COVER PAGE

Protocol Title	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
Protocol Short Title	Irrisept versus SoC in the prevention of surgical site infections
NCT Number	NCT02255487
Sponsor Name	Irrimax Corporation
Sponsor Address	1665 Lakes Parkway, Suite 102, Lawrenceville, Georgia 30043
Investigator (PI) Responsible for Conducting Research	Donald E. Fry, MD
Research Sites	The MetroHealth System, Cleveland, OH Regional One Health Research Institute, Memphis, TN The University of Florida, Tampa General Hospital, Tampa, FL Denver Health and Hospital Authority, Denver, CO The University of Texas Health Science Center at Houston, Houston, TX The University of Iowa, Iowa City, IA The University of Kentucky Research Foundation, Lexington, KY The University of Southern California, USC Medical Center, Los Angeles, CA The University of Texas Southwestern Medical Center, Dallas, TX The Medical College of Wisconsin, Milwaukee, WI The University of Washington, Harborview Medical Center, Seattle, WA The University of Cincinnati Health, Cincinnati, OH The University of Maryland, Baltimore, Baltimore, MD Baystate Medical Center, Springfield, MA Miami Valley Hospital, Dayton, OH The University of Texas Health Science Center at San Antonio, San Antonio, TX The University of Arizona, Tucson, AZ The University of Michigan, Acute Care Surgery, Ann Arbor, MI Saint Louis University, Saint Louis, MO
Date of IRB Approval for Protocol	10 FEB 2015
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Protocol Title: 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

Protocol Number: IRR-CT-901-2013-01

Protocol Date: August 01, 2014

Version: 1.0

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APPROVAL SIGNATURE PAGE

Protocol Title: 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

Protocol Number: IRR-CT-901-2013-01

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Protocol Date: August 01, 2014

Author(s): Page McNeill, RN, MSN, CNL, Page C. McNeill, Manager, Clinical Affairs
Sara C. Castle, *Clinical Consultant*
Mindy White, DPh, RPh, MBA, *Clinical Consultant*

Signature: _____ **Date:** _____

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Signature: _____ **Date:** _____

Approver: Carolyn Twomey, Vice President, Clinical Affairs, IrriMax® Corporation

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Approver: Gareth Clarke, Chief Executive Officer, IrriMax® Corporation

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Approver: Brian Parsons, Director, Quality, IrriMax® Corporation

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Approver: Kathleen Harris, Clinical Regulatory Consultant, 2Harris Consulting

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Start Date: **August 15, 2014**

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Irene Zhang, Clinical Data Management, Everest Clinical Research Inc.

INVESTIGATOR'S AGREEMENT AND CERTIFICATION

INVESTIGATOR:

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), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used throughout this study protocol:

Abbreviations and Definitions

AE	Adverse Event
AIS	Abbreviated Injury Scale
BMI	Body Mass Index
CFR	Code of Federal Regulations
CMS	Centers for Medicare & Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISF	Investigator Site File
PI	Principal Investigator
SAE	Serious Adverse Event
SIV	Site Initiation Visit
SOP	Standard Operating Procedures
SSV	Site Selection Visit
WHO	World Health Organization

Study Specific Abbreviations and Terms Definitions

ASA	American Society of Anesthesiologists Physical Status Classification
ATCC	American Type Culture Collection, non-profit bioresource center (BRC) and research
BP	Blood Pressure
CAUTI	Catheter Associated Urinary Tract Infection
C-diff	Clostridium difficile infection
CHG	Chlorhexidine Gluconate
CLABSI	Central Line Associated Blood Stream Infection
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
HAI	Healthcare Associated Infection
HICPAC	Healthcare Infection Control Practices Advisory Committee
HIV	Human Immunodeficiency Virus
HMPS-I	Harvard Medical Practice Study I
IFU	Instructions For Use
LOS	Length of Stay
MRSA	Methicillin-resistant Staphylococcus aureus
NSQIP	National Surgical Quality Improvement Project
OR	Operating Room
PATI	Penetrating Abdominal Trauma Index
PE	Pulmonary Embolus

POA	Present On Admission
SCIP	Surgical Care Improvement Project
SoC	Standard of Care
SSI	Surgical Site Infection
USP	United States Pharmacopeia
UTI	Urinary Tract Infection
VAP	Ventilator Associated Pneumonia

STUDY SUMMARY

Full Title of Protocol:	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
Protocol Number:	IRR-CT-901-2013-01
510(k) Number:	K080779
Study Duration:	6 – 9 months (*or until enrollment is met)*
Study Center(s):	12 – 14

Study Objective(s):

The hypothesis for this study is the use of the IrriSept system will decrease the prevalence of Surgical Site Infection (SSI) versus the Standard of Care (SoC) for patients with abdominal trauma or acute surgical abdomen.

Primary Objective:

- To compare the rate of SSI in the IrriSept system randomization group to the rate of SSI in Standard of Care randomization group.

Secondary Objective(s):

- To compare the hospital readmission rate of subjects receiving the IrriSept system to the hospital readmission rate of subjects receiving Standard of Care treatment.
- To compare the estimated hospital cost to charge ratio between the IrriSept system and Standard of Care.
- To compare the length of hospital stay between IrriSept system and Standard of Care.

Study Product:

Product Name: IRRISEPT™ Wound Debridement and Cleansing System

Registration Number: 3005706359

Product Status: Active

Registered Company: IrriMax Corporation

IrriSept system containing sterile 0.05% Chlorhexidine Gluconate (CHG) in water for irrigation, USP (99.95%), and sterile 0.9% normal saline packaged with 2 sterile IrriProbes, packaged for study use as a "kit". Two (2) complete "kits" will be used per the study specific IFU (Instructions for Use) for each subject randomized to Study Product.

Study Design:

This is a randomized, open-label, parallel-group study. The study consists of 3 parts: a Screening Phase typically performed in the Emergency Department, a randomized, open-label Treatment (Perioperative) Phase, and End of Study, a 30-day Follow-up.

Study Sample Size:

1100 screened, approximately 650 completed, 600 evaluated

Study Background:

1.1 HEALTHCARE ASSOCIATED INFECTIONS

One of the biggest revelations to the U.S. healthcare system as a whole may have been the frequency, magnitude, and consequences of preventable adverse events that occur during hospitalization. As a result of this issue, a quality focus began to take shape.

The concept of measuring and monitoring "adverse events" (which here intended as in healthcare, the realization and identification of a potentially preventable clinical event and their sequelae) arise in hospitalized patients as direct or indirect consequence of medical interventions was initiated more than three decades ago.[1] However, the term only gained popularity in 1991 upon the publication of the Harvard Medical Practice Study I (HMPS-I). [2] This was the first, large-scaled study determined to scientifically measure and quantify, the prevalence of "adverse events" and medical negligence in hospitalized patients. [3, 4]

As a result, healthcare moved quickly to identify primary 'threats to patients', to review and map out the processes involved in these threats, and develop clinical strategies to manage them. The identification of healthcare-associated infections (HAIs) was one part of this 'threat' identification. One of these infection threats is the surgical site infection (SSI). SSI is, a healthcare-associated infection (HAI) in which a wound infection occurs after an invasive surgical procedure. While most patients undergoing surgery do not acquire an SSI, infections have been estimated to develop in 1 to 3 of every hundred patients having surgery today in the US.[5]

One of today's most common SSI pathogens is methicillin resistant *Staphylococcus aureus* (MRSA). The brief history of MRSA as a pathogen indicates that it will likely continue to develop new virulence characteristics. Presently, MRSA accounts for approximately 30% of SSI infections.[6, 7] Alarmingly, vancomycin, along with most other antibiotics, is losing its effectiveness for prevention and treatment of MRSA and other opportunistic infections. Healthcare requires additional antibiotic choices developed for the treatment and prevention of both methicillin-sensitive and methicillin-resistant staphylococci.[8] It is likely that the increasing trends toward resistant organisms may undermine the effectiveness of existing recommendations and choices for antimicrobial prophylaxis.

