STATISTICAL ANALYSIS PLAN

for

Protocol CLP-01(Version F1.0)

An Independent Review of Safety Data from a Closed Clinical Study Using Irrisept (Protocol # IRR-CT-901-2013-01)

Final v1.0

Date: August 26, 2021

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LIST OF ABBREVIATIONS

AE	*adverse events*
ADE	*adverse device effects*
ADL	*activities of daily living*
CHG	*Chlorhexidine Gluconate*
CRF	*case report forms*
CSR	*clinical study report*
FDA	*U.S. Food and Drug Administration*
ITT	*intent-to-treat*
ICH	*International Committee for Harmonization*
ISO	*International Organization for Standardization*
MedDRA	*Medical Dictionary for Drug Regulatory Affairs*
PBRS	*Peachtree BioResearch Solution*
SAE	*serious adverse events*
SADE	*serious adverse device effects*
SAP	*statistical analysis plan*
SAS	*Statistical Analysis System*
SOC	*system organ class*
SoC	*standard of care*
US	*United States*
USADE	*unanticipated serious adverse device effects*

1. INTRODUCTION

1.1 Objectives

The objective of this retrospective review is to ensure that all safety data from the closed Irrisept study (IRR-CT-901-2013-01) have been accurately and completely identified, verified and independently adjudicated. The Sponsor (Irrimax® Corporation) will use the safety data from this review to complete a final study report and ensure the product risk assessment documentation is updated and completed.

1.2 Study Design

The closed study protocol allowed for enrollment of up to 1,100 subjects from 17 clinical sites. There were 625 subjects consented, where 600 subjects were randomized and received irrigation with either Irrisept system or the Standard of Care (SoC), and 450 subjects completed the study. The study duration and follow-up schedule in the closed study involved two visits: Visit 1 included screening, peri-operative and post-surgical; and Visit 2 was 30 days post-procedure.

This retrospective review will include all 625 previously consented subjects from the closed study. The review will assess for documentation of informed consent for these subjects. The subjects' source medical records will be reviewed for potential adverse events. There is no new subject enrollment or follow-up as part of this retrospective review.

2. ELABORATION OF STUDY PROTOCOL

2.1 Study Populations

The safety data will be analyzed on intent-to-treat (ITT) population, which includes all subjects who consented and were randomized in the closed study. Subjects will be categorized for analysis based on the actual irrigation product used during surgery (either Irrisept or SoC).

2.2 Study Endpoints

The previously defined safety endpoints from the closed study were clinical review and analysis of adverse events.

This retrospective review intends to complete the safety endpoint analysis of adverse events associated with use of Irrisept or SoC for irrigation. Note that this review does not include any evaluation of the efficacy or exploratory endpoints, as defined in the closed study Protocol IRR-CT-901-2013-01.

2.2.1 *Safety Data Definition*

All adverse events and device deficiencies as defined below will be recorded and verified based on the source documents from the closed study. For this retrospective review, the adverse event definitions are consistent with the closed study protocol. However, based on the International Organization for Standardization (ISO) 14155:2011 standard, a few clarifications within these definitions, have been implemented.

Adverse Event (AE):

An AE is any untoward medical occurrence in a subject or clinical investigation which does not necessarily have a causal relationship with the medical device under investigation, including

- Events that are related or not related to the study device (Irrisept), comparator (SoC), or a study procedure; or
- Events in users or other persons that are related to the study medical device (Irrisept).

Adverse events are categorized as serious or non-serious. A non-serious adverse event is any event that does not meet the definition of serious adverse event.

Serious Adverse Event (SAE):

An SAE is an adverse event that results in one of the following outcomes:

- Requires in-patient hospitalization or prolongation of existing hospitalization;
  - This criterion applies if the event requires in-patient hospitalization with an overnight stay in hospital or, if in the opinion of the Investigator, prolongs an existing hospitalization.
  - Hospitalizations for less than 24 hours with no admission are not considered "hospitalization".
  - A planned hospitalization for a pre-existing condition (including for an elective procedure or routinely scheduled treatment) or a procedure required as part of the clinical study which has not worsened does not constitute an SAE.
- Permanent impairment in body structure or function;
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment of a body structure or function;
- Is life-threatening;
- Results in congenital anomaly/birth defect; or
- Results in death

Adverse Device Effect (ADE)

An ADE is an adverse event that results from the presence or performance of the device or any component of the system, including any event resulting from:

- Deployment, implantation or operation of the device
- Malfunction of the device
- Insufficient or inadequate instructions for use
- Use error or intentional misuse of the device

Serious Adverse Device Effect (SADE)

An SADE is an adverse event related to the presence or performance of the device or any component of the system that results in one of the following outcomes:

- Requires hospitalization;
- Prolongs hospitalization;

- Life-threatening;
- Results in congenital anomaly/birth defect;
- Results in death.
- The SAE defined above is also apply to SADE.

