CLINICAL RESEARCH PROTOCOL

Treatment of Subcutaneous Abdominal Wound Healing Impairment after surgery without fascial dehiscence by Vacuum Assisted Closure™ (SAWHI–V.A.C.® Study) versus standard conventional wound therapy

SPONSOR

Private University of Witten/Herdecke gGmbH,
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Principal Coordinating Investigator
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GOOD CLINICAL PRACTICE (GCP) STATEMENT
This document is a protocol for a clinical research study involving human participants. This study is to be executed in accordance with all laws and regulatory standards governing the conduct of human clinical research in the jurisdiction in which the study is being performed.

ISO STATEMENT
This study was conducted in accordance with ISO 14155 and all applicable regulations, including the Declaration of Helsinki.

CONFLICT OF LAWS AND/OR GCP STANDARDS
In the event of a conflict between the rules, regulations, laws, and treaties of the United States and those of the international nation-state under whose jurisdiction any part of and/or all of the study is being performed, the more stringent of the 2 GCP standards shall be applied.

SIGNATURES

Name	Date	Signature
Dörthe Seidel, MD Principal Coordinating Investigator Steering Committee	17.9.2013	
Prof. Dr. Prof. h.c. E. A. Neugebauer Steering Committee	4.11.2013	
Prof. Dr. Rolf Lefering Statistician Steering Committee	17. 9. 2013	
Alex Hartnagel, M.Sc. KCI Clinical Research Manager Steering Committee	02 DEC 2013	

Signature of Clinical Investigator

I agree to adhere to the instructions and procedures described in the following study protocol and to ensure this study is conducted in accordance with the following directives and guidelines:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data as transposed into national law
- EU Medical Device Directive 93/42/EC as amended by Directive 2007/47/EC as amended into national law
- ISO 14155 and MEDDEV 2.7/3 related to AE definitions
- In the spirit of the Declaration of Helsinki concerning medical research in humans (latest edition)

Date	Name in printing letters	Signature

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
CCI	Coordinating Clinical Investigator
CE	European Conformity
CI	Clinical Investigator
cm	Centimeter
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
DCF	Data Clarification Form
EC	Ethics Committee
EOT	End of Treatment
EOMT	End of Maximum Treatment Time
EU	European Union
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IDMC	Independent Data Monitoring Committee
IQWiG	Institute for Quality and Efficiency in Health Care
ISO	International Organization for Standardization
ITT	Intent to Treat
KCI	Kinetic Concepts, Incorporated
KCI USA	Kinetic Concepts, Incorporated, United States of America
MD	Medical Doctor
mm Hg	Millimeters of Mercury
NPWT	Negative Pressure Wound Therapy
PCI	Principal Coordinating Investigator
PP	Per Protocol
PRO	Patient Reported Outcome
PTT	Partial Thromboplastin Time
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
RCT	Randomized Controlled Trial
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCWT	Standard Conventional Wound Therapy
SF-36®	SF-36v2™ Health Survey
UADE	Unanticipated Adverse Device Effect
V.A.C.	Vacuum Assisted Closure
ZKSI	Zentrum für Klinische Studien und Innovation (Center for Clinical Trials and Innovation)

SYNOPSIS

Study Title	**Treatment of Subcutaneous Abdominal Wound Healing Impairment after surgery without fascial dehiscence by Vacuum Assisted Closure™ (SAWHI–V.A.C.® Study) versus standard conventional wound therapy**
Investigators and Study Sites	This multicenter study will be conducted in hospital departments with the required manpower as well as the structural and scientific qualifications. Study therapy will be started in ambulatory care or in-hospital and may be continued in ambulatory care. Study sites and investigators will be listed in a separate document.
Classification and phase of trial	Examination of the clinical application of a CE-marked medical device (risk category 2 b);
Endpoints	Primary Endpoint Time (number of days) to achieve complete wound closure Verified by photo documentation and blinded, computer-based assessment as well as wound closure confirmation after 14 consecutive days (14 days -0 / + 3) Complete wound closure is defined as: ✓ 100% epithelialization ✓ No drainage from the wound ✓ No need for adjuvant therapy or dressing ✓ No presence of sutures Secondary Endpoints ▪ Incidence of confirmed and verified wound closure achieved after a maximum study observation / treatment period of 42 days (+ 14 days to observe sustained closure). ▪ Recurrence of wound opening after confirmed wound closure ▪ Reduction of wound size over time ➢ Reduction in wound volume over time ➢ Reduction in wound surface area over time Safety Endpoints Incidence of serious adverse events including mortality of any cause (within 132 days from the time of initiation of therapy) Incidence of wound-related adverse events and adverse device events (within the study treatment period of maximum 42 days) Patient Reported Outcome (PRO) Quality of Life (QoL) (SF-36®) Pain Patient Satisfaction Health Economic Endpoints Direct medical resource use (diagnostics, medication, specific wound therapy, treatment and medical attendance, reinterventions, rehospitalisations) Indirect resource use (restrictions of productivity besides absence from the workplace (activities of daily living); non-productive time for gainfully employed)