1.1 ANTIBIOTIC RESISTANCE

Antibiotics have saved the lives of millions world-wide. They opened up new frontiers in medicine and surgery that would be impossible without them.[9] Bacteria have the ability to develop resistance to antibiotics through a variety of different mechanisms. The uncanny ability bacteria have to survive against healthcare's best chemistry is demonstrated by the stark reality of untreatable infections. Unfortunately, Western civilization has created this conundrum as a direct result of misuse and overuse of antibiotics. Experts are warning the healthcare industry we have now entered the post-antibiotic era. Healthcare practitioners are now in the position of having patients with an infection that would formerly have been treated effectively, and today, no available antibiotic will work, for the infection.

1.2 SURGICAL SITE INFECTION

There are an estimated 300,000 SSIs annually, accounting for 17% of all HAIs [11]. This significant surgical adverse event is attributed to shortened hospital stays, early discharge, outpatient surgery, and the lack of a community based infection control and prevention systems. Once a patient is discharged from the acute care environment, robust tracking ends – this results in a shortage of quality data.[10] In-patient surgical patients

in the US have a reported 2%-5% incidence of SSI.[11] Mortality associated with SSI is 3% overall. Patients with a SSI have a 2-11 times greater risk of death, and 75% of deaths among patients with SSIs are directly attributable to their SSI.[11] The morbidity associated with SSI also includes long-term disabilities.[11] SSI adds on average 7-10 days to the length of stay (LOS). Keep in mind, this data is compiled from inpatient admissions. 60%-70% of surgery today is outpatient – this data only speaks to minority of the surgical population. Between suspected under-reporting and the challenge of outpatient surgery lack of post-discharge follow-up data, these healthcare economic numbers are likely quite low. Finally, the cost of an SSI can range from $3,000.00 for a UTI (Urinary Tract Infection) [11] to $110,000.00 in cardiac surgery.[12] In total joints infections alone, the annual costs for US hospitals ranged as high as $566 million in 2009, and is estimated in 2020 to exceed $1.6 billion.[13]

Process improvement projects like the Surgical Care Improvement Project (SCIP) and the National Surgical Quality Improvement Project (NSQIP) have driven process measure standardization.[14] Process measures constitute the focal point of surgical quality studies. Yet, high levels of compliance with such processes have not correlated with improved outcomes.[15] The majority of surgical site infections are preventable. Measures can be taken in the pre-, intra- and postoperative phases of care to reduce risk of infection. [16]

1.3 SURGICAL IRRIGATION

Surgeons have sought methodologies to reduce surgical site infections and improve patient outcomes for centuries, and their efforts have resulted in a variety of practices across specialties, resulting in the lack of a standardized process.[17] The use of a surgical irrigation solution is one such example. The goal of surgical irrigation is to remove particulate matter, foreign bodies, bone fragments, and clots, and to improve visualization of the surgical field, ultimately to render the surgical wound as clean as possible prior to closure. The goal of surgical irrigation as an intervention is to reduce the potential for surgical site infections.

1.3.1 SURGICAL IRRIGATION – VOLUME

There is a lack of consensus on an ideal wound irrigation volume. The literature has revealed varied amounts of irrigation solutions used, often reflecting the size of the surgical wound. These volumes have run the gamut from several hundred milliliters to 10 or more liters. The volume depends upon the surgeon preference, surgical procedure, location of the wound, and wound classification.

1.3.2 SURGICAL IRRIGATION – PRESSURE

Evidence in the literature today as well as recommendations from the American College of Surgeons and others recommends less than 15psi to reduce the risk of deep seeding of bacteria into the tissue and into bone.[17] Delivery of irrigation under lower (less than 15psi) and controlled pressure assists in the removal of debris and contaminants from the wound. Higher pressure increases the risk of embedding bacteria and other potentially infectious materials into the surrounding tissues.[18] It has been demonstrated that a psi of 8-12 is required to interrupt bacterial attachment to the tissue wall. [18]

1.3.3 SURGICAL IRRIGATION - ANTIBIOTICS

The addition of antibiotics to irrigation fluid has become common practice. Various antibiotics are commonly identified in the literature when describing surgical irrigation (e.g. bacitracin, gentamycin, clindamycin, or combination of the two, vancomycin, or other antibiotics). The literature clearly does not support the efficacy or safety of surgical irrigation with antibiotics. Of recent significance, the Healthcare Infection Control Practices Advisory Committee (HICPAC) recommendations state: “there remains a need to develop a more effective surgical irrigation that delivers the right pressure and solution to reduce surgical site infection in the face of declining antibiotic effectiveness.” [19]

1.3.4 SURGICAL IRRIGATION – ANTISEPTICS

Topical antiseptics have long been employed to render the skin clean and to reduce potential pathogens. There are some in-vitro and in-vivo (primarily, but not limited to, animal studies) studies exploring the use

of antiseptics as irrigation solutions. The most common antiseptic agents added to irrigation solutions are 2-4% chlorhexidine (both gluconate and acetate), alcohol, povidone iodine at various concentrations, sodium hypochlorite, and hydrogen peroxide. The literature has reported the potential for qacA, qacB, and smr genes in MRSA have been associated with increased chlorhexidine use, the first occurring in a Canadian ICU. Authors recommend periodic monitoring of organism susceptibility in order to detect any rise in either gene associated with resistance, as well as phenotypic testing to identify any other mechanisms of resistance to chlorhexidine in the future. [20] Some researchers have tried to create resistant organisms to chlorhexidine in vitro. Although they have had limited success doing this in a Petri dish, the results cannot be applied to clinical use since the concentrations of the chlorhexidine used were significantly below the clinical concentrations of chlorhexidine used. [21] Each one of these have reported one or more side effects including delayed wound healing, lymphocyte, keratinocyte or chondrocyte toxicity and subsequent necrosis, irritation, and localized sensitivity or allergic reaction to the tissue.

1.4 BACKGROUND ON CHLORHEXIDINE GLUCONATE 0.05% IN WATER FOR IRRIGATION

The IrriSept® system consists of three sterile trays. Tray 1 contains IrriSept® Step 1, which is a sterile bottle of 450 mL 0.05% Chlorhexidine Gluconate (CHG) in 99.95% water. Tray 2 contains Step 2, which is a sterile bottle of 450 mL of sterile 0.9% Normal Saline. The bottles are identical in shape and size, with a clear distinction in labeling between Step 1 and Step 2; their unique design allows the solutions to be delivered under the ideal pressure as determined by the surgeon via manual compression for wound and surgical irrigation. The third tray contains two sterile IrriProbe applicator tips that are to be attached to the bottles immediately prior to use on the sterile field.

The IrriSept system is a 510(K) FDA- cleared device for cleansing and debridement of wounds. IrriSept® has been on the market for greater than three (3) years and has been used in over 50,000 surgeries in numerous healthcare organizations in the U.S.

IrriSept is unique as compared other CHG antimicrobial products (excluding CHG mouthwashes). Higher concentration topical CHG antimicrobial agents on the market today carry a black box warning 'For External Use Only'. IrriSept does not have this warning. Safety and efficacy data below demonstrate safety and efficacy of the investigational device. Other high concentration topical CHG antimicrobial products also carry a black box warning and contraindication stating 'do not use in contact with the meninges'. IrriSept does not have this warning. In the safety and efficacy data an *in-vivo* animal neurotoxicity study demonstrates the safety of IrriSept in contact with the meninges. The IrriSept system delivers pressures of up to 8-11 psi. This is dependent on distance from the tissue, angle of application and pressure created by the user.

See the IRR-CT-901-2013-01 Investigator's Brochure for further details.

1.4.1 SAFETY AND EFFICACY DATA

The main targets for IrriSept® safety and efficacy were initially identified as tissue cytotoxicity, sensitivity, and irritation. In safety studies, IrriSept successfully passed cytotoxicity, sensitization and irritation studies as required in the ISO 10993 document for medical devices. A summary of IrriSept clinical studies is presented below in Table 1.

