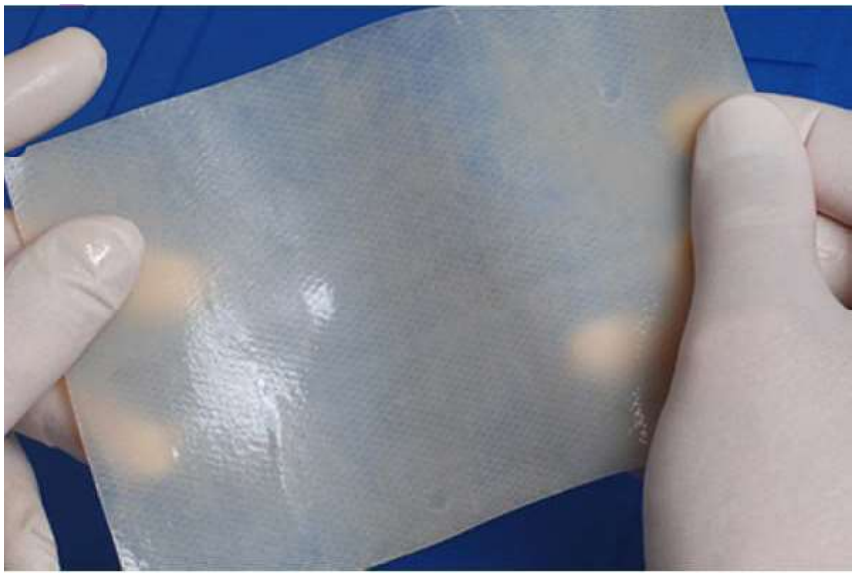

Figure 1: Gentrix™ Surgical Matrix (6-layer)

2.2.2 Gentrix Surgical Matrix Plus (8-layer):

Gentrix™ Surgical Matrix Plus (8-Layer) is composed of porcine-derived extracellular matrix, also known as urinary bladder matrix. The device is supplied in a multilayer sheet configuration in sizes up to 10 cm x 15 cm and packaged in double peel-open pouches. The device is terminally sterilized using electron beam irradiation.

Figure 2 : Gentrix™ Surgical Matrix Plus (8-layer)

2.2.3 Gentrix Surgical Matrix Thick:

Gentrix™ Surgical Matrix Thick is composed of a porcine-derived extracellular matrix, also known as urinary bladder matrix. The device is supplied in a multi-layer sheet configuration in sizes up to 30 cm x 40 cm and packaged in double peel-open pouches. The device is terminally sterilized using electron beam irradiation. Animal studies have shown device resorption in approximately 240 days.

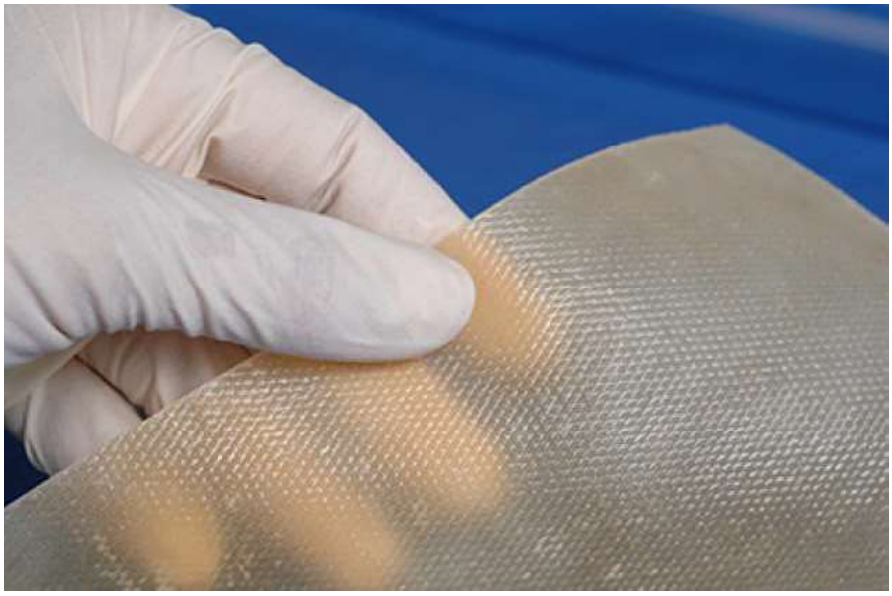

Figure 3 : Gentrix™ Surgical Matrix Thick

2.2.1 Study Device Intended Purpose

The Gentrix Surgical Matrix Devices were used within label in this retrospective study. There were no specific medical or surgical procedures involved in the use of the study devices, other than the standard of care. A full description of the medical and surgical procedures related to the Gentrix Surgical Matrix Devices is available in the Instructions for Use.

