IRRIMAX CORPORATION

AN INDEPENDENT REVIEW OF SAFETY DATA FROM A CLOSED CLINICAL STUDY USING IRRISEPT (PROTOCOL # IRR-CT-901-2013-01)

Protocol Short Title:	Retrospective Independent Safety Review of Closed Irrisept Study
Protocol Identifying Number:	CLP-01
Sponsor:	Irrimax® Corporation 1665 Lakes Parkway, Suite 102 Lawrenceville, GA 30043
Protocol Version and Date:	Version 1.0; 9 December 2019
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PROTOCOL APPROVAL

Protocol Number: CLP-01

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

Protocol Version: Version 1.0

Protocol Date: 9 December 2019

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REVISION HISTORY

Version	Date	Summary Description of Changes
1.0	9 December 2019	Original

STATEMENT OF INVESTIGATOR COMPLIANCE

This protocol is a retrospective review of existing safety data previously collected in a closed clinical study.

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices (GCP) and all applicable laws and regulations.
- Maintain all information supplied by Irrimax in confidence and, when this information is submitted to an Institutional Review Board (IRB) or Ethics Committee (EC), it will be submitted with a designation that the material is confidential.
- Comply with all IRB or EC requirements for this study.
- Ensure that all personnel who have been delegated responsibilities for this study are trained on the protocol and adequately informed of their associated responsibilities prior to participation in this study.

This document contains confidential information belonging to Irrimax Corporation, and therefore, may not be disclosed to any other person or entity without the prior written permission of the Sponsor unless such disclosure is required by law or regulation.

Investigator Signature

I have read and understand the contents of the clinical protocol including this Statement of Investigator Compliance. I agree to follow and abide by the guidelines set forth in this document.

_____

Principal Investigator Name (print)

_____ _____

Principal Investigator Signature Date

Table of Contents

1. PROTOCOL SUMMARY

An Independent Review of Safety Data from a Closed Clinical Study Using Irrisept (Protocol # IRR-CT-901-2013-01)	
Study Type	Retrospective Review
Short Title	Retrospective Independent Safety Review of Closed Irrisept Study
Study Objective	The objective of this retrospective review is to ensure that all safety data from the closed study have been accurately identified, verified and independently adjudicated. The Sponsor will use the safety data from this review to complete a final study report and ensure the product risk assessment documentation is current and complete.
Study Design	Retrospective review of safety data previously collected in a closed randomized clinical trial (Protocol IRR-CT-901-2013-01) prospectively-conducted between 2013 and 2016.
Study Sites	17 sites who originally participated and enrolled subjects in the closed study
Study Population	625 subjects who were previously consented in the closed study. There is no new subject enrollment involved in this retrospective review. The study population, including inclusion and exclusion criteria, was previously defined in the closed study protocol.
Study Duration/ Follow-up	There is no subject follow-up involved in this retrospective review. The study duration and follow-up was previously defined in the closed study protocol.
Key Study Parameters	Preexisting safety data from the closed clinical study including all adverse events and any reports of device deficiencies.
Key Study Endpoint	As defined in the closed study Protocol IRR-CT-901-2013-01, this retrospective review will complete the safety endpoint analysis of adverse events associated with use of of Irrisept as compared to use of the Standard of Care for irrigation.

2. BACKGROUND INFORMATION

2.1 Study Rationale

Between 2013 and 2016, an Irrimax-sponsored prospective clinical study entitled, *"A Phase IV, multicenter, prospective, randomized, controlled clinical study to compare the IrriSept system versus Standard of Care (SoC) on the prevalence of Surgical Site Infection (SSI) in patients with abdominal trauma or acute surgical abdomen"*, IRR-CT-901-2013-01, was conducted in the United States under IRB approval. A total of 19 sites were planned to participate in the study with only 17 sites enrolling subjects in the study, as listed above. A total of 625 subjects were consented and 600 subjects were randomized (1:1) and received irrigation either with Irrisept or the Standard of Care. Subjects were followed through study completion, and Protocol IRR-CT-901-2013-01 was previously closed with the IRBs. However, the Contract Research Organization and Sponsor's executive management responsible

for undertaking this study during that period of time (2013-2016) were unable to complete the necessary monitoring activities and final data reporting.