Table 1: Summary of IrriSept Safety and Efficacy Clinical Studies

STUDY TITLE	PURPOSE	SUMMARY	CONCLUSION
Cytotoxicity Assay in L-929 Mouse Fibroblast Cells for Liquids	Evaluate IRRISEPT cytotoxicity in a mammalian cell line.	Cultures of L-929 cells (mouse fibroblast) were plated with IRRISEPT and positive and negative controls for a period of 72 hours. Cultures were evaluated for cytotoxic effects by microscopic evaluation after 24, 48 and 72± hour incubation period. At all evaluations, IRRISEPT was rated as "mildly reactive" with no signs of extensive cell lysis. Positive and negative controls displayed complete and no cell lysis, respectively.	IRRISEPT 450mL is considered non-cytotoxic under the conditions of this test.
ISO Intracutaneous Reactivity Test (Albino rabbits, New Zealand White strain, female)	To determine if IRRISEPT causes local irritation in the dermal tissue of rabbits.	Each rabbit received intracutaneous injections of IRRISEPT and control. The animals were observed daily for abnormal clinical signs. The appearance of each injection site was noted at 24±2, 48 ±2, and 72±2 hours post injection. The tissue reactions were rated for gross evidence of erythema and edema. None of the animals on study showed abnormal clinical signs during the 72 hour test period.	IRRISEPT 450mL is considered a non-irritant under the conditions of this test.
Rat Wound Model to Determine Wound Irritation Resulting from a Wound Irrigation Solution	To compare wound irritation that might develop in response to irrigation with IRRISEPT and Saline (control)	Two full dermal thickness wounds were surgically created on either side of the spine. Each wound was immediately irrigated for ten seconds with either test (IRRISEPT) or control (Saline). The test article sites were rinsed with saline for ten seconds following irrigation. At 24, 48, and 72 ±2 hours, wounds were evaluated and scored for erythema and edema. Other adverse changes at the wound sites were recorded and reported. None of the animals on study showed abnormal clinical signs during the 72 hour test period.	IRRISEPT 450mL is considered a non-irritant under the conditions of this test.
ISO Guinea Pig Maximization Sensitization Test Method for Liquid Test Articles	To evaluate the allergenic potential or sensitizing capacity of IRRISEPT.	Test animals were injected with IRRISEPT™ and saline control. One week later, the animals were topically patched with IRRISEPT and controls for a period of 48 ±2 hours. Following a two-week rest period, the animals were topically patched again for 24 ± 2hours. The dermal patch sites were observed for erythema and edema 24 ± 2 and 48 ± 2 hours after patch removal. None of the animals in the study showed abnormal clinical signs during the test period.	IRRISEPT 450mL did not elicit a sensitization response under the conditions of this test.

In-Vitro Kinetic Time-Kill Studies: demonstrate antimicrobial with 0.05% CHG activity. Dr. C. Edmiston, Medical College of Wisconsin, demonstrated a Time Kill at 1 minute for both ATCC and clinical isolate strains in Table 2 below.[20]

Table 2: Summary of Antimicrobial Time to Kill with 0.05% CHG

Bacteria	One Minute	Bacteria	One Minute
Pseudomonas aeruginosa	>99.9999%	*Staphylococcus aureus MRSA (CI)*	>99.999%
Pseudomonas aeruginosa (CI)	>99.9999%	*Staphylococcus aureus MSSA (CI)*	>99.999%
Klebsiella pneumoniae	>99.9999%	*Enterococcus faecium (CI)*	>99.99%
Enterobacter aerogenes (CI)	>99.9999%	*Enterococcus faecium (CI)*	>99.99%
Escherichia coli (CI)	>99.9999%	*Streptococcus pyogenes (CI)*	>99.99%
Escherichia coli (CI)	>99.9999%	*Staphylococcus epidermidis*	>99.999%
Acinetobacter baumannii (CI)	>99.9999%	*Staphylococcus epidermidis (CI)*	>99.999%

Acute Systemic Toxicity: the objective of this study was to demonstrate the safety of the IrriSept System through evaluation of systemic toxicity in mice models.

The test article, IrriSept Wound Debridement and Cleansing System, was evaluated for acute systemic toxicity in mice. A single 20 mL/kg dose of test article one, IrriSept with 0.05% CHG, was injected into a group of 5 animals by the intraperitoneal route. Similarly, a second group of 5 animals was dosed with test article two, IrriRinse with 0.9% sodium chloride USP solution. The control group was injected with 0.9% normal saline, National Formulary. The animals were observed immediately and at 4 hours after dosing and daily for 7 days. The animals were weighed prior to dosing and daily for 7 days thereafter. Weight gain and activity are considered measures of thriving and are a significant clinical observation for the study. All animals gained weight, thrived and remained clinically normal throughout the study. There was no mortality or evidence of systemic toxicity from either portion of the test article. The test article met the test requirements.

Neurotoxicity: The objective of this study was to demonstrate the safety of the IrriSept System through evaluation of systemic and neurological toxicity and local effects after implantation in a chronic rabbit dorsal laminectomy model. This study was a randomized, controlled, (not blinded) study design. The study enrolled 14 female and 14 male New Zealand white rabbits. The animals were assigned to one of two study cohorts.

The study required evaluation using an in vivo model in order to properly assess the local, neurological, and systemic responses to the test article. The rabbit model was selected for this evaluation due to rabbits being an established animal species for dorsal laminectomy models and accepted for such studies by the appropriate regulatory agencies. This study is required of all new or different materials used in the spine by the FDA. Results demonstrated no neurotoxicity in the spine and brain fixed histology slides, nor in any of the ten target organs tested. Analysis of the study endpoints indicate IrriSept is safe, with no systemic neurologic toxicity or significant local effects after implant, in a chronic rabbit model.

Protocol Synopsis

This is a Phase IV, multi-center, prospective, randomized controlled, comparator clinical trial. Twelve to fourteen (12-14) Level I Trauma Centers throughout the United States will participate as research sites conducting this protocol. After the research site receives Institutional Review Board (IRB) approval, patients between the ages of 18-70 years old who undergo open abdominal laparotomy for abdominal trauma or acute surgical abdomen within thirty-six (36) hours of initial presentation to their healthcare organization may be eligible for study inclusion. Exclusion criteria includes: known allergy to chlorhexidine gluconate (CHG), Abbreviated Injury Scale (AIS) score of six (6), American Society of Anesthesiologists Physical Status Classification (ASA) score of five (5) or greater, female subjects who are pregnant and/or breast feeding, those patients undergoing a damage control laparotomy, a drain is placed within the wound or an intra-abdominal drain exits through the primary incision, reoperation occurs through the primary incision or transgresses the primary incision as the index procedure within 30 days, and those enrolled in a concurrent, ongoing interventional, randomized clinical trial.

Patient risk factors will be assessed at screening include chronic uncontrolled hypertension, chronic heart disease, chronic renal disease, chronic pulmonary disease, diabetes mellitus, HIV, chronic liver disease, a BMI of less than 18 or above 40, coagulopathy, current long-term steroid use, current smoker, and current cancer. Additional assessments include PATI (Penetrating Abdominal Trauma Index), AIS and ASA scores, and adherence to SCIP prophylactic antibiotic-specific guidelines. Other measures to be documented will include antibiotic used and surgical skin preparation used. The following present on admission (PoA) characteristics are documented: shock, (systolic BP < 90 mm Hg), intubation, active infection, transfusion of blood/blood products and primary injury in trauma or primary organ(s) in the acute abdomen. Intra-operative SSI risk factors including drains, staple versus sutures, surgical time (skin to skin), blood/blood products, and body temperature below 36^{o}C are assessed and risk adjusted in the final analysis.