2.2.2 Study Device Contraindication

Patients with known sensitivity or allergy to porcine materials.

2.2.3 Required Training and Experience

Previously trained on the use of the devices, the investigator must have used the devices within label in this study. Integra LifeSciences Corporation did not train, nor dictate, the surgery

technique(s). The investigator must meet certain expectations per Sponsor Standard Operating Procedures (SOPs).

2.2.4 Device Accountability

Given the retrospective data collection of this study, no device accountability will be performed for the purposes of this study.

2.2.5 Device Traceability

Devices will be tracked by type, size, and lot numbers, as applicable, which will be part of the data entered into the database of this retrospective study.

2.3 Study & Design Rationale

This is a single-arm, single-center, retrospective study to collect in routine use additional safety data and demonstrate the performance of Integra Gentrix® Surgical Matrix for reinforcement of ventral hernia repairs. Routine use data between November 1, 2017, and present (90 days prior) will be collected retrospectively at 1 site. This study adds to the available data evaluating the safety and effectiveness of Gentrix Surgical Matrix in ventral hernia repair, particularly in a real-world population.

3 Objectives and Endpoints

3.1 Primary Objective

The primary objective of this study is to capture existing clinical performance data to confirm the continued performance of the Gentrix® Surgical Matrix.

Existing clinical data support the safety and performance of the Gentrix® Surgical Matrix. There are currently no safety concerns with these products. This clinical investigation will confirm the safety and performance of the Gentrix® Surgical Matrix and identify any unknown side-effect.

3.2 Safety Objective

The safety objective of this study is to capture existing Gentrix® Surgical Matrix Complication data in the immediate post-operative period of 90 days.

Gentrix® Surgical Matrix Complications are defined but not limited to:

- Seroma
- Abscess
- Dehiscence

- Hematoma
- Wound necrosis
- Ileus
- Fistula
- Delayed wound healing

3.3 Primary Endpoint

The primary endpoint of this retrospective study is the incidence of post-operative complications requiring procedural intervention within 90 days post index procedure.

3.4 Secondary Endpoints

1. Incidence of early post-operative complications (Surgical Site Occurrences) within 90 days post index procedure (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing).
2. Incidence of Surgical Site Infections (SSIs) within 90 days post index procedure.
3. Incidence of later post-operative complications occurring after 90 days post index procedure.
4. Incidence of hernia recurrence confirmed by clinical assessment.
5. Incidence of reoperation requirement due to index repair.

3.5 Tertiary Endpoints

1. Average length of hospital stay (LOS) post index procedure (measured in days).
2. Rate of opioid usage following procedure as determined by % of prescriptions filled and refilled.

4 Study Design

4.1 Overall Design

The Gentrix Ventral Hernia Repair study is a single-arm, retrospective, single-center, post-market study.

4.2 Scientific Rationale for Study Design

This study adds to the available data evaluating the safety and effectiveness of Gentrix Surgical Matrix in ventral hernia repair, particularly in a real-world population.

4.3 End of Study Definition Overview

The end of the study is defined as completion of Case Report Forms (CRFs) for the last subject in this retrospective study.

5 Study Population

5.1 Inclusion Criteria

1. Patients between 22 years and 80 years old (inclusive) at time they underwent abdominal wall reconstruction utilizing Gentrix® Surgical Matrix as a reinforcement graft during the time period between November 1, 2017, and present (90 days prior to the start of the data collection).

2. Subject underwent abdominal wall reconstruction for a hernia(s) using Integra® Gentrix® Surgical Matrix.

5.2 Exclusion Criteria

1. Subject has known allergy to porcine-derived products.

2. Subject required use of Gentrix® device and a second non-Gentrix surgical mesh in the same plane or in different planes for single hernia e.g. Gentrix sublay and a synthetic device in the onlay position.

3. Subject had active necrotizing fasciitis or any current known uncontrolled systemic infection.

4. Subject had uncontrolled diabetes, defined as Hb1AC value >7% within 12 weeks prior to index procedure.

5. Subject has been diagnosed with cirrhosis and/or ascites.

5.3 Description of the site

One site in the USA will be selected to participate in this study. The study site will be selected based upon their experience with the subject device, their clinical expertise, expected commitment to have available data for eligible study patients, and their ability to fulfill general requirements in the Sponsor's SOPs and to comply with this protocol.

5.4 Point of Enrollment & Enrollment Period

There are no physical participants as this is a retrospective study. The requirement for consent being waived, the patients will not provide informed consent to allow use of their data. There is no traditional enrollment period in this study. Data will begin to be collected from the first patient who meets all the eligibility criteria.

This study is anticipated to have a data collection period of one month from initiation of the site until data delivery.

The total expected duration of the study is, therefore, approximately 3 months.