In 2019, the Sponsor, under new management, intends to fulfill the Sponsor responsibilities by preparing a final study report for Protocol IRR-CT-901-2013-01. Upon recent review of the previously reported safety data from this closed study, the Sponsor determined that remonitoring of the subjects' source records is necessary to ensure complete and accurate reporting. Furthermore, an independent review of the device-related safety data by a Medical Monitor is needed.

Therefore, the Sponsor is initiating a retrospective review of the safety data, specifically all adverse events (AEs) and any device deficiencies that occurred in the closed clinical study based on the subjects' source records, including identifying any events or deficiencies that may not have been previously reported on case report forms (CRFs). The purpose of this retrospective review is to ensure all safety data on Irrisept are known and the product risk assessment documentation is current. All reported AEs will be assessed by an independent Medical Monitor. Device-related adverse events will be evaluated for any required reporting to regulatory authorities.

The Sponsor does not intend to repeat the prospective clinical study IRR-CT-901-2013-01 or obtain any new information that was not previously collected in the subjects' source records for the closed study. The Sponsor's intent is solely to ensure all safety data are reported accurately and completely. This retrospective review will not recover or remonitor the previously reported efficacy data.

The subjects who participated in the closed clinical study (IRR-CT-901-2013-01) have been consented and signed an informed consent form and authorization to use and disclose protected health information under the HIPAA Privacy Rule for that study. As a retrospective review of subjects' data previously collected under the closed study, there should be no need for any additional informed consent of the subjects for this review. This review poses no risks to the previously enrolled subjects, and the subjects' prior authorization to use and disclose protected health information remains in effect with only the Sponsor and the Contract Research Organization, working on behalf of the Sponsor, having access to review the subjects' medical records to verify the accuracy of the safety data as reported on the CRFs.

2.2 Product Description

In the closed clinical study (IRR-CT-901-2013-01), subjects were randomized to receive irrigation with Irrisept (study medical device) or with the Standard of Care , which was determined at the sole discretion of the Investigator or institution. Refer to the *U.S. Investigator's Brochure for Irrisept Wound Debridment and Cleansing System* for detailed product information and a report of prior investigations, including literature, pre-clinical and clinical studies.

Irrisept® Wound Debridement and Cleansing System is an irrigation device comprised of a bottle of 0.05% Chlorhexidine Gluconate (CHG) in 99.95% Sterile Water for Irrigation, USP and an applicator.

Irrisept is a wound cleansing delivery system with mechanical action that effectively loosens and removes wound debris. The CHG is a preservative to inhibit microbial growth in the solution.

Irrisept is a prescription device and a combination product intended for use by healthcare professionals. Irrisept received 510(k) clearance (K080779) from the U.S. Food and Drug Administration (FDA) and has been marketed in the U.S. since 2009.

This retrospective review is non-significant risk because the review involves only assessment of previously collected subject data. This retrospective review does not involve any subject participation or use of any product.

3. STUDY OBJECTIVE

The objective of this retrospective review is to ensure that all safety data from the closed Irrisept study have been accurately and completely identified, verified and independently adjudicated. The Sponsor will use the safety data from this review to complete a final study report and ensure the product risk assessment documentation is current and complete.

4. STUDY DESIGN

This is a retrospective review of existing safety data from a prospective randomized clinical trial, conducted between 2013 and 2016, which was closed without a final clinical study report being issued.

5. STUDY POPULATION AND FOLLOW-UP

The study population, including inclusion and exclusion criteria, was defined in the closed study Protocol IRR-CT-901-2013-01. The closed study protocol allowed for enrollment of up to 1,100 subjects. At the 17 sites who enrolled subjects in the closed study, 625 subjects were consented, 600 subjects were randomized and received irrigation with either Irrisept or the Standard of Care, and 450 subjects completed the study. The study duration and follow-up schedule were previously defined in the closed study protocol. 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 Protocol IRR-CT-901-2013-01. The review will assess for documentation of informed consent for these subjects, and 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.

6. STUDY ENDPOINT

The closed study Protocol IRR-CT-901-2013-01 defined primary and secondary efficacy, exploratory and safety endpoints. The previously defined safety endpoint from this closed study was a clinical review and analysis of adverse events.