Exploratory endpoints at study completion include: infection (superficial, deep, organ space), ventilator associated pneumonia (VAP), catheter associated urinary tract infection (CAUTI), central line associated blood stream infection (CLABSI), deep vein thrombosis (DVT), pulmonary embolus (PE), acute cardiac event, Clostridium difficile (C-diff) infection, MRSA infection, mortality and length of stay (LOS).

The Standard of Care (SoC) irrigation arm subjects receive routine surgical irrigation Standard of Care (SoC). It should be noted that routine SoC is at the sole discretion of the investigator and institution and may or may not involve surgical wound irrigation. If irrigation is used, it will be delivered by bulb syringe or pour method but not a pressure device, which can range from a syringe with a cannula to jet lavage.

STUDY DETAILS

Study Rationale/Purpose:

The primary objective of this study is to compare the rate of surgical site infections in the IrriSept system randomization group to the rate of surgical site infections in the Standard of Care randomization group. There are three secondary objectives:

- To compare the hospital readmission rate of subjects receiving the IrriSept system to the hospital readmission rate of subjects receiving Standard of Care treatment.
- To compare the estimated hospital cost to charge ratio between the IrriSept system and Standard of Care.
- To compare the length of hospital stay between IrriSept system and Standard of Care.

Inclusion Criteria:

1. Is male or female, 18 to 70 years of age,
2. Has provided written informed consent
3. Has experienced abdominal trauma, blunt or penetrating requiring open abdominal laparotomy with primary closure or acute surgical abdomen requiring open abdominal laparotomy with primary closure
4. Undergoes the required surgical procedure within 36 hours of presentation to the healthcare system.

Exclusion Criteria:

1. Known allergy to Chlorhexidine Gluconate (CHG)
2. Abbreviated Injury Scale (AIS) score of six (6)
3. American Society of Anesthesiologists Physical Status Classification (ASA) score of five (5) or greater
4. Female volunteers who are pregnant and/or breast feeding
5. Damage control laparotomy
6. Drain is placed within the wound or an intra-abdominal drain exits through the incision
7. Reoperation occurs through the same incision or transgresses the same incision as the index procedure within 30 days
8. Abdomen opened prior to operating room
9. Currently enrolled in a clinical trial

Surgical Interventions

Open abdominal laparotomy with primary closure independent of intra-operative findings.

Ethical Conduct of the Study

This clinical trial will be conducted in accordance with the ethical principles having their origin in the Declaration of Helsinki and consistent with International Code of Harmonisation (ICH), Good Clinical Practices (GCP) and applicable regulatory requirements. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

This study will be conducted in accordance with SOPs (Standard Operating Procedures) of the investigator site, which are designed to ensure adherence to GCP guidelines as required.

Avoidance of Investigator Bias

Principal investigators with little or no knowledge and/or experience with the IrriSept system were specifically chosen to participate in this trial for purposes of minimizing investigator bias.

Duration of the Study

This Phase IV study is estimated to complete enrollment within 6-9 months; however, enrollment will remain open until the study goal is met.

Written Informed Consent

It is the investigator's responsibility to obtain witnessed, written Informed Consent Form (ICF) from each study participant (and/or their guardians/legally authorized representatives) after providing a full explanation of the protocol procedures, risks, and alternative medical options (if any), and responding to the patient's questions and concerns prior to his/her participation in the study. The ICF must be written in simple, non-technical, lay terminology in a language in which the patient is fluent, and must be signed prior to any screening performed in conjunction with this study or any modification in the patient's ongoing medical treatment intended to qualify him/her for study participation. The investigator must retain the completed ICF as part of each subject's study records and provide a copy of the signed ICF to the subject.

The study candidate should understand the ICF before signing and dating it. The IRR-CT-901-2013-01 study ICF will be available in 2 languages (English and Spanish), at study sites where the potential subject population is both English and Spanish speaking, study personnel whom are bilingual and qualified to conduct an informed consent in both English and Spanish, will receive both ICFs.

The ICF will be revised to reflect any significant study modifications and this information will be communicated to study participants (e.g., due to protocol amendment, significant new safety information, or administrative changes relevant to study subjects). The investigator must provide a copy of the proposed revision of the ICF to the sponsor for review and comments prior to submission for approval by the IRB/IEC. All subjects enrolled in the study at the time of IRB/IEC approval of a revised ICF must sign the revised ICF as soon as practical. A signed original, of each ICF, must be kept with the subject's source documents.

The consent process will adhere to Health Insurance Portability and Accountability Act (HIPAA), ICH/GCP and any other applicable local regulatory and legal requirements. The study candidate will be given a copy of the ICF to read and after discussion of any questions and confirmation by the investigator or a qualified staff member, the study candidate must provide witnessed (if applicable), written, dated consent.

Each study candidate must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. An unsigned copy of an IRB/IEC and sponsor-approved informed consent form must be prepared in accordance with ICH E 6 Section 3, and all applicable local regulations, i.e., Federal Regulations, Title 21, CFR Part 50, and provided to the sponsor. The original signed ICF for each subject will be verified by the sponsor and kept in the study center's investigator site files.

Participant Recruitment and Withdrawal

Patients will be asked to participate in this study if they meet the primary inclusion criteria and none of the exclusion criteria.

As per ICH/GCP, subjects will have the option to discontinue their participation at any point during the study.

Each institution will be placed on a recruitment hold after five subjects have undergone Visit 1 until a study monitor is able to review the data to ensure compliance with the protocol. Every effort will be made to assure monitoring occurs without hindering subject recruitment.

Study Methodology

Study subjects, who meet all inclusion and no exclusion criteria, and are deemed eligible for enrollment by the Principal Investigator (PI) or designee, will be enrolled in this study. After consent, subjects will be randomized

on a 1:1 ratio. They will receive either IrriSept for surgical irrigation or they will receive routine surgical Standard of Care (SoC). It should be noted that routine Standard of Care is at the sole discretion of the investigator and institution and may or may not involve surgical wound irrigation.

Each subject will be given a unique identification code that will be recorded in source documentation and in the Study Device Log and on all other study documentation pertaining to that individual.

Two complete IrriSept study kits will be dispensed to each study subject who is randomized to the IrriSept system. Subjects who are randomized to Standard of Care (SoC) will proceed with their surgical procedure without any study intervention.

For subjects randomized to the IrriSept arm, surgical irrigation will follow the IFU in the package insert. Practitioners will dissect to the fascia and irrigate as directed. Once the fascia is opened irrigation will be limited to normal saline only. Finally, after closing the fascia, practitioners will irrigate with a new IrriSept study kit.

Each of the study kit bottles (2 bottles in each IrriSept system kits) must be used. The study specific Instructions for Use (IFU) are provided in Appendix I. The study product must be used as a stand-alone device and may ***not*** be used in conjunction with any other irrigation methods above the fascia.

IrriMax clinical team members will conduct a Site Initiation Visit (SIV) for all study personnel. The SIV will occur prior to any subjects being screened or enrolled in the IRR-CT-901-2013-01 at the site. The purpose of the SIV is to provide study site personnel the opportunity to be trained on the conduct of the study and familiarize themselves with all study documents while having the opportunity to ask any questions of the clinical team.

During the SIV, site personnel will receive the following training and documents:

1. Protocol and Tool Kit Training
2. Review of Informed Consent Form process
3. Adverse Events/Serious Adverse Event Reporting Forms and Process
4. Responsibilities of the Principal Investigator and study staff
5. Source Document/CRF Completion Guidelines
6. Proper Use and Storage of the Study Product
7. Regulatory Binder Review
8. Miscellaneous

STUDY PROCEDURES:

Visit 1: Screening Phase

The following data will be collected once consent has been obtained and the subject is deemed eligible for enrollment by the Principal Investigator or designee.