5.5 Screen Failures

Screen failures are defined as subjects created by the site on the Case Report Form (CRF) who do not meet one or more eligibility criteria for participation in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information to be collected on the CRF includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). This will be documented on the Screening and Enrollment log.

5.6 Strategies for Recruitment

The retrospective chart review will include the full consecutive series of patients between 22 years and 80 years old who underwent abdominal wall reconstruction for a hernia with Integra Gentrix® Surgical Matrix during the time period between November 1, 2017, and present (90 days prior). Subjects from that consecutive series will be included in the study based on the defined inclusion and exclusion criteria. Collection of patients' data treated with the Gentrix® Surgical Matrix per routine/standard of care use and in accordance with the Instructions for Use (IFU).

The institutional charts from the study site will constitute the source documents, and data from such charts will be collected using a study-specific eCRF by the site responsible or their designee(s). Each patient should be included in the study only once. Patient screening will rely on manual selection of institutional charts or other means. In these cases, every effort should be made to identify every possible eligible patient. In order to be eligible for the study, patients should meet all of the eligibility criteria.

5.7 Risk/Benefit Assessment

5.7.1 Risks associated with Study device

Complications and reactions are possible with any soft tissue repair, including but not limited to: infection, increased chronic inflammation, allergic reaction, unexplained fever or chills, excessive redness, acute and chronic pain, swelling, tender scars, adhesions, seroma formation, fistula formation, hematoma, recurrence of tissue defect, delayed or failed incorporation of graft, urinary or fecal incontinence,
delayed or failed incorporation of graft, mesh or suture erosion or extrusion, and injury to the bladder, bowel, blood vessels.

5.7.2 Risks Associated with Participation in the study and mitigation

As this retrospective study involves data collection, there are only minimal risks associated with participation. There are no additional device-related risks for this study. There are, however, privacy (loss of confidentiality) risks associated with participation in the study.

Participation in the study does not submit the patient to any additional procedures or exams outside the customary standard of care. Patient confidentiality and privacy is strictly held in trust by the participating investigator, their staff, and the Sponsor. The patient's data will be given a code to assure that the data can only be traced with the use of an identifier. The identifier will be stored securely in the local research institute. Data that is shared with the sponsor will only contain the code. The patient's name and any other identifiable information will be omitted. All national data protection laws will be respected including the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data shared with the sponsor will be encoded and maintained in a secure electronic database that is compliant with 21 CFR Part 11 requirements on electronic records and electronic signatures.

5.7.3 Anticipated Clinical and device Benefits

There is no direct benefit. Information learned from this study might help researchers to better understand medical treatments and disease processes or procedures in order to better help others in the future.
The data collected from the study will be used to inform the device manufacturer about the safety and performance of the device when used in accordance with the device labelling.

5.7.4 Rationale of Risks/Benefits Ratio

The participation in the study does not add risks to the patients, thus the benefit is judged to outweigh the overall residual risks.

6 Study Assessments and Procedures

6.1 Schedule of Data Collection

6.1.1 Screening

- The procedures to be completed are:
  - ✓ Retrospective chart review will include the full consecutive series of patients between 22 years and 80 years old who underwent abdominal wall reconstruction for a hernia with Integra Gentrix® Surgical Matrixbetween November 1, 2017, and present (90 days prior).
  - ✓ Creation on the eCRF of a new case book for each eligible subject. Each created case book assigns the eligible subject with a study number.
  - ✓ Completion of Worksheets/ eCRFs: Site will transcribe/transmit the below-mentioned patients' data in study worksheets & eCRFs. The patients' data will originate from existing medical and other patient records.
- The patients' data to be collected are:
  - ✓ Eligibility:
    - *Inclusion Criteria: Ensure the subject meets the inclusion criteria.*
    - *Exclusion Criteria: Ensure the subject does not meet any of the exclusion criteria.*
  - ✓ Demographics: gender, year of birth, height, weight, race, ethnicity, nicotine and alcohol use history.
  - ✓ Medical history: Obtain subject 's medical history up to 3 years prior to surgery. Medical history is considered relevant when related to any of the study eligibility criteria, or when it may affect any of the clinical investigation endpoints, at the discretion of the investigator. Relevant medical history covers at a minimum Ventral Hernia related medical history treated in this study.

6.1.2 Index Surgery

The patients' data to be collected at the index surgery are:

- Ventral Hernia Details: Location and size of the ventral hernia(s), CDC Wound Class (the highest one) and complications associated with Hernia(s) repair.
- Surgery Details: Surgical approach (Robotic, Laparoscopic, Robotic assisted, Laparoscopic assisted, MIS converted to open, Open), Times related to the different steps of the index surgery.
- Type of the Gentrix Surgical Matrix Used.