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

7. STUDY DATA PARAMETERS

The study data parameters are limited to the preexisting safety data from the closed study. This retrospective review involves identification, verification and adjudication of all adverse events in the study for all enrolled subjects based on the source medical records. The adverse events will be summarized by group, type, severity and device-relatedness. In addition, as part of the safety data review of the closed study, any device deficiencies with Irrisept documented in the source records during the closed study when the study device was used will be identified, even if the deficiency was not associated with an adverse event. Any device deficiencies will be investigated to ensure the deficiency could not lead to an adverse event if the problem were to recur.

7.1 Safety Data Definitions

All adverse events and device deficiencies as defined below will be recorded and verified based on the source documents from the closed clinical study. The closed study (Protocol IRR-CT-901-2013-01) defined adverse events based on a combination of references (i.e., International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) (1996), International Organization for Standardization (ISO) 14155:2011 standard, and 21 CFR Part 812). For this retrospective review, the adverse event definitions are consistent with the closed study protocol; however, a few clarifications based on the ISO 14155:2011 standard have been described within these definitions.

7.1.1 *Adverse Event*

As defined in Protocol IRR-CT-901-2013-01, an **Adverse Event** (**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.

As described in ISO 14155, an adverse event includes:

- events that are related or not related to the study device (Irrisept), comparator (Standard of Care), 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, as listed below.

7.1.2 Serious Adverse Event

As defined in Protocol IRR-CT-901-2013-01, a **Serious Adverse Event** (**SAE**) is an adverse event that results in one of the following outcomes: requires hospitalization; prolongs hospitalization; is life-threatening; results in congenital anomaly/birth defect; or results in death.

Furthermore, as described in ISO 14155, a serious adverse event includes any adverse event that has led to a serious deterioration in health that resulted in:

- 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.

7.1.3 *Adverse Device Effect*

As defined in Protocol IRR-CT-901-2013-01, an **Adverse Device Effect** (**ADE**) is an adverse event that results from the presence or performance of the device or any component of the system.

As described in ISO 14155, an adverse device effect includes 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

7.1.4 Serious Adverse Device Effect

As defined in Protocol IRR-CT-901-2013-01, a **Serious Adverse Device Effect** (**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; is life-threatening; results in congenital anomaly/birth defect; or results in death. The same ISO 14155 clarifications as documented above for SAE also apply to SADE.

7.1.5 Unanticipated Serious Adverse Device Effect

As defined in Protocol IRR-CT-901-2013-01, a **Unanticipated Serious Adverse Device Effect** (**USADE**) or **Serious Unexpected Device Effect** is 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, or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subject.

As described in ISO 14155, 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, as documented in the following section.

7.1.7 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)

[1] U.S. Food and Drug Administration website, "FDA Drug Safety Communication: FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate"; accessed September 2, 2016 at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-rare-serious-allergic-reactions-skin-antiseptic

TABLE 1: POTENTIAL RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS FOR IRRISEPT		
Potential Risk	**Risk Assessment and Risk Mitigations**	**Potential Anticipated Effects**
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 I 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 labeled 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

TABLE 1: POTENTIAL RISKS AND ANTICIPATED ADVERSE DEVICE EFFECTS FOR IRRISEPT		
Potential Risk	**Risk Assessment and Risk Mitigations**	**Potential Anticipated Effects**
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

7.1.8 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 labeling. A device deficiency does not need to be related to an adverse event.

7.2 Safety Data Reporting

7.2.1 Safety Data Reporting Responsibilities

The responsibilities for safety data reporting in this retrospective review are summarized below.

- **Investigator**: The Investigator is responsible for recording all previously identified and newly identified adverse events and device deficiencies on the CRFs. Investigators must record on the source document and eCRF their opinion concerning the AE severity, relationship of the AE to device, seriousness categorization per the event definitions, and whether any device effect is anticipated or unanticipated. The Investigator will follow all IRB/EC and institutional reporting requirements of AEs and SAEs, including for any new safety information or adverse events which may be identified retrospectively. Investigators are required to prepare and submit complete, accurate and timely reports on this clinical investigation to the Sponsor, IRB/EC and/or regulatory authorities, when necessary.

- **Contract Research Organization (CRO)**: The CRO is responsible for source data review of AEs and device deficiencies. As needed for monitoring activities, the CRO is responsible for appropriate follow-up with the Investigator, Sponsor and independent Medical Monitor, as per the study's Medical Monitoring plan. The CRO is also responsible for data management of this retrospective review.