- Date and time subject presents to the Facility
- Subject demographics (Date of Birth, Gender, Height, Weight)
- Abbreviated Injury Scale (AIS) and/or Glasgow Coma Scale (GCS)
- Surgical Risk Factors
- Present On Admission (POA) risk factors
- Record relevant collected laboratory values as per CRF
- Denote any Screening Phase Protocol Deviations

Visit 1: Perioperative Phase

The Perioperative Phase will begin when preoperative activity is initiated and will conclude when the subject leaves the post-anesthesia care unit. Acutely ill subjects may bypass recovery and receive post-anesthesia care in the Intensive Care Unit (ICU). The end of the perioperative phase will be defined as when the patient is "handed off" and report is given to the ICU or surgical floor staff.

Pre-Operative Assessments

Pre-Op Assessment information will be collected and documented in the subject's hospital chart and transcribed to the corresponding case report form (CRF). Pre-Op Assessments include:

- Type of prophylactic antibiotic administered
- Time of prophylactic antibiotic administration
- ASA Physical Status Classification System score
- Whether or not a warming strategy (device or other means) was initiated prior to surgery
- Randomization of subject to Standard of Care irrigation or IrriSept system

Intra Operative Assessments/Procedures

The first assessment is completed immediately after subject is admitted to the Operating Room (OR). OR Assessments include:

- Date and Time surgical procedure started
- Subjects randomized to the IrriSept system will receive irrigation specific to the IrriSept study kit IFU.
- Subjects randomized to Standard of Care will receive surgical wound irrigation at the discretion of the investigator.
- Use of the IrriSept system will be documented using the organization's standard medical and nursing records (e.g. the surgeons operative report, OR nursing record, anesthesia record, charge master) in subjects who are randomized to this treatment group.

Visit 1: Post-Surgical Assessments

The first assessments are completed immediately after the subject is admitted to the post-operative area. Post-Surgical Assessments include:

- Complete Procedure related questions
    - Location of surgical site incision
    - If drains were used during the procedure and the location(s)
    - If the subject experienced hypothermia during the procedure
    - Type of surgical skin preparation used during the procedure
    - Type of skin closure used during the procedure
    - Confirmation the surgery resulted in primary closure
- Complete remaining appropriate assessment scales
    - Primary injury notation and score *(complete appropriate/applicable scale*)*:
        - Blunt Trauma Score*, or
        - Penetrating Abdominal Trauma Index (PATI)*, or
        - Acute Abdomen Surgery Index*

Other Instructions

The following activities are also required to be recorded, per incident, on study specific logs in the CRF and/or documented in source:

- Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs) and Unanticipated Serious Adverse Device Effects (USADEs)
- Dispensing and accountability of the investigational device kits
- Recording of Protocol Deviations

Visit 2: End of Study

All study subjects will be scheduled to attend Visit 2, which is 30-days post index procedure (+/-3 days) visit. If a subject is not able to attend Visit 2, a designated research staff member may conduct as many assessments as possible, by telephone, and complete the CRF as appropriate. If a subject was seen for a Standard of Care (SoC) follow-up visit prior to the study specific Visit 2, and is not able to attend the Visit 2, data collected at the SoC visit should be referenced during the Visit 2 phone call and on the Visit 2 CRF.

If the subject has expired prior to Visit 2, the site must complete as much of the CRF as possible.

Subjects who withdraw from the study prior to Visit 2 will be considered non-evaluable and will not be followed beyond the point of withdrawal or termination from the trial. Evaluable subjects completing the trial will not be followed beyond 30 days for study purposes.

Assessments include:

- Subject status
- Documentation of any additional hospital admissions and surgeries
- Assessment of current Surgical Site condition
- Documentation of Surgical Site Infection (SSI)
- Recording of cultures, if SSI documented
- Documentation of any Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effects (ADEs), Serious Adverse Device Effects (SADEs) and Unanticipated Serious Adverse Device Effects (USADEs)
- Documentation of all Antibiotic Concomitant Medications used post-operatively through Visit 2
- Recording of Protocol Deviations

Table 3: A schematic of all study procedures

IRR-CT-901-2013-01 Schedule of Events	*SCHEDULE OF EVENTS*			
	Visit 1			Visit 2 / End Of Study 30-DAYS POST PROCEDURE
	SCREENING PHASE	PERI-OPERATIVE PHASE	POST SURGICAL PHASE / ET	
Informed Consent/Assent (Subject/Surrogate/LAR)	X		X	
Demographics	X			
Inclusion/Exclusion Criteria Review	X	X	X	
Record Surgical Risk Factors	X			
Record Present on Admission Status	X			
Primary Injury for Penetrating Abdominal Trauma, *if applicable*			X	
Primary Injury for Blunt Trauma, *if applicable*			X	
Primary Injury for Acute Abdomen Surgery, *if applicable*	X		X	
Complete Abbreviated Injury Score (AIS)	X			
Complete Glasgow Coma Scale (GCS)	X			
Record Lab Results (serum and cultures) *if applicable*	X			
Record ASA Physical Status Classification System Score		X		
Subject Randomization, Study Drug Dispensing and Compliance		X		
Record Perioperative assessments		X		
Assess Presence of Surgical Site Infection (SSI)				X
Record SSI Risk Factors				X
Record Study Adverse Events and Serious Adverse Events	X	X	X	X
Record and Report Study Adverse Device Effect, Serious Adverse Device Effect, and Unanticipated Serious Adverse Device Effect (USADEs)		X	X	X

Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effect (ADEs), Serious Adverse Device Effect (SADEs), and Unanticipated Serious Adverse Device Effect (USADEs)

In accordance with ICH/GCP reporting guidelines and ISO/DIS 14155 draft standard, Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Device Effect (ADEs), Serious Adverse Device Effect (SADEs), and Unanticipated Serious Adverse Device Effect (USADEs) will be collected and recorded throughout the duration of the trial. The investigator and facility should report all AEs, SAEs, which <u>are not device attributed</u> in line with facilities internal adverse event reporting procedures.

The investigator *should not* report device attributed events without prior consultation with the study's Medical Monitor. The investigator is also responsible for ensuring that all AEs and SAEs are recorded on the Adverse Event Log and all reportable ADEs (ADEs, SADEs, USADEs) are recorded and reported to the Sponsor in accordance with instructions in this section.

Device attributed adverse events, device attributed serious adverse events and device attributed unexpected adverse events will be reported by the Sponsor of the clinical trial in line with current FDA regulatory requirements.

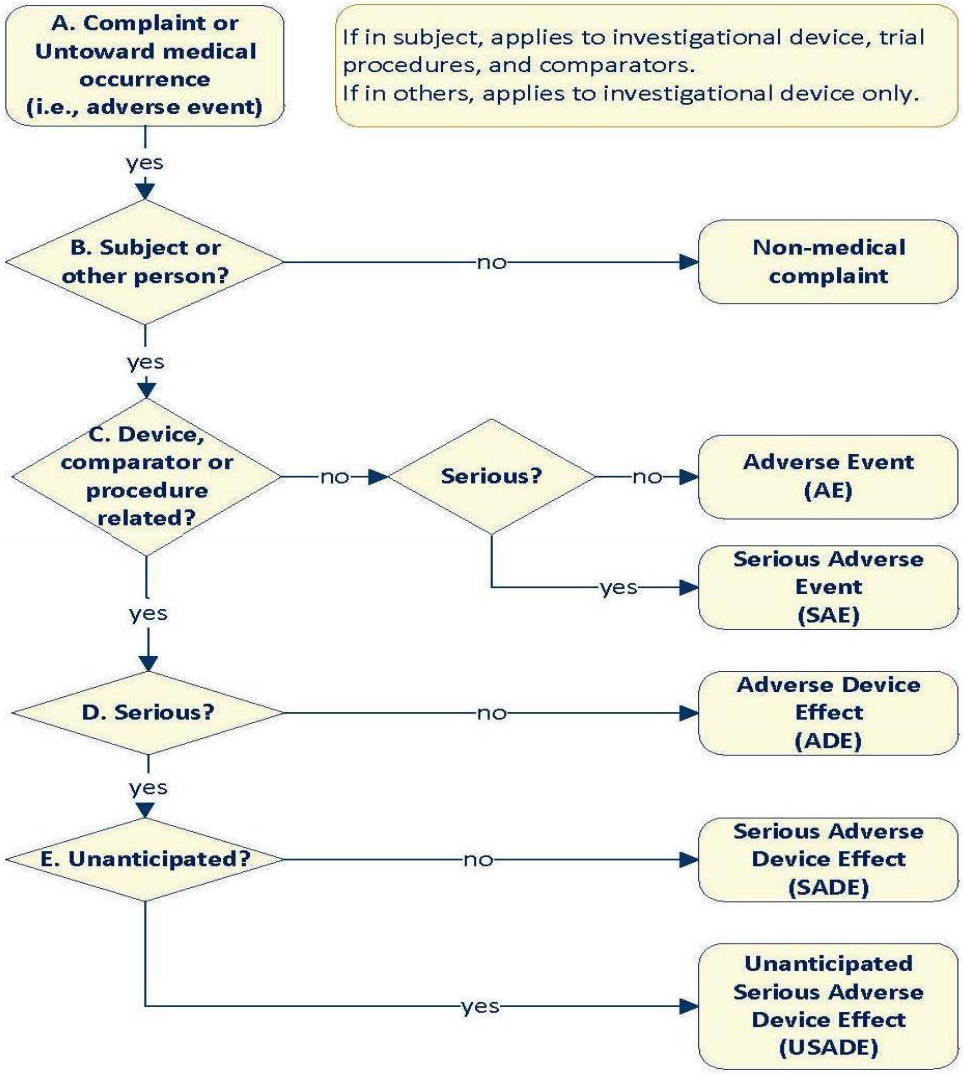
Definitions for safety reporting purposes in this trial are as follows:

