Statistical Analysis Plan

A Prospective Analysis of the Use of Gentrix® Surgical Matrix for Soft Tissue Reinforcement in Ventral Hernia Repair as Long Term Follow Up to T-GENVIH-002 Study

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Short Title: Gentrix Ventral Hernia Repair Long Term Follow Up Study

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Title: **A Prospective Analysis of the Use of Gentrix® Surgical Matrix for Soft Tissue Reinforcement in Ventral Hernia Repair as Long Term Follow Up to T-GENVIH-002 Study**

Protocol No: **T-GENVIH-003**

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INTEGRA LIFESCIENCES CORPORATION SIGNATURE PAGE

The undersigned have approved this Statistical Analysis Plan for use in this 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 Harmonization
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 Even
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOA	Schedule of Activities
SOP	Standard Operating Procedures
SSI	Surgical Site Infection
SSO	Surgical Site Occurrence
SSOPI	Surgical Site Occurrences Requiring Procedural Intervention
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-003.

3. STUDY OBJECTIVES

The primary objective of this study is to collect additional safety data and demonstrate the performance of Integra Gentrix® Surgical Matrix for reinforcement of ventral hernia repairs from a sub-population of participants in the T-GENVIH-002 study, specifically those with laparoscopic or robotic repair. Prospective data will be collected and assessed for later post-operative surgical site events and complications in the post-operative period from the last timepoint of data collection in T-GENVIH-002 to present. The safety objective of this study is to capture existing Gentrix® Surgical Matrix Complication data in the longer term period post primary repair procedure, not previously reported in T-GENVIH-002 study. 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 and particularly in the sub-population of minimally invasive surgery (MIS) cases (i.e., laparoscopic and robotic) from the GENVIH-002 study.

3.1 Primary Endpoint

The primary endpoint of this study is the incidence of clinically confirmed recurrence of the primary hernia to date, including not previously reported in T-GENVIH-002 study

3.2 Secondary Endpoint

1. Incidence of self-reported recurrence (i.e., bulge) of the primary hernia to date, including not previously reported in T-GENVIH-002 study.
2. Incidence of Surgical Site Occurrences requiring procedural intervention (SSOPI) of the primary hernia repair to date, not previously reported in T-GENVIH-002 study.
3. Incidence of Surgical Site Occurrences (SSOs) of the primary hernia repair to date (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing), including not previously reported in T-GENVIH-002 study.
4. Incidence of Surgical Site Infections (SSIs) post primary hernia repair to date, including not previously reported in GENVIH-002 study.
5. Incidence of reoperation requirement of the primary hernia repair to date, including not previously reported in GENVIH-002 study.

3.3 Safety Endpoint

The safety endpoint of this study is the incidence of complication data in the later post-operative period to date, not previously reported in the T-GENVIH-002 study.

4. STUDY DESIGN

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

5. STUDY PROCEDURE

This retrospective study specifically aims to collect data from the day of the primary hernia surgical repair procedure longer term post-operatively to date, including not previously reported in T-GENVIH-002 study. Data will be collected via a phone visit and questionnaire administered by the study coordinator (or, in the alternative, an in-office visit and questionnaire administered by the study coordinator) and entered into an electronic data capture system by the site. The following data will be collected on the Long Term Follow Up (LTFU) of the primary hernia repair.

The patients will 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. The total expected duration of the study is approximately 3 months.

Table 1: Schedule of Data Collection Activities

***Prospective Data Collection**	**Screening**	**Subject Visit 1**
Eligibility/Consent	X	
Complete Case Report Form(s)	X	X
¥Adverse Events	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 necessary. 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, the subgroup of T-GENVIH-002 subjects underwent Laparoscopic or Robotic surgery. The sample size is not based on hypothesis testing. The planned sample size for this study will be approximately 21 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 will be summarized and provided from T-GENVIH-002 study. By subject listings will be provided for each subject reported if necessary.

9.2.3 Medical History

The subject's relevant medical history will be summarized and provided from T-GENVIH-002 study. By subject listings will be provided for each subject reported if necessary.

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 from T-GENVIH-002 and current study. Only immunomodulators and opioids are to be reported. By subject listings will be provided for each subject reported if necessary.

9.2.5 Surgery Evaluation

Not applicable.

9.2.6 Follow-Up Visit 1 Questionnaire

The 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:

1. Incidence of Surgical Site Occurrences requiring procedural intervention (SSOPI) of the primary hernia repair to date, not previously reported in T-GENVIH-002 study.

2. Incidence of Surgical Site Occurrences (SSOs) of the primary hernia repair to date (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing), including not previously reported in T-GENVIH-002 study.
3. Incidence of Surgical Site Infections (SSIs) post primary hernia repair to date, including not previously reported in GENVIH-002 study.
4. Incidence of clinically confirmed recurrence of the primary hernia occurred to date, including not previously reported in T-GENVIH-002 study.
5. Incidence of self-reported recurrence (i.e., bulge) of the primary hernia to date, including not previously reported in T-GENVIH-002 study.
6. Incidence of reoperation requirement of the primary hernia repair to date, including not previously reported in GENVIH-002 study.

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 Recurrence Survival Analyses

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

9.2.9 Safety and Complications

All complications during the index surgery, discharge and follow-up 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 and Safety Endpoints will be analyzed based on the Visit 1 Questionnaire report.

9.3.1 Analysis of the Primary Endpoints

The incidence of clinically confirmed recurrence of the primary hernia occurred to date, including not previously reported in T-GENVIH-002 study will be 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 Surgical Site Occurrences requiring procedural intervention (SSOPI), incidents of Surgical Site Occurrences (SSOs) (seroma, abscess, dehiscence, hematoma, wound necrosis, ileus, fistula, delayed wound healing), incidence of Surgical Site Infections (SSIs), incidence of self-reported recurrence (i.e., bulge), reoperation requirement of the primary hernia repair to date, including not previously reported in GENVIH-002 study. The proportion of subjects with the incidents will be presented.

9.3.3 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.

9.3.4 Analysis of Adverse Events

The incidence rate of each of the adverse device effects from the 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.