- Intraoperative Details: Surgical Plane of graft placement, Graft fixation, Component separation, Concomitant procedure, Stoma presence, and Fascial closure.
- Adverse Events: Information will be collected on any adverse event that the subject is experiencing during or after the surgical procedure.
- Device Deficiency: Medical records will be reviewed for DDs that were documented during the timeframe of treatment with the subject device.

  Note: Completion of Worksheets/ eCRFs: Site will transcribe/transmit the above-mentioned patients' data in study worksheets & eCRFs. The patients' data will originate from existing medical and other patient records.

6.1.3 Discharge

Since the index surgery, the patients' data to be collected at discharge are:

- Post-operative complications requiring procedural intervention
- Post-operative complications (Surgical Site Occurrences)
- Surgical Site Infections (SSIs)
- Hernia recurrence confirmed by clinical assessment
- Reoperations due to index repair
- Adverse Events: Information will be collected on any adverse event that the subject is experiencing during or after the surgical procedure.
- Concomitant Medications: Immunomodulators as well as opioids.

  Note: Completion of Worksheets/ eCRFs: Site will transcribe/transmit the above-mentioned patients' data in study worksheets & eCRFs. The patients' data will originate from existing medical and other patient records.

6.1.4 Follow-Up Visit

The time frame for follow up visits is up to 1 year or shorter, as applicable.

Since previous visit, the patients' data to be collected at the follow-up visit(s) are:

- Post-operative complications requiring procedural intervention
- Post-operative complications (Surgical Site Occurrences)
- Surgical Site Infections (SSIs)
- Hernia recurrence confirmed by clinical assessment
- Reoperations due to index repair

- Adverse Events: Information will be collected on any adverse event that the subject is experiencing during or after the surgical procedure.
- Concomitant Medications: Immunomodulators as well as opioids.
  Note: Completion of Worksheets/ eCRFs: Site will transcribe/transmit the above-mentioned patients' data in study worksheets & eCRFs. The patients' data will originate from existing medical and other patient records.

6.1.5 Study exit

The patients' data to be collected at study exit are:

- Study Exit Type
  Note: Completion of Worksheets/ eCRFs: Site will transcribe/transmit the above-mentioned patients' data in study worksheets & eCRFs. The patients' data will originate from existing medical and other patient records.

6.2 Concomitant Medication Review

Only immunomodulators and opioids are to be reported on the Concomitant Medication (ConMed) CRF.

6.3 Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Authorized, qualified clinical research associate (CRA) of Integra LifeSciences will accomplish the monitoring of the collected retrospective data per the study specific clinical monitoring plan.

The investigator and study staff 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 study-related documents. The site will participate in an initiation visit and will be trained on the study protocol, the eCRF and study related responsibilities. One on-site visit will occur once the study site has completed the eCRFs, so that the Clinical research Associate from Integra LifeSciences can verify the collected data to the source documents (100% source data verification).

The onsite Close-Out Visit may be a combined visit with the monitoring visit.

7 Safety Assessments and Reporting

7.1 Definitions

The table below contains the definitions being used for safety assessment as part of this study:

Table 2: List of AE Terms and Definitions

This list of terms should be edited to remove those which do not concern the study.	
Term	**Definition**
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. And this definition includes any event resulting from use error or from intentional misuse of the investigational device.
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated of unanticipated. This definition includes events related to the investigational medical device; events related to the procedures involved and, for users or other persons, this definition is restricted to events related to investigational medical devices.
Anticipated Serious Adverse Device Effect (ASADE)	A serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. **Note 1:** Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **Note 2:** This definition includes device deficiencies related to the investigational medical device or the comparator.

This list of terms should be edited to remove those which do not concern the study.	
Term	**Definition**
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instruction for use.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. **Note:** SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered Serious Adverse Device Effects.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a life-threatening illness or injury, or a permanent impairment of a body structure or a body function including chronic diseases, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment **Note:** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
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

This list of terms should be edited to remove those which do not concern the study.	
Term	**Definition**
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. **Note 1:** Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. **Note 2:** Procedures associated with the use of a device should be addressed in the risk assessment, which makes it possible to determine whether the procedure related SAEs are Unanticipated Serious Adverse Device Effect or not.

7.2 Reporting of Safety Information

7.2.1 Non-Reportable Event

All Adverse Events, related or not related to the study device or study index procedure by the investigator, are required to be reported in this study.

