Statistical Analysis Plan

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

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1. LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ADE	Adverse Device Effect
CFR	Code of Federal Regulations
CSF	Cerebrospinal fluid
eCRF	Electronic Case Report Form
EMR	Electronic Medical Records
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Integra	Integra LifeSciences Corporation
IRB	Institutional Review Board
LOS	Length of Hospital Stay
MedDRA	Medical Dictionary for Regulatory Activities
PMCF	Post Market Clinical Follow-up.
SADE	Serious Adverse Device Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOA	Achedule of Activities
SOP	Standard Operating Procedures
SSI	Surgical Site Infection
SSO	Surgical Site Occurrence
USADE	Unanticipated Serious Adverse Device Event

2. INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of the clinical study. The methods and procedures are intended to support the generation of study report, including detailed descriptions of the populations and methodologies, as well as summary tables, listings and graphics.
This statistical analysis plan (SAP) is based on Version 1.0 of the Protocol #T-GENVIH-002.

3. STUDY OBJECTIVES

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

3.1 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.

3.2 Secondary Endpoint

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.

3.3 Teritary 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

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

5. STUDY PROCEDURE

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 will be collected via medical records, study worksheets, and entered into electronic data capture system by the site.

Enrollment period will be approximately 1 month. Total duration of the study will be approximately three months.

Table 1: Schedule 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

6. PROTOCOL DEVIATION

Protocol violations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to closure of the database to ensure all important violations are captured and categorized.

A major protocol deviation is any significant protocol deviation that threatens the scientific validity of the data collection for a subject or is a serious violation of ethical study compliance and GCP. Examples of major protocol deviations include but are not limited to the following:

- Violation of inclusion/exclusion criteria at enrollment

7. ANALYSIS POPULATION

Enrolled: The enrolled population includes all eligible subjects based on the defined inclusion and exclusion criteria.

Intent-to-Treat (ITT) Population: All subjects who are enrolled into the study, provide informed consent waiver, and receive study intervention.

Per-Protocol (PP) Population: All subjects in the full Analysis Set not identified as major protocol violations.

The endpoints analysis will be based on the Intent-To-Treat population. The per-protocol set will be supportive and will be used to assess the robustness of study results if neccesary. Safety analysis will be based on the Intent-To-Treat population.

8. SAMPLE SIZE DETERMINATION

Subjects from that consecutive series will be included in the study based on the defined inclusion and exclusion criteria, and sample size is not based on hypothesis testing. The planned sample size for this study will be approximately 35 treated subjects.

9. STATISTICAL ANALYSES

9.1 General Statistical Considerations

Descriptive statistics will be used to summarize study outcomes. No formal statistical testing will be performed. The study objectives will be presented by summary statistics.

For categorical data, frequencies 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.

A separate Table Listing Graphs (TLFs) will be provided.

All statistical analysis will be conducted using SAS® for Windows, version 9.4 or later.

9.2 Study Subjects

9.2.1 Disposition of Patients

The disposition of all subjects in the study will be provided for all available data. The numbers of subjects signed informed consent waiver, screen failed, enrolled, completed, and discontinued during the study will be summarized. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

9.2.2 Demographics

Baseline demographics Gender, Age, Race, Nicotine use will be summarized descriptively. By subject listings will be provided for each subject reported.

9.2.3 Medical History

The subject's relevant medical history (up to 3 years prior to surgery) will be summarized and presented by count and percentage of subjects as captured on the CRFs. Types of Body Systems and Category will be summarized by frequency. By subject listings will be provided for each subject reported.

9.2.4 Concomitant Medication

The subject's relevant medication history (i.e. medication taken up to prior to surgery) and relevant concomitant medication (i.e. current medication) will be summarized and presented by count and percentage of subjects as captured on the CRFs. Only immunomodulators and opioids are to be reported. By subject listings will be provided for each subject reported.