Unanticipated Serious Adverse Device Effect (USADE)

A USADE is any serious adverse effect on:

- Health or Safety;
- 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;
- Any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subject.

An unanticipated serious adverse device effect is an effect by which its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Device Deficiency

A Device Deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety and performance. Device deficiencies include malfunctions, use errors and inadequate labelling. A device deficiency does not need to relate to an adverse event.

2.2.2 *Anticipated Adverse Device Effects Associated with Use of Irrisept*

Table 1 lists the potential risks associated with use of Irrisept based on the product risk analysis and the potential adverse device effects that are anticipated with these risks. Potentially serious adverse device effects (anticipated SADE) have been assessed as a lower probability of occurrence.

TABLE 1: POTENTIAL RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS FOR IRRISEPT

Potential Risk	Risk Assessment and Risk Mitigations	Potential Anticipated Effects
Allergic or anaphylactic response to CHG	**Potential for allergic reaction** • Potential allergy to CHG is known to occur with other products containing CHG. However, serious allergic reaction is rare based on data published by the U.S. FDA on topical skin products containing CHG.1 • Product is labeled as do not use in patients with CHG allergy. • A known CHG allergy was an exclusion criterion in the closed study protocol.	**ADE**: Minor non-serious allergic reaction (e.g., rash, dermatitis, itching, rhinitis) **SADE**: Serious or life-threatening allergic reaction requiring medical intervention (e.g., shortness of breath, tachycardia, tightness in throat, dizziness, anaphylactic reaction)
Exposure to bio-incompatible material or chemical with potential for adverse tissue reaction	**Potential for toxicity reaction** • Patient contact materials have passed biocompatibility testing per ISO standard 10993-1. • Manufacturing process validations and quality control procedures have been completed to ensure product integrity and quality.	**ADE**: Minor tissue irritation, as manifested by symptoms such as pain, erythema, edema, itching, burning **SADE**: Severe adverse tissue reaction that requires or prolongs hospitalization, or requires medical or surgical intervention to prevent permanent impairment

Exposure to non-sterile or contaminated product	**Potential for infection** • Product is aseptically-filled and bottle and applicator surfaces are terminally sterilized. • Sterilization, packaging and manufacturing process validations have been completed to ensure product integrity and sterility. • Product contains CHG, which acts as a preservative to inhibit microbial growth in the solution, and the product has been tested to show preservative effectiveness. • Bottle and applicator are sequentially double wrapped with CSR wrap serving as a microbial barrier. • Product has been tested to show stability and sterility are maintained over the labelled shelf life. • Surgical patients routinely receive antibiotics as part of the pre-op and post-op surgical care regimen since surgical site infection is a known complication of any surgery type.	**ADE**: Minor surgical site infection, wound infection or abscess, as manifested by symptoms such as erythema, edema, pus, fever, chills, pain **SADE**: Severe infection that requires or prolongs hospitalization, or requires medical or surgical intervention to prevent permanent impairment
Use of product for irrigation affects wound healing	**Potential for delay in wound healing** • Patient contact materials have passed biocompatibility testing per ISO standard 10993-1. • Manufacturing process controls ensure product is not contaminated with any particulates from manufacturing.	**ADE**: Minor wound dehiscence, non-healing wound, granuloma or adhesion **SADE**: Severe wound dehiscence or non-healing wound that requires or prolongs hospitalization, or requires medical or surgical intervention to prevent permanent impairment
Ineffective use of product with inability to remove wound debris	**Potential for ineffective irrigation or incomplete irrigation** • Surgeon routinely visually assesses surgical wound bed for effective debridement and clearance of particulates and wound debris. • Saline is routinely available for surgical irrigation in the event that the Irrisept bottle cannot be used.	**ADE**: Minor non-healing wound, granuloma, adhesion, adverse tissue reaction or infection **SADE**: Severe non-healing wound, granuloma, adhesion, adverse tissue reaction or infection that requires or prolongs hospitalization, or requires medical or surgical intervention to prevent permanent impairment
Incompatibility with other therapies used during the procedure	**Potential for incompatibility with other therapies (e.g., concomitant medications, other therapies used during surgery)** • No known incompatible medications or therapies with Irrisept. • Irrisept is used an irrigation solution with short term exposure to the wound and surrounding tissues and is not ingested or injected.	**ADE**: Minor adverse tissue reaction **SADE**: Severe adverse tissue reaction that requires or prolongs hospitalization, or requires medical or surgical intervention to prevent permanent impairment

3. STATISTICAL METHODS

3.1 General

All data will be analyzed using the Statistical Analysis System (SAS®; Version 9.2 or higher).