7.2.2 Severity

Each adverse event will be classified according to three (3) levels of severity. The Sponsor and the investigator will use the following definitions to assess the severity of the adverse event:

Mild – Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

Moderate – Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

Severe – Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

7.2.3 Causality

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

Each AE will be classified according to four (4) different levels of causality:

Not related: Relationship to the device, or procedures can be excluded when:

- the event has no temporal relationship with the use of the study devices, or the procedures related to application of the study devices;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event

Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Causal relationship: the serious adverse event is associated with the investigational device, or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;

- the investigational device or procedures have an effect on;

- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The Sponsor and the investigator will distinguish between the adverse events related to the study device and those related to the procedures (any procedure specific to the study). An adverse event can be related both to procedure and the study device.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the IFU, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the investigator will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator assessment is not available and/or the Sponsor remains uncertain about classifying the adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting not be delayed.

Particular attention shall be given to the causality evaluation of unanticipated serious adverse events. The occurrence of unanticipated events related to the use of the device could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

7.2.4 Foreseeable adverse events and anticipated adverse device effects

The following adverse events are outlined in the device's Instructions for Use:

Infection, increased chronic inflammation, allergic reaction, unexplained fever or chills, excessive redness, acute and chronic pain, swelling, tender scars, adhesions, seroma formation, fistula formation, hematoma, recurrence of tissue defect, anastomotic stricture formation and leaks, dyspareunia, vaginal shortening, vaginal bleeding, atypical vaginal discharge, groin and/or buttock and/or leg pain, urinary or fecal incontinence, delayed or failed incorporation of graft, failure to repair a prolapse, recurrent prolapse, mesh or suture erosion or extrusion, and injury to the bladder, bowel, blood vessels, and/or nerves of the pelvis.

7.3 Reporting Requirements

7.3.1 Reporting of AEs and SAEs

The investigator will determine if there has been a potentially device or procedure related adverse event or potentially device or procedure related serious adverse event. All potentially device or procedure related adverse events and potentially device or procedure related serious adverse events must be reported on the "Adverse event" form of the eCRF.

Potentially device or procedure related adverse events and potentially device or procedure related serious adverse events will be evaluated and differentiated by:

- Seriousness of the event;
- Causality of the event (in relation to the device or procedure);
- Severity of the event.

All potentially device or procedure related AEs and potentially device or procedure related SAEs must be collected for all enrolled subjects starting from the time of enrollment through the last Follow-up. Each AE must be described as follows:

AE Term: A medically defined diagnosis/symptom. Use the highest level of evidence available.

Level 1: Diagnosis (highest level)

Level 2: Symptoms

Level 3: Signs (lower level)

AE Description: Explain the circumstance of becoming aware of the event, how the subject explained the circumstances surrounding the onset of the event, the underlying cause (the diagnosis), coexisting disease, or other condition or complaint involving the event.

AE Duration: Document by entering the date of onset (start date) and date of resolution (stop date).

AE Causality: Document causal relationship between event and the investigational product and Study Procedure (related, possible, probably, not related,).

AE Seriousness: Document as serious or not serious

AE Severity: Document as mild (transient and easily tolerated by the subject), moderate (discomfort and interrupts normal activities), or severe (incapacitating with inability to work or do usual activity)

Action(s) Taken and/or Treatment(s): Document as none, medication, hospitalization, surgical, and/or other. Any prescribed medication should be noted in the subject's medical records and transcribed onto the AE and Concomitant Medications CRFs. If a surgical or invasive procedure is required for an AE, document the procedure on the Invasive Procedure Log.

Outcome: Document as recovered without sequelae, recovered with sequelae, ongoing, death, or other. AEs will be followed until a resolution has occurred, until a resolution is no longer expected, the pre-existing condition returns to baseline conditions, or the subject exits the study.

7.3.2 Reporting Device Deficiency

All device deficiencies (DDs) related to the identity, quality, durability, reliability, usability, safety or performance of the study device including the analysis of used or explanted study device, where applicable, shall be documented throughout the study and managed by the sponsor.

The principal investigator shall record every observed device deficiency on the "Device Deficiency" form, together with an assessment for all enrolled subjects starting from the time of enrollment through the last Follow-up visit. Each DD must be described as follows:

Deficiency Type:

- Identity (Packaging/Labeling)
- Quality (Structure/Appearance)

- Durability (ability to withstand wear, pressure, or damage)
- Usability (use error, misuse, abnormal use)
- Reliability (Performs in a consistent manner)
- Safety (Impact on Patient Care)
- Performance (Functions according to the IFU)

When the deficiency was noted

If the deficiency was associated with an AE

If the deficiency might have led to:

- Adverse Effect
- Serious Adverse Device Effect

Device deficiencies shall be managed by the sponsor in accordance with written procedures for the control of non-conforming product. The sponsor shall take appropriate corrective and preventive actions to protect the safety of subjects, users and other persons.

In case of DD that could have led to SADE, the sponsor determines whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

Every attempt should be made by the Site to save or collect the defective device, and if appropriate, the packaging, for return to the Sponsor. A qualified company representative will investigate and determine root cause and corrective actions as applicable, and directives will be provided to the site if warranted.