Design	Multicentre, multinational, randomized controlled, observer-blinded clinical superiority trial
Number of Study Participants	Adaptive trial design with a maximum number of 552 participants to be analysed with interim analysis after 250 patients
Diagnosis	Primary closed abdominal wound with wound healing disorder in the postoperative course after surgical intervention without fascial dehiscence manifested as one or more of the following: ▪ a wound with spontaneous dehiscence ▪ a wound that requires an active reopening of the suture by the treating physician ▪ a wound that cannot be closed by primary intention and requires further treatment to achieve permanent closure
Inclusion Criteria	➢ Written informed consent ➢ Post-surgical subcutaneous abdominal wound healing impairment ➢ Minimum wound size eligible for the application of the randomized treatment ➢ Inclusion, randomization, adequate wound pre-treatment (Debridement) and start of therapy within 48 hours after reopening of the wound, diagnosis for nonclosable wound or in case of spontaneous wound dehiscence
Exclusion Criteria	➢ Age < 18 years ➢ Noncompliance with study procedures, visit schedule or follow up ➢ Pregnancy ➢ Present or nonclosable defect of the abdominal fascia ➢ Any pre-existing or ongoing organ system failure, that cannot be stabilized or solved by appropriate medical treatment ➢ Necrotic tissue with eschar present ➢ Non-enteric and unexplored fistulas ➢ Malignancy of the wound ➢ Use of any other device based on the principle of negative pressure wound therapy on the study wound within ≤ 8 days prior to screening ➢ Competing therapies or procedures ➢ Simultaneous participation in competing clinical trials
Intervention	Vacuum Assisted Closure® (V.A.C.®) Therapy
Control	Standard conventional wound therapy (SCWT) according to institutional clinical standards
Study Treatment	All patients at the time point of randomisation / inclusion or during the active treatment period of 42 days that are eligible for outpatient care and have reasonable access to it, have to be transferred to outpatient care.
Duration of Treatment	Up to 42 days (end of maximum treatment time (EOMT))
Follow up	General follow-up at Day 132 Additional follow up at Day 87 for study participants with nonclosed wounds at Day 42

Evaluation Criteria	Effectiveness: The primary endpoint is defined as time to achieve complete wound closure (in study participants where wound closure was confirmed as sustained for a minimum of 14 days). Safety: Wound-related AE and adverse device events within the study treatment period of 42 days, and SAE including mortality of any cause within 132 days after randomisation.
Statistics	The primary efficacy parameter, time to complete wound closure, will be compared between the two treatment groups using a log rank test. In addition, as a supportive analysis, a Cox proportional hazards regression will also be used in order to assess if there is a difference between treatment groups while accounting for the effect of study center and wound size (appropriate baseline and medical history parameters will also be considered). The secondary efficacy parameter, incidence of complete wound closure, will be analyzed using a Chi-square test comparing the two treatment groups. As a supportive statistical analysis, logistic regression will also be implemented with factors in to model to include treatment, study center, and wound size (appropriate baseline and medical history parameters will also be considered). Reduction in wound area (cm^2) and wound volume (cm^3) will be assessed using a 3-factor (treatment group, study center, and time) analysis of covariance with baseline wound area (or volume) recorded at baseline to be used as a covariate. One planned interim analysis will be performed when 250 study participants have completed the first phase of the study. The interim analysis will validate the assumptions made for the study sample size calculation and will determine if sample size re-estimation is warranted.
Ethics	This study will be conducted in accordance with Good Clinical Practice and applicable regulations.
Principal Coordinating Investigator	Dörthe Seidel, MD Centre for Clinical Trials and Innovation (ZKSI) IFOM - Institute for Research in Operative Medicine Faculty of Health Private University Witten/Herdecke gGmbH Ostmerheimer Str. 200 , Building 38 51109 Cologne, Germany Tel.: +49 (0)221 9895726 Email: doerthe.seidel@uni-wh.de
Sponsor	Private University of Witten/Herdecke gGmbH Alfred-Herrhausen-Str. 50 58448 Witten, Germany
Statistician	Prof. Dr. R. Lefering Institute for Research in Operative Medicine University of Witten/Herdecke Tel.: +49 (0)221 9895716 Email: rolf.lefering@uni-wh.de

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsorship

The Institute for Research in Operative Medicine (IFOM) as part of the Private University of Witten/Herdecke gGmbH is initiating the clinical investigation, whereas the Private University of Witten/Herdecke assumes responsibility as Sponsor. The clinical trial is funded by KCI. IFOM, acting for the University of Witten/Herdecke gGmbH, oversees implementation of the study and is responsible for data analysis, report, and publication.

1.2 Investigators

Principal Coordinating Investigator (PCI)

The Principal Coordinating Investigator (PCI) has responsibility for the overall conduct of the clinical trial. The PCI is responsible for controlling the technical direction and academic quality of the project, and will ensure that the trial is carried out in compliance with the terms, conditions, and policies of the Sponsor.