- **Medical Monitor**: Each AE will be assessed by an Independent Medical Monitor for severity, relatedness to the device, seriousness categorization per the event definitions, and whether any device effect is anticipated or unanticipated. A firewall will be established between the Sponsor and its CRO representatives, and the independent Medical Monitor to reduce bias in adjudication of AEs.

- **Sponsor:** The Sponsor will assess all adverse device effects determined to be related to Irrisept based on the independent adjudication of the Medical Monitor. The Sponsor will investigate any reported device deficiencies as part of the complaint handling process and to ensure the deficiency could not lead to an adverse event if the problem were to recur. The Sponsor is responsible for any required safety reporting to the FDA or other regulatory authorities, such as per 21 CFR 803 (Medical Device Reporting), as applicable.

7.2.2 Specific Considerations for AE Reporting

1. Abnormal Vital Signs and Laboratory Values
   Per Protocol IRR-CT-901-2013-01, it is the Investigator's responsibility to review all vital sign findings or laboratory results for possible AEs. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign or laboratory abnormality should be classified as an AE. A vital sign or laboratory result should be reported as an AE if it meets any of the following criteria:

   - Results in a change in study product use (treatment interruption)
   - Clinically significant in the Investigator's judgment

2. AEs Occurring Secondary to Other Events
   Per Protocol IRR-CT-901-2013-01, AEs occurring secondary to other events (e.g., cascade of events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events.

3. Persistent or Recurring AEs
   Per Protocol IRR-CT-901-2013-01, a persistent AE extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on an AE CRF.

   A recurrent AE resolves between patient evaluation time points and subsequently recurs, and each recurrence should be recorded separately on an AE CRF.

4. Use of Diagnosis for AE Reporting
   Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”.

5. Preexisting Medical Conditions
   Per Protocol IRR-CT-901-2013-01, a preexisting medical condition is present at the screening visit for that study. Preexisting medical conditions should be recorded on the AE CRF.

6. Deaths
   Per Protocol IRR-CT-901-2013-01, all deaths that occur during the study, regardless of relationship to the study device, must be recorded on the AE CRF. Death should be considered an outcome and not a distinct event. The event or condition that contributed to the fatal outcome should be recorded on the AE CRF. The term “sudden death” should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes, pulmonary embolus (air embolus or fat embolus), or catastrophic stroke, in a patient without preexisting cardiac disease or history of TIA or stroke, within one hour of onset of acute symptoms, or in the case of unwitnessed death, within 24 hours of when the patient was last seen alive and stable.

7.2.3 AE Relationship to the Device

The AE relationship to device will be determined by the Investigator and recorded on the AE eCRF. The independent Medical Monitor will provide for a separate adjudication on the Sponsor’s behalf for all identified AEs.

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any alternative causes to determine whether or not an AE is considered to be related to the study device or Standard of Care. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study device or Standard of Care
- Course of the event, considering especially the effects of anesthesia and surgery

- Known association of the event with the study device/Standard of Care or with similar products
- Known association of the event with the surgical interventions under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

Device causality will be assessed as follows:

- **Unrelated:** Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE; or based upon available information regarding subject history, a relationship between the device and AE is unlikely. If an AE is classified to be 'unrelated' then the suspected causality of the AE must be documented on the source and eCRF. Causality can include AEs related to the surgical procedure, pre-existing conditions, or intercurrent conditions/intervention.

- **Unlikely Related:** Event or laboratory test abnormality, with a time of use of the device that makes a relationship improbable (but not impossible). Disease or use of other drugs and procedures may provide plausible explanations.

- **Possibly Related:** The AE follows a reasonable sequence from the time of device use but could also have been produced by the subject's clinical state or by other drugs or procedures administered to the subject.

- **Probably Related:** The AE follows a reasonable sequence from the time of device use, and follows a known response pattern for use of the device. The event is unlikely to be attributed to a disease or other drugs or procedures.

- **Definitely Related:** The AE follows a reasonable sequence from the time of device use, follows a known response pattern for use of the device and no other reasonable cause exists.

7.2.4 AE Severity

The AE severity will be determined by the Investigator and recorded on the AE eCRF. AE severity will be scored as follows:

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

8. STATISTICAL ANALYSIS

The statistical analysis is summarized below. Further details of the analysis will be specified in the Statistical Analysis Plan (SAP).