Safety data will be summarized by study device group in summary tables. Continuous variables will be presented by descriptive statistics: n, mean, standard deviation (SD), median, minimum, and maximum, and categorical variables will be tabulated by frequency count and percentage.

3.2 Subject Disposition and Demographics

- Subject disposition will be summarized on ITT population by device group.
- Demographics will be summarized on ITT population by device group using descriptive statistics. Individual demographic data listing will also be provided.

3.3 Medical History and Concomitant Medications

- Individual data listings of general medical history and allergy history will be provided for the subjects of ITT population.
- Individual data listing of concomitant medication data will be provided for the subjects of ITT population. Subjects taken concomitant medication to treat AE/ADE will also be listed.

3.4 Adverse Events Analysis

AE rates will be summarized on ITT population by type of AE, occurrence rate, severity and device-relatedness, as defined below. The summary tables will document the event descriptions, the total number of events, and the number and the percentage of subjects affected in each device group to inform the Sponsor's product risk assessment.

All AEs will be coded using MedDRA. AE summaries will be presented by device group using the MedDRA level hierarchy (system organ class, high-level group term, high-level term, and preferred term) as follows:

- Overall (i.e., regardless of severity or relationship to treatment)
- By severity grade
- By relationship to study product according to the mapping scheme below:
  - Potentially related: will include all AEs with a relationship rating of "definitely", "probably" or "possibly".
  - Unlikely/not related: will include all AEs with a relationship rating of "unlikely" or "unrelated".

3.5 Device Deficiency Analysis

- Device deficiencies will be summarized on ITT population by type of deficiency and any relevant information about the deficiency. Individual device deficiency data will be provided.

3.6 Handling of Missing Data

For Safety data, missing data will not be imputed in general for Safety analysis. However, the below are some exception for conservative consideration.

- If the severity of an AE (ADE) is missing, then the AE (ADE) will be considered as "Severe".

- If the relationship to the study device of an AE is missing, then the AE will be considered as "Potentially Related" to study agent.

3.7 Protocol Deviations

Not applicable.

3.8 Key Data Items

Study Analysis Population Definition:

- Intended-To-Treat (ITT) population: All subjects who consented into the study and were randomized to use either irrigation product (Irrisept or SoC).

Important Derived Variables:

- Age = (Screening Date – Date of Birth +1)/365.25.
- Concomitant Medication and Treatments: The medications and treatments started after enrolled to the study (date of Informed Consent).
- Treatment emergent AE or ADE (TEAE/TEADE): Any AE (ADE) started on or after the day of using study device.

Formulas of Metric Conversion:

- 1 inch = 2.54 cm
- 1 lb = 0.4536 kg
- ℃ = (℉ – 32)x5/9

AE Severity

GRADE	DESCRIPTION
0	No AE (or within normal limits)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

AE Relationship to Study Device

By relationship to study product according to the mapping scheme below:

- Potentially related: including the ratings of "definitely", "probably" or "possibly"
- Unlikely related: including the ratings of "unlikely" or "unrelated"

3.9 Change to Planned Protocol Analysis

Not applicable.

4. OUTPUT PLANNED FOR THE STUDY REPORT

4.1 Tables to be Included in Study Report

4.1.1 *Summary of subject information*

1. Table [TDS01] Subject Disposition – ITT population
2. Table [TSC01] Summary of Surgical Procedure by Device Group – ITT Population
3. Table [TDM01] Summary of Demographics – ITT Population
4. Table [TDA01] Summary of Study Device Deficiencies – ITT Population

4.1.2 *Summary of AE*

5. Table [TAE01] Number (%) of Subjects with Adverse Events by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
6. Table [TAE02] Number (%) of Subjects with Serious Adverse Events by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
7. Table [TAE03a] Number (%) of Subjects with Adverse Events **Grade 2 or Less** by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
8. Table [TAE03b] Number (%) of Subjects with Adverse Events **Grade 3 or Higher** by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
9. Table [TAE04] Number (%) of Subjects with Adverse Events Potentially Related to Study Device by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
10. Table [TAE05] Number (%) of Subjects with Adverse Events by Preferred Term and Overall Frequency – ITT Population
11. Table [TAE06] Number (%) of Subjects with Serious Adverse Events by SAE Criteria – ITT Population
12. Table [TAE07] Number (%) of Subjects with Adverse Events by Onset Time and Outcome – ITT Population
13. Table [TAE08] Number (%) of Subjects with Adverse Events by Severity and Relationship to Study Device – ITT Population
14. Table [TAE09] Number (%) of Subjects with Adverse Events by Action Taken and Irrisept Device Use Information – ITT Population