If the site documents a DD, the site will report the event in accordance with the following parameters. **It should be noted that no documents should be submitted to any regulatory agency without communicating with the Sponsor beforehand to assure accuracy and completeness of the information.**

For DDs, the principal investigator shall:

- report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect and documented in the AE CRFs as noted above,
- report to the IRB/EC device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or by the IRB,
- report to regulatory authorities device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and

- supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

shall be reported as specified as stated below.

Device deficiencies shall be managed by the sponsor in accordance with written procedures for the control of non-conforming product. The sponsor shall take appropriate corrective and preventive actions to protect the safety of subjects, users and other persons.

For DDs, the sponsor shall:

- report or ensure the reporting, to the IRB by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the IRB,
- report to regulatory authorities, within the required time period, all serious adverse events including serious health threat and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP,
- report all relevant safety information to the DMC, if established, according to written procedures

7.3.3 Regulatory Reporting and Timelines

- **Report by the Investigator to the Sponsor**

The sponsor shall implement and maintain a system to ensure that the reporting of the reportable events as defined under Section 7.2.1 Non-Reportable Event will be provided by the investigator to the sponsor immediately, but not later than 5 calendar days after investigation site study personnel's awareness of the event.

- **Report to the IRB**

Prior to initiation of the study, reporting requirements of AEs and DDs for the IRB will be verified and documented. Reporting will occur according to the requirements set forth by the involved IRB and/or national requirements.

8 Lost to follow up

A participant will be considered lost to follow-up if he or she fails to return for follow up visit per the standard of care of the site.

9 Data-Management

9.1 Methods for data collection and data entry

An EDC system which is a 21 CFR Part 11-compliant data capture system with eCRF designed and the study database built will be used for the purposes of this clinical investigation. The data entered into the eCRF in the EDC system will be fully source document verified (SDV), reviewed and cleaned. Queries will be issued to the site via the EDC system and are to be resolved by the investigator or his designee using the EDC system. An audit trail in the system is available for tracking all information including the site user enters, modifies or deletes the study data and query resolution.

Data review and data cleaning will be completed on a regular basis. The study data will be reviewed and cleaned to ensure that there are no outstanding data discrepancies prior to database lock. Any changes to the database after that time will require written agreement by Integra LifeSciences Corporation.

A data-management Plan is prepared to document precisely the procedures for the study database development, data review, data cleaning and query resolution.

9.2 Source Data Requirements

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator or its delegate will perform primary data collection drawn from original documents (printed, optical or electronic document containing source data). Data to be collected for purposes of the clinical investigation must not be entered directly into the eCRF before being recorded first in the source documents. All source documentation must be available for review by the study monitor during monitor visit. Source data is defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. All

source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and device deficiency will be entered into EDC system, a 21 CFR Part 11-compliant data capture system, provided by the Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

The investigator shall ensure the accuracy, completeness, legibility and timelines of the data reported in eCRF and in all required documentation. Data reported on the eCRF shall be supported by the source documents with any discrepancies being explained. Any corrections made to documents will be done according to ISO 14155 guidelines. If an item is not available or is not applicable, this fact should be indicated; no space is to be left blank. The investigator who has signed the clinical investigation plan signature page or his/her authorized designee is to personally sign the eCRFs to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be completed in a timely manner after the subject's visit. Failure to meet the documentation requirements may lead to the disqualification of an investigator.

9.3 Confidentiality and Data privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

9.4 Study Record Retention

The Principal Investigator and Integra LifeSciences will maintain accurate, complete, and current records relating to participation in this study. If the Principal Investigator wishes to assign the responsibility of maintaining the study files to someone else or move them to another location, he/she should consult with Integra LifeSciences in writing regarding the change. The Principal Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed.

Upon study completion, the investigator on one hand and Integra LifeSciences on the other hand will maintain all study records for the minimum time required by the US law and regulation and in accordance with 21 CFR 812, Subpart G.

10 Statistical Considerations

The detailed analyses methods will be described in the Statistical Analyses Plan (SAP).

10.1 Statistical Hypotheses

This is a retrospective, single-arm, single center post-market study to capture existing clinical performance data to confirm the continued performance of the Gentrix® Surgical Matrix. A formal hypothesis does not apply to this study. Subjects from that consecutive series will be included in the study based on the defined inclusion and exclusion criteria.

- **Primary Endpoint(s):**

The primary endpoint of this retrospective study is the incidence of post-operative complications requiring procedural intervention within 90 days post index procedure.