9.2.5 Surgery Evaluation

Operative details will be summarized and presented by count and percentage of subjects as captured on the Surgery CRF. These information include but not limited to:

- 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.

By subject listings will be provided for each subject reported.

9.2.6 Discharge and Follow-Up Visits

Discharge and Follow-Up Visits details will be summarized and presented by count and percentage of subjects as captured on the CRF. These information include but not limited to:

- 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

By subject listings will be provided for each subject reported.

9.2.7 Study Exit

Study exit type will be summarized and presented by count and percentage of subjects as captured on the Study Exit CRFs. By subject listings will be provided for each subject reported.

9.2.8 Time to Hernia Reoccurance Survival Analyses

Time to reoccurance Kaplan-Meier Curve will be provided for all subjects with hernia reoccurance at follow-up visits.

9.2.9 Safety and Complications

All complications during the index surgery, discharge and followup visits including Device Deficiency and Adverse Event will be summarized. By subject listings will be provided for each subject reported.

9.3 Endpoint Analysis

Primary, Secondary, Teritory and Safety Endpoints will be analysed based on the surgery evaluation, Discharge and Follow-Up report.

9.3.1 Analysis of the Primary Endpoints

The incidence of post-operative complications requiring procedural intervention within 90 days post index procedure.willbe summarized. The proportion of subjects with the incidents will be presented.

9.3.2 Analysis of the Secondary Endpoints

The following incidents by subjects will be summarized: 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). Incidence of Surgical Site Infections (SSIs) within 90 days post index procedure. Incidence of later post-operative complications occurring after 90 days post index procedure. Incidence of hernia recurrence confirmed by clinical assessment. Incidence of reoperation requirement due to index repair.

9.3.3 Analysis of the Teritory Endpoints

Average length of hospital stay (LOS) post index procedure (measured in days) and rate of opioid usage following procedure as determined by % of prescriptions filled and refilled will be summarized and presented.

9.3.4 Analysis of Device Deficiency

Device deficiencies will be presented by the nature of the device deficiency (e.g. mechanical failure, shunt pathway obstruction, etc.). Each device deficiency will be summarized on a patient basis by tabulating the counts and percentages of subjects with the deficiency. For the patient-based results, a deficiency which occurred multiple times for the same patient will only be counted once. Device deficiency will also be presented on a deficiency basis, where the number of occurrences of each deficiency will be presented. The analysis of device deficiencies will be performed in the enrolled population. By subject listings will be provided for each subject reported.

9.3.5 Analysis of Adverse Events

The incidence rate of each of the adverse device effects through Index Surgery, Discharge and follow-up visit will be presented. The incidence of adverse events and serious adverse events will be tabulated (frequencies and percentage of patients) by severity and relationship to device and procedure. The analysis of safety will be performed in the enrolled population.

Descriptive statistics will be provided for safety endpoints by surgical procedure. All safety summaries will be presented for the full analysis population. Adverse Device Events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. All ADEs will be listed. A summary of the frequency count and percentage of subjects reporting each ADE category will be produced for all reported ADEs and SADEs. Relationship of AE verbatim text to group terms and body systems will also be reported. A listing of withdrawals due to ADEs will be provided. Deaths and SADEs will be listed should they occur.

AE listing includes Onset Date, AE Term, Relation to Device, Relation to Procedure, Pattern, Seriousness (SAE), Severity, Treatment, Medication, Surgical, Outcome, End Date. By subject listings will be provided for each subject reported.

10. SUBGROUP ANALYSIS

Subgroup analyses may be performed, in which the analysis of endpoints will be presented within subgroups based surgical approach and type of the Gentrix Surgical Matrix Used.

11. MISSING DATA

Reasonable efforts will be made to obtain complete data for all subjects. Nevertheless, given the nature of this study (i.e. Retrospective), it is anticipated that missed visits/evaluations will occur and hence there will be missing data on some of the endpoints. Missing data will not be imputed.

12. INTERIM ANALYSES

There will be no planned interim analyses for this clinical investigation.

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