- **Adverse Event:** Any untoward medical occurrence in a subject or clinical investigation which does not necessarily have a causal relationship with the medical device under investigation.
- **Serious Adverse Event:** An adverse event that results in one of the following outcomes: requires hospitalization; prolongs hospitalization; is life-threatening; results in congenital anomaly/birth defect; results in death.

- **Adverse Device Effect:** An adverse event that results from the presence or performance of the device or any component of the system.
- **Serious Adverse Device Effect:** 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; results in death.
- **Serious Unexpected Device Effect:** 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.

The Decision Tree in Figure 1 below is an adaptation of Annex F of the 2009 ISO/DIS draft standard and can be used to differentiate the adverse events for this trial. Detailed information as to how to this decision tree will be used and how adverse events will be reported can be found in the study reference binder.

Figure 1. Decision Tree for Classification of Adverse Events [21]



Reporting of Adverse Events

Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs) begins as soon as a subject signs consent. Reporting of device related Adverse Events will begin at the Perioperative Phase (when the study device is employed). All subjects will be closely monitored and questioned regarding the occurrence of AEs. AEs must be documented on an AE Log and on the CRF as appropriate. If no AEs have been observed for a subject during the course of the study this must also be clearly indicated on the AE page of the CRF and documented in the subject's source documentation. SAEs must be additionally documented. For each AE or SAE, the following information will be recorded:

- Identified AE/SAE (e.g. erythema)
- Start/Stop Time and Date of AE/SAE
- Severity
- Action taken for the event
- Duration of AE/SAE
- Relationship to Study Product
- Outcome
- Level of Seriousness

All AEs and SAEs must be treated in accordance with established standards of medical care. In recording AEs and SAEs the diagnosis, if known, is preferred rather than a listing of signs and symptoms. The onset or start of the AE/SAE should be the time and date that the symptoms started medical condition/disease present prior to the subject starting the study and that has worsened during study participation. The onset or start time and date of AEs or SAEs secondary to the worsening of a pre-existing condition should be the time and date on which the condition was known to have worsened.

Methods and Timing for Capturing and Assessing Safety Parameters

For each AE, including SAEs, and ADE, including SADE and USADE ("Adverse Event") the investigator will make assessment of seriousness, severity, and causality.

Adverse Event Documentation
Investigators will seek information on adverse events at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's source document and on the Adverse Event Log.

Assessment of Causality of Adverse Events
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 product, indicating a "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study product
- Course of the event, considering especially the effects of anesthesia and surgery
- Known association of the event with the study product or with similar treatments
- 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

Procedures for Recording Adverse Events
Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event CRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event CRF.

Adverse Events Occurring Secondary to Other Events
In general, 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 on the Adverse Event CRF.

Persistent or Recurrent Adverse Events
A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event CRF. The initial severity of the events should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event CRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence should be recorded separately on the Adverse Event CRF.

Abnormal Vital Signs
Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an AE if it meets any of the following criteria:

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

It is the investigator's responsibility to review all vital sign findings. **Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.**

Deaths
All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study product, must be recorded on the Adverse Event CRF and immediately reported to the Sponsor.

Death should be considered an outcome and not a distinct event. The event or condition or condition that contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event 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.

Preexisting Medical Conditions
A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the CRF.

Immediate Reporting Requirements from Investigator to Sponsor

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately using the toll free number **+1.844.477.4778** and in writing using the ADE Report Form via email EventReport@irrisept.com or fax using the toll free number **+1 844. 325-0440, under no circumstance** should the reporting take place **more than 18 hours** after the investigator learns of the event. All device attributed events will require review and discussion with the Investigator and Medical Monitor.

The following is a list of events that the investigator must report to the Sponsor **within 18 hours** after learning of the event, regardless of relationship to study product:

- ADEs

- SADEs
- USADEs

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 18 hours after becoming aware of the information). New significant information includes the following:

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Addition narrative information on the clinical course of the event

Investigators must comply with local requirements for reporting AEs and SAEs to the local health authority and IRB/EC.

Follow Up of Patients After Adverse Events

Investigator Follow-Up
The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed to be stable by the investigator, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered to be related to study product or trial related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event CRF and in the patient's medical record to facilitate source data verification. Ongoing AEs and SAEs at study conclusion will be noted as such on the AE log and signed by the investigator.

Sponsor Follow-Up
For ADEs, the Sponsor or designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultants reports, autopsy results) in order to perform an independent medical assessment of the reported case.

Direct Access to Source Data/Documents

The investigators and institution(s) involved in this study will permit direct access to study-related documents, subject charts, medical records, and/or the "ghost" equivalent for the purposes of study monitoring. This includes, but is not limited to subject source documents, regulatory inspections, and all other documents and/or processes that pertain to ICH/GCP study conduct and compliance.

Criteria For Removal From The Study

If, at any time, a subject develops or meets any of the exclusionary criteria, the subject will be removed from the study and receive the Standard of Care as prescribed by the primary investigator or designee.

If, at any time, the investigator determines the subject is no longer appropriate for study treatment or suitable for participation in the research trial, the subject will be removed from the study and receive the Standard of Care as prescribed by the primary investigator or designee.

Study Monitoring:

Prior to study start, IrriMax Corporation representatives will visit the investigator and facility to review the protocol and procedures to be followed for the IRR-CT-901-2013-01 study and confirm the facility's ability to conduct the study. This visit is known as the Site Selection Visit (SSV). Due to timing or confidence in the ability of an investigator and facility, the SSV may be combined with the SIV. Monitoring visits will be performed in relationship to site recruitment rates. The frequency of monitoring will coincide with recruitment rates, as

defined in the monitoring plan, in order to confirm continuing compliance with regulatory standards, GCP, and protocol requirements.

The sponsor will designate a study monitor, or the study monitor of the designated CRO, will maintain contact with the investigator and designated staff by telephone, and/or letter, and/or email between visits. Monitoring visits to the investigational site will be conducted by the assigned monitor(s). Frequency will be contingent upon enrollment. The investigator will allow the study monitor to inspect the clinical facilities. The eCRF and subject's corresponding source documentation are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with federal regulations. All records at the investigational site are subject to inspection by health authorities including the FDA. In accordance with International Conference on Harmonisation (ICH) E6 Section 6.10, source documents include, but are not limited to the following:

- Study specific source documentation
- Copies or transcribed health provider notes, certified for accuracy after production
- Recorded data from automated instruments such as (ECGs, rhythm strips, electroencephalograms (EEGs), pulmonary function tests, etc.)
- Records of telephone contacts
- Evaluations checklists
- Study Product distribution and accountability logs maintained by study personnel
- Correspondence between physicians or memoranda to IRBs/IECs regarding any subject's treatment

Statistical Methodology:

Endpoints

Efficacy

Primary

The primary efficacy endpoint is the rate of SSI observed within 30 days from the date of index operation.