- **Secondary Endpoint(s):**
  1. Incidence of early post-operative complications (Surgical Site Occurrences) within 90 days post index procedure (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing).
  2. Incidence of Surgical Site Infections (SSIs) within 90 days post index procedure.
  3. Incidence of later post-operative complications occurring after 90 days post index procedure.
  4. Incidence of hernia recurrence confirmed by clinical assessment.
  5. Incidence of reoperation requirement due to index repair.
- **Tertiary Endpoint(s):**
  1. Average length of hospital stays (LOS) post index procedure (measured in days).
  2. Rate of opioid usage following procedure as determined by % of prescriptions filled and refilled.

10.2 Sample Size Determination

Subjects from that consecutive series will be included in the study based on the defined inclusion and exclusion criteria. The planned sample size for this study will be approximately 35 treated subjects.

10.3 Populations for Analyses

Full Analysis set (FAS): All subjects who enroll in the study, provide informed consent waiver, and receive study intervention.

Per-Protocol (PP) Set: All subjects in the full Analysis Set not identified as major protocol violations (defined to be protocol violations that may have a significant impact on subject outcomes, i.e., eligibility criteria not met). This population will be clearly defined prior to data analysis.

The primary analysis will be based on the full analysis set. The per-protocol set will be supportive and will be used to assess the robustness of study results. Safety analysis will be based on the full analysis set.

10.4 Statistical Analyses

10.4.1 General Approach

Descriptive statistics will be used to summarize study outcomes. For categorical data, frequency counts and percentages will be provided. For continuous data, descriptive statistics, including

sample size, mean, median, standard deviation, and range of values (i.e., minimum and maximum values) will be provided.

All data collected in this study will be provided in subject data listings. Data collected in this study will be reported using summary tables and graphs as appropriate to the data. Descriptive summary statistics (n, mean, median, standard deviation, minimum and maximum) will be calculated for the continuous variables and/or frequencies and percentages will be produced for the categorical variables.

10.4.2 Measures to Minimize Bias: Randomization and Blinding

This study does not include a randomization or blinding component. When screening subjects for the study, Investigators should offer participation to any/all patients who may meet the inclusion and exclusion.

10.4.3 Analysis of the Primary Endpoint(s)

The primary endpoint for this study is descriptive statistics of the incidence of post-operative complications requiring procedural intervention within 90 days post index procedure.

10.4.4 Analysis of the Secondary Endpoint(s)

Descriptive statistics will be provided for the following secondary endpoints:

1. Incidence of early post-operative complications (Surgical Site Occurrences (SSOs)) within 90 days post index procedure (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing).
2. Incidence of Surgical Site Infections (SSIs) within 90 days post index procedure.
3. Incidence of later post-operative complications occurring after 90 days post index procedure.
4. Incidence of hernia recurrence confirmed by clinical assessment.
5. Incidence of reoperation requirement due to index repair.

10.4.5 Analysis of the Tertiary Endpoint(s)

Descriptive statistics will be provided for the following tertiary endpoints:

1. Average length of hospital stays (LOS) post index procedure (measured in days).
2. Rate of opioid usage following procedure as determined by % of prescriptions filled and refilled

10.4.6 Safety Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and presented in by-subject listings. The number and percent of subjects experiencing any AE, any related AE, and discontinuations due to an AE will be tabulated. Treatment-emergent AEs will be tabulated (frequencies and percentages) by Preferred Term (PT) within System Organ Class (SOC). If a subject experiences more than one occurrence of the same AE, and these differ in severity and/or causality, the AE will be tabulated according to the greatest severity and nearest relationship to the device. A listing of subjects who withdraw from the study due to AEs will be presented, and the incidence of AEs leading to study discontinuation will be summarized. Deaths and SAEs will be listed should they occur.

10.4.7 Baseline Descriptive Statistics

Demographic and baseline data (e.g., medical history and concomitant medication) will be listed and tabulated for those subjects who enroll in the study.

10.4.8 Planned Interim Analyses

There is no planned Interim analysis.

10.4.9 Sub-Group Analyses

Subgroup analyses may be performed for surgical approach and type of the Gentrix Surgical Matrix Used.

10.4.10 Tabulation of Individual participant Data

All data collected in this study will be provided in subject data listings by study visit.

10.4.11 Sensitivity Analyses

All data will be analyzed as they were collected in the database. Missing data will not be imputed.

11 Regulatory, Ethical, Compliance and Operational Considerations

11.1 Informed Consent and Informed Consent Process

For this study, a waiver from the IRB was obtained for the informed consent and the informed consent process.

11.2 Protocol Amendment

Investigator may not modify (amend) this clinical investigation plan without obtaining written concurrence of the Sponsor, involved Ethics Committee(s), and applicable regulatory authorities.

11.3 Protocol Deviations

A Deviation is an Instance of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator is not allowed to deviate from the CIP without first receiving approval in writing from the Sponsor.