4.1.3 *Summary of ADE*

15. Table [TADE01] Number (%) of Subjects with Adverse Device Effects by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
16. Table [TADE02] Number (%) of Subjects with Serious Adverse Device Effects by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
17. Table [TADE03] Number (%) of Subjects with Unanticipated Serious Adverse Device Effects by MedDRA System Organ Class, High Level Group Term, High Level Term and Preferred Term – ITT Population
18. Table [TADE04] Number (%) of Subjects with Adverse Device Effects by Preferred Term and Overall Frequency – ITT Population

19. Table [TADE05] Number (%) of Subjects with Serious Adverse Device Effects by SADE Criteria – ITT Population

4.2 Listings to be Included in the Clinical Study Report

4.2.1 *Listings of subject information*

1. Listing [LDS01] Discontinued Subjects – ITT Population
2. Listing [LSC01] Surgical Procedure Information – ITT Population
3. Listing [LDM01] Demographic Characteristics – ITT Population
4. Listing [LMH01] General Medical History – ITT Population
5. Listing [LMH02] Allergy History – ITT Population
6. Listing [LCM01] Concomitant Medications and Therapies – ITT Population
7. Listing [LPD01] Study Product (Irrisept Device) Deficiency – ITT Population
8. Listing [LPD02] Study Product (SoC Device) Deficiency – ITT Population

4.2.2 *Listings of AE*

9. Listing [LAE01a] Adverse Events (Irrisept Device Group) – ITT Population
10. Listing [LAE02a] Serious Adverse Events (Irrisept Device Group) – ITT Population
11. Listing [LAE03a] Adverse Events Grade 2 or Less (Irrisept Device Group) – ITT Population
12. Listing [LAE04a] Adverse Events Grade 3 or Higher (Irrisept Device Group) – ITT Population
13. Listing [LAE05a] Adverse Events Potentially Related to Study Device (Irrisept Device Group) – ITT Population
14. Listing [LAE06a] Adverse Events Result Death (Irrisept Device Group) – ITT Population
15. Listing [LAE01b] Adverse Events (SoC Device Group) – ITT Population
16. Listing [LAE02b] Serious Adverse Events (SoC Device Group) – ITT Population
17. Listing [LAE03b] Adverse Events Grade 2 or Less (SoC Device Group) – ITT Population
18. Listing [LAE04b] Adverse Events Grade 3 or Higher (SoC Device Group) – ITT Population
19. Listing [LAE05b] Adverse Events Potentially Related to Study Device (SoC Device Group) – ITT Population
20. Listing [LAE06b] Adverse Events Result Death (SoC Device Group) – ITT Population

4.2.3 *Listings of AED*

21. Listing [LADE01a] Adverse Device Events (Irrisept Device Group) – ITT Population
22. Listing [LADE02a] Serious Adverse Device Events (Irrisept Device Group) – ITT Population
23. Listing [LADE03a] Unanticipated Serious Adverse Device Events (Irrisept Device Group) – ITT Population
24. Listing [LADE01b] Adverse Device Events (SoC Device Group) – ITT Population
25. Listing [LADE02b] Serious Adverse Device Events (SoC Device Group) – ITT Population
26. Listing [LADE03b] Unanticipated Serious Adverse Device Events (SoC Device Group) – ITT Population

5. REFERENCES

Protocol: An Independent Review of Safety Data from a Closed Clinical Study Using Irrisept (Protocol # IRR-CT-901-2013-01), Final v1.0, December 9, 2019, Irrimax® Corporation.

6. ATTACHMENT: THE SHELLS OF TABLES, FIGURES AND LISTINGS PLANNED FOR CLINICAL STUDY REPORT

Approval for Statistical Analysis Plan

Title:	**An Independent Review of Safety Data from a Closed Clinical Study Using Irrisept (Protocol # IRR-CT-901-2013-01)**
Reference:	**CLP-01/SAP**
Version:	**1.0**
Date effective:	
Author:	**Dion Chen, Ph.D., Peachtree BRS**

Author's signature: Dion Chen Date: 09/07/2021

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Reviewer/Approver	**Chevy J. Brown, MPH, CCRC**
Position:	**Manager, Clinical Trials, Irrimax Corporation**

Signature for sponsor: Chevy Brown Date: 09/07/2021

Name of Reviewer/Approver	**Todd Stein**
Position:	**Senior Vice President**

Signature for sponsor: DocuSigned by: Todd Stein 6AB23CCAE17D4D9 Date: 09/21/2021