Secondary

The secondary efficacy endpoints will include the following;

- The length of stay in the hospital
- Rate of readmission to the hospital, within 30 days from the date of the index operation
- Estimated costs of the index hospitalization

Exploratory Endpoints

The following outcomes will be reviewed as exploratory endpoints:

- Superficial surgical site infection (SSI)
- Deep surgical site infection (SSI)
- Organ/space surgical site infection (SSI)
- Ventilator associated pneumonia (VAP)
- Catheter associated urinary tract infection (CAUTI)
- Central line associated blood stream infection (CLABSI)
- Deep vein thrombosis (DVT)
- Pulmonary embolus (PE)
- Acute cardiac event

- Clostridium difficile (C-diff) infection
- MRSA infection
- Mortality

Safety

The safety of the IrriSept irrigation unit will be assessed through the clinical review and analysis of adverse events.

Randomization

Subjects who meet all inclusion and exclusion criteria will be centrally randomized in the OR in a 1:1 ratio to either the study product group or the control group, in accordance with a computer-generated block randomization schedule prepared by a non-study statistician. A unique randomization number and associated treatment assignment will be made using an interactive web-based response system (IWRS). Randomization will be stratified by center with no center allowed to enroll more than 120 subjects.

Statistical Methods

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. A separate Statistical Analysis Plan (SAP) with further details than presented here will be finalized prior to first patient enrolled to minimize any bias, as the study is non-blinded.

Power and Sample Size

The determination of sample size for this study is based on the primary objective to demonstrate the superiority of the IrriSept irrigation unit versus conventional standard of care in patients who undergo open abdominal laparotomy for abdominal trauma or acute surgical abdomen within 36 hours of initial presentation to their healthcare organization. The primary endpoint is the rate of SSI observed within 30 days (+/- 3 days) from the date of the index operation.

Based on historical data, it is assumed that the rate of SSI within the standard of care group will be ≥ 20%. A total of 600 patients (300 per group) will provide ≥ 90% power to demonstrate a reduction in the rate of SSI, up to 50%, assuming a control group rate for SSI of ≥ 20%, based on a two-sided Chi-square test with a 5% significance level. The following table shows the power achieved under various combinations of control group SSI rates and relative treatment differences.

Table 2.1: Power associated with a total sample size of 600 (n=300/group), based on a two-sided Chi-square test with a 5% significance level.

Control Group SSI Rate	Relative Treatment Difference (IrriSept/Control)		
	50% Reduction	40% Reduction	30% Reduction
15%	83%	62%	38%
20%	93%	76%	50%
25%	98%	87%	61%

It is anticipated that approximately 1100 patients will be screened, 650 patients will be enrolled, to obtain 600 evaluable patients, based on a non-evaluable rate of approximately 5%. All calculations were carried out in SAS version 9.2 using the comparison for two independent proportions procedure in PROC POWER.

Analysis Populations

Intention-to Treat (ITT)

The intention-to-treat population will be defined as all randomized subjects. Subjects will be assigned to a group based on the group they were randomized to.

Per-Protocol Population (PP)
Within the ITT population, subjects will be considered evaluable if they completed the 30 day follow up visit. Subjects who are withdrawn from the study prior to the 30 day follow up will be designated “non-evaluable” and excluded from the PP population.

Safety Analysis Set (SAS)

The safety analysis set will consist of all randomized subjects who underwent an emergency operation. The safety analysis set will be used for all safety analyses. Subjects will be assigned to a group based on the actual procedure received.

Efficacy Analyses

Primary Endpoint

For the primary endpoint, the number and proportion of patients with a SSI observed within 30 days from the date of emergency operation will be summarized by treatment group, along with the difference and 95% confidence interval for the difference (based on the Wald method). If a patient is missing their end of study assessment, or if they died prior to the end of study assessment, they will be classified as having met the primary endpoint of a SSI. A comparison between treatment groups will be made using the Cochran-Mantel-Haenszal test, stratified by site. The two-sided p-value, the adjusted relative risk (**IrriSept/Control**) and 95% confidence interval of the relative risk (based on the Wald method) will be reported. The study will be deemed successful if the two-sided p-value for the end of study treatment difference is < 5%.

It is anticipated that treatment groups will be well balanced with respect to baseline and demographic characteristics as well as risk factors for SSI, however if there are imbalances these will be accounted for in a supportive analysis using logistic regression. In these analyses, a logistic regression model with treatment as a fixed categorical variable and key baseline/demographic variables that are imbalanced will be included in the model to obtain adjusted estimates of the treatment effect in the form of odds ratios with two-sided 95% confidence intervals. Identification of variables to include will be based on comparisons between the two groups using appropriate two-sided tests based on the underlying distribution of the data. Those variables that are found to be significant ($p < 0.05$) will be included in the model.

Secondary Endpoints

The rate of readmission within 30 days from the date of the abdominal surgical procedure will be analyzed using the same methods as described for the primary endpoint.

The length of stay in the hospital will be calculated as the difference between the date of discharge and the date of admission, plus 1 day. Length of stay will be summarized by treatment group using descriptive statistics. As length of stay data tends to be highly skewed, a comparison of the LOS between the two treatment groups will be made by modeling the log LOS using a mixed effect model with a fixed effect term for treatment and a random component for center. This means and 95% confidence intervals for the difference between treatment groups will be back transformed and presented along with the two-sided p-value from a two-sample t-test.

An additional analysis will seek to define risk-adjusted length of stay outliers and whether there are observed differences between the two study populations. Using the post-operative length of stay as the dependent variable, a linear model will be used by employing those patients in the study who had no complications identified through the entire 30 day postoperative period. Again, hospital variables will be used. The observed length of stay for all patients will then be compared to the expected length of stay from the model to determine

excess lengths of stay in the two groups of patients. A moving average control chart will then be used by methods previously published to identify length of stay outliers based upon the prediction model within each hospital.[22-24] For each hospital, the total predicted length of stay will be set equal to the total observed length of stay in the control chart computation. The 2-σ, 2.5-σ, and 3-σ outliers by this method will identify the worst complications and whether there are differences in occurrences between the two treatment groups. A summary of the number and proportion of outliers will be presented by treatment group.

To assess cost of care differences between the two study populations, the UB-04 will be used to provide the total hospital charges for each study subject. These charges will be converted to cost estimates by using the hospital all-payer cost-to-charge ratio.[25] Hospital cost for all patients in the trial without complications will be used to define the uncomplicated risk-adjusted cost of hospitalization for this study cohort. Hospital cost will be the dependent variable and stepwise forward regression will be used to define statistically significant independent variables. Hospital variables will be used. The determination of excess costs of care will then be determined at the hospital level. Total predicted costs will be set equal to total observed costs, and excess costs will be determined by subtracting (observed) – (predicted) for all patients. These cost excesses will then be summarized by treatment group using descriptive statistics, and a comparison between groups made using the Wilcoxon Rank Sum test.

Exploratory Analyses

Univariate assessment of categorical risk factors and of continuous risk factors will be assessed to identify whether differences exist between the two populations of patients in the frequency of independent variables following patient randomization. Risk factors with $P<0.05$ on univariate analysis will then be used to create a forward stepwise logistic regression model to predict SSI. Hospital dummy variables will be employed to remove hospital effects. Logistic coefficients will be defined for the clinical variables including the use of the IrriSept irrigation system. Odds ratios and confidence intervals will be established to evaluate statistical significance, or lack thereof, of the IrriSept system. An additional benefit of this modeling will be the development of risk equations that combine administrative, clinical, and laboratory data into the prediction of SSI in this population of patients.