8.1 AE Analysis

AE rates will be summarized 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 study group to inform the Sponsor's product risk assessment.

As documented in Protocol IRR-CT-901-2013-01, adverse events will be coded using MedDRA. AE summaries will be presented by study 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".

8.2 Device Deficiency Analysis

Device deficiencies will be summarized by type of deficiency and any relevant information about the deficiency.

8.3 Analysis Population

The safety data will be analyzed for the Intent to Treat population of all subjects who were consented and randomized in the prior closed study protocol. Subjects will be categorized for analysis based on the actual irrigation product used during surgery (Irrisept or Standard of Care).

9. DATA HANDLING

9.1 Data Collection and Reporting

Data from the closed study were previously entered into an electronic data capture (EDC) system between 2013 and 2016. New electronic case report forms (eCRFs) and a new database have been created for the retrospective review and clinical monitoring functions. All required data for this study will be collected on standardized eCRFs within a 21 CFR Part 11 compliant EDC system.

A new eCRF will be completed for all previously consented subjects indicating verification of informed consent and whether any adverse events or device deficiencies were identified in the closed study Source records. Any identified AEs will be entered on a new AE eCRF. Any identified device deficiencies will be entered on a new Device Deficiency eCRF. The data to be collected are summarized below.

- For all subjects:
    - Verification of documentation of informed consent from closed study in the Source
    - Verification of signed and dated IRB-approved informed consent document
    - Verification of randomization and randomization assignment
    - Documentation of actual irrigation product used during closed study
    - Documentation of the subject's medical diagnosis requiring open abdominal laparotomy as defined in the closed study eligibility criteria
    - Documentation of the reason for open abdominal laparotomy (e.g., trauma or acute surgical abdomen)
    - Description of the nature of trauma or acute surgical abdomen and what specific surgical procedures were performed
    - Verification of whether the subject experienced any adverse events in the closed study based on review of Source records
    - Verification of whether any device deficiencies were documented in the closed study Source records
    - Copy of redacted Source operative notes to provide relevant information for adjudication of any adverse events

- For subjects who have an adverse event identified in the closed study Source records:
    - Dates of event report and when site became aware of event
    - Demographics (e.g., age, gender, race, weight, height)
    - Allergy, medical and surgical history
    - Concomitant medications taken
    - Adverse event term, type, description, onset date and timeline relative to device use, resolution date, outcome, severity and relationship to device
    - For serious events, criteria meeting SAE/SADE definition, dates of hospital admission and discharge, and/or date and cause of death, as applicable
    - Investigator's medical opinion of likely cause of the event and device relationship
    - Description of device use during closed study, including any problems with the device or actions taken with the device as a result of the adverse event

- For subjects who have a device deficiency related to Irrisept identified in the Source records:
    - Dates of report and verification Irrisept was used for irrigation in closed study
    - Description and nature of deficiency
    - Documentation of whether the deficiency was related to any adverse event
    - Investigator's opinion if the deficiency could result in an adverse event if it were to recur

The Investigator or designee is responsible for completing, in a timely manner, an eCRF for each subject and all eCRFs for previously reported or newly detected AEs and device deficiencies. The Investigator or designee is responsible for reviewing completed eCRFs to attest that all data entered are complete and accurate after the monitor finishes the source document verification process. The Investigator is responsible for reviewing and signing each eCRF to indicate the Investigator has thoroughly inspected data and certifies its completeness and accuracy.

9.2 Monitoring Procedures

Clinical site monitoring is conducted to ensure that the reported study safety data are accurate, complete, and verifiable. A Clinical Monitoring Plan will be developed by the CRO that details the retrospective chart review of existing safety data in the clinical study, IRR-CT-901-2013-01.

Informed consent forms for all subjects who were previously consented in the clinical study, Protocol IRR-CT-901-2013-01, will be checked for proper recordkeeping and signatures All subjects' source medical records will be reviewed for any potential adverse events or device deficiencies. All identified AEs and device deficiencies in the Source medical records will undergo CRF review with 100% source data verification. Completed eCRFs will be verified by the monitor at the study site during the monitoring visit(s). The clinical monitors will be unblinded as to the study randomization assignment.

The study may also be subject to a quality assurance audit by the Sponsor and/or an inspection by regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

Separately, a Medical Monitoring Plan will be developed for this clinical study and will describe the process for reviewing and adjudicating all AEs. The independent Medical Monitor will be unblinded to the study randomization assignment.