Such deviations are documented on eCRFs and reported to the Sponsor as soon as possible.

11.4 Publication Policy

Integra LifeSciences Corporation may at any time publish the results of and information pertaining to the participating subject only to compliance with regulatory requirements pertaining to patient protected health information.

After closure of the clinical investigation, the results will be summarized in a Clinical Investigation Report, which will be submitted to the investigator, and appropriate regulatory authorities. This Clinical Investigation Report will include a summary of the results based on a statistical evaluation and clinical assessment.

The conditions under which an investigator may publish results from this study in any form are defined in detail in the clinical trial agreement.

The clinical investigation will be registered in a publicly accessible database (www.clinicaltrials.gov) prior to start of recruitment, contents will be updated throughout study conduct and results will be entered at study completion.

12 References

[1]Bosanquet DC, Ansell J, Abdelrahman T, et al. Systematic review and meta-regression of factors affecting midline incisional hernia rates: analysis of 14,618 patients. Plos One. 2015;10:e0138745.

[1] Poulose BK, Shelton J, Phillips S, Moore D, Nealon W, Penson D, et al. Epidemiology and cost of ventral hernia repair: making the case for hernia research. Hernia 2012;16:179-83.

[2]Luijendijk RW, HopWC, VanDen TolMP et al. A comparison of suture repair with mesh repair for incisional hernia. N. Engl. J. Med. 343(6), 392–398 (2000).

[3]Burger JW, Luijendijk RW, Hop WC, Halm JA, Verdaasdonk EG, Jeekel J. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann. Surg. 240(4), 578–583 (2004).

[4]Novitsky YW, Fayezizadeh M, Majumder A, Neupane R, Elliott HL, Orenstein SB (2016) Outcomes of Posterior Component Separation with Transversus Abdominis Muscle Release and Synthetic Mesh Sublay Reinforcement. Ann Surg 264(2):226–232. https://doi.org/10.1097/SLA.0000000000001673

[5]Schneeberger S., Phillips S., Huang L.C., Pierce R.A., Etemad S.A., Poulose B.K. Cost-Utility Analysis of Biologic and Biosynthetic Mesh in Ventral Hernia Repair: When Are They Worth It? J. Am. Coll. Surg. 2019;228:66–71. doi: 10.1016/j.jamcollsurg.2018.10.009.

[6]Skipworth JR, Vyas S, Uppal L, Floyd D, Shankar A. Improved outcomes in the management of high-risk incisional hernias utilizing biological mesh and soft-tissue reconstruction: a single center experience. World J Surg. 2014;38(5):1026–1034.

[7]Smart NJ, Marshall M, Daniels IR (2012) Biological meshes: a review of their use in abdominal wall hernia repairs. Surgeon 10(3):159–171

[8]Basta et al. Assessing complications and cost-utilization in ventral hernia repair utilizing biologic mesh in a bridged underlay technique. Am J Surg. 2015:209(4):695-702.

[9] Augenstein V, Colavita P, Wormer B, Walters A, Bradley J, Lincourt A, et al. CeDAR: Carolinas equation for determining associated risks. J Am Coll Surg 2015;221:S65-6.

[10]Huntington, C. R., Cox, T. C., Blair, L. J., Schell, S., Randolph, D., Prasad, T., Lincourt, A., Heniford, B. T., & Augenstein, V. A. (2016). Biologic mesh in ventral hernia repair: Outcomes, recurrence, and charge analysis. Surgery, 160(6), 1517–1527. https://doi.org/10.1016/j.surg.2016.07.008

[11] Song C, Liu E, Tackett S, Shi L, Marcus D. Procedural volume, cost, and reimbursement of outpatient incisional hernia repair: implications for payers and providers. J Med Econ. 2017 Jun;20(6):623-632. doi: 10.1080/13696998.2017.1294596. Epub 2017 Feb 28. PMID: 28277031.

13 APPENDIX I

Table 3: List of 45Devices and SKU #

Device Name	Type:	SKU #	Size(s)
Gentrix™ Surgical Matrix (6-Layer)	PSMX	PSMX0505	5cm x 5cm
		PSMX0710	7cm x 10cm
		PSMX1015	10cm x 15cm
Gentrix™ Surgical Matrix Plus (8-Layer)	MSPL	MSPL0507	5cm x 7cm
		MSPL0710	7cm x 10cm
		MSPL1010	10cm x 10cm
		MSPL1015	10cm x 15cm
Gentrix™ Surgical Matrix Thick	PSMT	PSMT1020	10cm x 20cm
		PSMT1620	16cm x 20cm
		PSMT2020	20cm x 20cm
		PSMT2025	20cm x 25cm
		PSMT2030	20cm x 30cm
		PSMT3030	30cm x 30cm
		PSMT3040	30cm x 40cm