Multiplicity

As there is a single primary endpoint, and no formal unblinded interim analyses that will utilize the primary endpoint to modify the trial, no adjustment for multiplicity is planned. No adjustment for multiplicity is planned for the analysis of secondary endpoints

Sub-groups

To determine whether the treatment effect is consistent across various subgroups, the estimate of the odds ratio (and 95% CI) for the primary endpoint will be estimated and displayed using forest plots for the following sub-groups:

- Age category (≤65 vs. >65 years)
- Gender (female, male)
- Emergency laparotomy for trauma exclusively vs. laparotomy for emergency general surgery

For the analysis of each sub-group, a logistic regression model for the primary endpoint will be used, with terms for treatment group, the sub-group and the sub-group by treatment interaction. The odds ratios and 95% CI's within each sub-group category will be reported, along with the p-value for the interaction term.

Safety Analyses

All safety analyses will be presented using the safety analysis set. No formal hypothesis testing will be conducted.

Adverse Events

Adverse events will be coded using MedDRA (Version 17.x). All AEs that occur after the start of surgery (cut time) will be summarized using frequency counts and percentages. Summaries will be presented by treatment

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 (mild, moderate, severe, or life threatening)
- By relationship to study product (potential relationship to study product or unlikely/no relationship to study product) according to the mapping scheme below:
    - Potentially related: will include all AEs with a relationship rating of “definite”, “probably” or “possibly.”
    - Unlikely/not related: will include all AEs with a relationship rating of “unlikely” or “unrelated.”

Unless otherwise specified, at each level of patient summarization in reporting the incidence of the AEs, a subject will be counted once if the subject reported one or more events. If more than one occurrence of an event is reported, the event of the worst severity or the worst-case relationship assessment will be summarized.

AEs leading to premature discontinuation and serious AEs (SAEs) will also be summarized by treatment group and relationship. AEs leading to premature discontinuation will be defined as any AE with an action taken equal to “permanently discontinued.”

Demographics and Baseline Summaries

Demographic variables (e.g., age, gender, race, ethnicity) and baseline characteristics (e.g., medical history, PATI, AIS and ASA scores, adherence to SCIP prophylactic antibiotic-specific guidelines, surgical skin preparation used, shock, (systolic BP < 90 mm Hg), intubation, active infection, transfusion of blood/blood products, primary injury in trauma or primary organ(s) in the acute abdomen and intraoperative risk factors), will be summarized by treatment group. The comparability of the treatment groups for relevant demographic and baseline characteristics will be assessed by descriptive statistics. No statistical hypothesis tests will be performed. For continuous data, summaries will include the number of observations, mean, standard deviation, median, 25th and 75th quartiles, minimum and maximum values. For categorical data, frequency counts and percentages will be reported.

Concomitant Medications/Antibiotics

Concomitant medications are medications that are taken at any time after enrollment. Concomitant medications will be coded using the WHO Drug Dictionary and summarized by drug class and preferred term for each treatment group. The summaries will present the number and percentage of patients using each medication in each treatment group. Patients may have more than one medication per preferred term. At each level of summarization, a patient is counted once if he/she reported one or more medications at that level.

Disposition

A clear accounting of disposition including, the number and percentage of patients screened, randomized, and completed, as well as the primary reasons for screen failure and reasons for early discontinuation of therapy will be reported overall and by treatment group.

Subjects who withdraw from the study (either voluntarily or involuntarily) or do not complete the required End of Study visit will be designated as “non-evaluable.” Any data collected on these subjects will not be used in the final efficacy analysis. For those who withdraw consent, screen fail information will be collected. For those subjects lost to follow-up will be noted in the database as early termination. Subjects who are classified as “non-evaluable” will be replaced to the extent required to enroll 600 evaluable subjects.

Interim Analyses

An interim analysis is planned when approximately 33% and 66% of the total number of patients has been enrolled. The purpose of these interim analyses is to monitor safety and study conduct. At the second interim analysis, the sample size will be re-estimated using the conditional power approach.

All persons involved in the conduct and analysis of the study will remain blinded to the results of the interim analysis.

Test Material Compliance and Accountability:

An initial supply of Study Product will be supplied to the study site, by IrriMax Corporation, at least one (1) week prior to study commencement.

Procedures and instructions for Study Product dispensing and accountability will be provided in the Investigator Site Binder.

Investigator Site Responsibilities:

Study site personnel involved in the conduct of IRR-CT-901-2013-01 must read and demonstrate understanding of the protocol, source documents, case report forms and all other documentation required to enroll qualified subjects and complete the study documentation in an agreed timeframe.

Additionally, study site personnel who agree to conduct the study must complete required training (Site Initiation Visit) and agree to receive and properly account for study materials, including but not limited to:

- Study Product
- Study Materials

The study product and materials must remain in the study environment at all times during study conduct.

Study personnel are responsible for ensuring that documentation forms are properly completed. Lastly, study personnel must understand the study process for reporting and documenting Adverse Events (AEs) on the Adverse Event study log, to and on behalf of the sponsor as well as following any AE procedures in place at the facility.

Subjects' Responsibilities:

Subjects must agree to participate in the study as documented in the information contained in the ICF.

Subjects may discontinue their participation at any time during the study as per ICH GCP guidelines.

IrriMax Corporation Personnel Responsibilities:

IrriMax Corporation personnel will be on-site, when possible, to conduct a Site Initiation Visit to ensure study training of all study personnel.

Data monitoring will also be conducted by IrriMax staff or representative on-site. Frequency and total number of monitoring visits will be determined by recruitment rate and monitoring plan.

Appendices and other Study References:

Essential regulatory documents and other study-specific documents and forms will be provided to investigational sites in a comprehensive study reference binder.

Appendix I: Study Specific Instructions for Use (IFU)

References:

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APPENDIX I: Study Specific Instructions for Use (IFU)

TO BE RETAINED BY CIRCULATOR

Protocol: IRR-CT-901-2013-01
STUDY SPECIFIC INSTRUCTIONS FOR USE (IFU):

1. Twist off seal caps from IrriSept® Step 1 and IrriRinse® Step 2 bottles.
2. Remove IrriProbe® applicators from tray and attach to bottles.
3. **After initial incision and dissection to the fascia, and before opening the fascia,** suction the surgical wound bed thoroughly to prevent dilution of IrriSept.
4. Invert IrriSept Step 1, direct fluid into wound, squeezing firmly with both hands, ensuring coverage of all areas of the wound bed and filling the wound space.
5. **Allow solution to dwell for one (1) minute.**
6. Suction residual fluid from the wound bed.
7. Invert IrriRinse Step 2, direct fluid into wound, squeezing firmly with both hands, ensuring coverage of all areas of the wound bed and filling the wound space.
8. Suction residual fluid from the wound bed.
9. At completion of Step 1 and Step 2, discard used bottles and applicators.
10. Use normal saline irrigation for all work below the level of the fascia.
11. **Prior to final closure repeat previous steps with second kit (unit carton)** by twisting off seal caps from IrriSept Step 1 and IrriRinse Step 2 bottles.
12. Remove IrriProbe applicators from tray and attach to bottles.
13. **After fascia closure,** suction the surgical wound bed thoroughly to prevent dilution of IrriSept.
14. Invert IrriSept Step 1, squeeze firmly with both hands, direct fluid into wound, ensuring coverage of all areas of the wound bed and filling the wound space.
15. **Allow solution to dwell for one (1) minute.**
16. Suction residual fluid from the wound bed.
17. Invert IrriRinse Step 2, squeeze firmly with both hands, direct fluid into wound, ensuring coverage of all areas of the wound bed and filling the wound space.
18. Suction residual fluid from the wound bed.
19. At completion of irrigation, discard used bottles and applicators.