9.3 Source Documents

The Investigator must permit authorized representatives of the Sponsor and the IRB/EC to inspect facilities and original records relevant to this study. The study documents must be made available at reasonable times for inspection and duplication, if required, by a properly authorized representative of the U.S. FDA or other local or foreign regulatory authorities in accordance with regulatory requirements. The clinical monitors or auditors will check the eCRF entries against the source documents and inspect study files, subject medical records and other related study documents as required. These personnel will not disclose any protected health information.

As described in the ICH GCP Guidelines and ISO 14155, 'essential documents', including eCRFs, source documents, previously collected informed consent forms, laboratory test results, and device records, should be retained by the Investigator for at least 2 years or in accordance with institutional procedures. The Investigator must obtain written permission from the Sponsor prior to the destruction of any study document.

Investigators should maintain information in the study subject's medical records that corroborate data collected on the eCRFs. To comply with these regulatory requirements, the following information will be maintained:

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria from the closed study protocol
- Dated and signed notes on the day of entry into the study including the study investigator, study name, subject number assigned and a statement that consent was obtained
- Information related to AEs and device deficiencies
- Discharge summaries/procedure reports

9.4 Quality Assurance and Control

Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Following written CRO Standard Operating Procedures (SOPs), the monitors will verify that this retrospective review is conducted, and data are generated, documented and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

9.5 Protocol Amendments

All protocols and amendments will be prepared by the Sponsor. If it becomes necessary to issue a protocol amendment during the course of the study, the Sponsor will notify the Investigators and collect documented Statement of Investigator Compliance to the amendment.

10. ETHICAL AND REGULATORY CONSIDERATIONS

The Sponsor and any third party (i.e., CRO) to whom aspects of the study management or monitoring have been delegated are committed to: compliance with the regulatory and IRB/EC requirements in the conduct of this retrospective study; ensuring Investigators are properly trained on study protocol and data collection procedures; monitoring the Investigators' compliance; submitting timely required reports; and keeping Investigators informed. This study will be conducted in compliance with the study protocol, Good Clinical Practices (GCP), U.S. Code of Federal Regulations (CFR), ISO 14155 and the Declaration of Helsinki.

Visits to Investigator sites will be conducted by the Sponsor or representatives of the Sponsor to inspect study data, subjects' medical records and CRFs in accordance with current ICH GCP and the respective local and national government regulations. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in ICH GCP and ISO 14155.

The protocol and any other study-specific documents shall be reviewed and approved by the appropriate IRB/EC prior to any retrospective data collection. Continued written approval must be obtained from the IRB/EC, as applicable according to regional and local requirements. Any updates to IRB/EC-approved documents may require re-approval before implementation of the changes.

11. SUBJECT DATA CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the participating Investigators, their staff, the Sponsor and their representatives. This confidentiality is extended to the clinical information relating to subjects previously enrolled in the closed clinical study (Protocol IRR-CT-901-2013-01). 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.

12. RECORDKEEPING

The Investigator will maintain records in accordance with ISO 14155 and ICH GCP:

- Current and past versions of the IRB/EC-approvals
- Current clinical protocol and current and past IRB/EC-approved consent form(s)
- Any correspondence related to this protocol including with regulatory authorities (e.g., FDA)
- IRB-related documentation: IRB membership list and/or assurance number, correspondence (including submissions and approval notifications), any safety or protocol deviation reports, and annual or interim reports
- Signed Clinical Trial Agreement
- Signed Investigator Agreements and financial disclosure forms for participating Investigators
- Curriculum vitae (Investigator and Sub-Investigators)
- Previously signed and dated informed consent forms
- eCRF and Source Documents (laboratory and testing results, procedure reports, progress notes, physician and/or nursing notes, and subject office files, record of any complications, and/or AEs with supporting documentation)
- Site Visit Log (for Monitor sign-in)
- Monitoring confirmation and follow-up letters
- Copies of relevant Sponsor-Investigator correspondence
- Reports (includes AE reports and final reports from Investigator)

13. CLOSE-OUT PROCEDURES

Routine close-out activities will be conducted to ensure that each site's records are complete, all documents needed for the Sponsor's files are retrieved, all study data issues have been resolved, and all parties are notified.