The Principal Coordinating Investigator (PCI) of this trial is:
Dörthe Seidel, MD
Centre for Clinical Trials and Innovation
Institute for Research in Operative Medicine
Faculty of Health
University of Witten/Herdecke
Ostmerheimer Str. 200, Building 38
51109 Cologne, Germany

Clinical Investigator (CI)

The Clinical Investigator (CI) is defined as the responsible lead investigator at each study site. Clinical Investigators will be listed on a separate document.

Subinvestigator (SI)

The Subinvestigator is defined as any other physician involved in the conduct of the Clinical Trial at the respective trial site.

1.3 Statistician

The statistician will conduct all analyses mentioned in chapter 9 including the interim analysis and safety analysis.

The statistician of this trial is:
Prof. Dr. Rolf Lefering
Institute for Research in Operative Medicine
Faculty of Health
University of Witten/Herdecke
Ostmerheimer Str. 200, Building 38
51109 Cologne, Germany

1.4 Steering Committee

Responsibilities

The Steering Committee‘s primary responsibility is to ensure that the study is conducted in accordance with the protocol, all pertinent countries’ laws; and regulatory authorities, industry, institutional and corporate-related laws, regulations, guidance, and standard operating procedures. The Steering Committee must ensure operational excellence and the delivery of quality data as well as its publication in an unbiased manner in an appropriate peer-reviewed journal.

Membership

The Steering Committee will be composed of the following individuals:

Edmund A. Neugebauer
Institute for Research in Operative Medicine (IFOM)
Private University of Witten/Herdecke gGmbH

Dörthe Seidel
Institute for Research in Operative Medicine (IFOM)
Private University of Witten/Herdecke gGmbH

Rolf Lefering

Institute for Research in Operative Medicine (IFOM)
Private University of Witten/Herdecke gGmbH

Alex Hartnagel
KCI Europe Holding B.V.

1.5 Independent Data Monitoring Committee

To ensure data integrity and unbiased clinical decisions, IFOM and KCI will convene an Independent Data Monitoring Committee (IDMC). An IDMC is an independent group of relevant experts, external to a study that reviews and evaluates accumulating study data from an ongoing research study. The structure and voting membership of the IDMC ensures that critical decisions made while the results of a study are still blinded will be free of conflicts of interest. Membership includes individuals with pertinent clinical, scientific, and statistical expertise in the therapeutic area. The IDMC members will develop a charter that will detail the functions the IDMC will be asked to perform for the study.

The IDMC will be independent of IFOM, KCI, PCI, regulatory agencies, Ethics Committees (ECs), CI, or Subinvestigators. IFOM and KCI will appoint an IDMC chair who may make recommendations for IDMC members and will give final approval of all members. The IDMC will assist in maintaining the quality of study conduct. Whenever possible, the IDMC will communicate directly with and receive data from IFOM's data management group. The IDMC will provide an endpoint assessment/adjudication function, which will involve reviewing important endpoints reported by CIs to determine whether the endpoints meet protocol-specified criteria.
Members of the IDMC will be designated by the Steering Committee. The IDMC is responsible for examining efficacy as well as participant-safety issues and is independent from the Steering Committee as well as from IFOM and KCI. The IDMC reviews the cumulative safety data for evidence of treatment harm and benefit; the IDMC will be supplied regularly with the tabulation of SAEs. A safety review will occur at every IDMC meeting. The IDMC may decide in the interest of healthcare to terminate the trial or a treatment arm of the trial before recruitment is finished – for instance, if an unacceptably high rate of AEs is seen in participants or if issues arise

that prevent successful completion of the study. Throughout the study, the IDMC will closely examine the incidence rates of SAEs.

Other than serving a review and oversight role, the IDMC will not be involved in the conduct of the trial. For this study, only blinded data will be provided to the IDMC.

2 BACKGROUND

2.1 The medical problem

Wound healing impairment after surgical procedures is a common problem of health care. The occurrence of wound healing impairment of the abdominal wall represents a multi-disciplinary, treatment, and cost-intensive problem of clinical life whether it is caused by infectious or non-infectious reasons. [1-3]

Only a few clinical trials have been conducted regarding the use of negative pressure wound therapy for subcutaneous abdominal wound healing impairment [4-6]; thus, a large randomized clinical trial that is able to make a statement concerning effectiveness and universal validity of this innovative therapy option is still missing.

2.2 Wound healing impairment after abdominal surgery

Complications associated with surgical incisions range from annoying to life threatening and can be more common and serious than those related to the primary surgical procedure. These complications include wound healing disorders caused by the surgical procedure itself, by patient-related factors, or both. (Table 1)

Table 1: Factors that affect surgical wound healing

Surgical factors	Patient-related factors	Other factors
Contamination status	Diabetes	Tissue perfusion
Pre-existing infection	Smoking	Normovolaemia / Hypovolaemia
Performed procedures	Poor nutrition	Perioperative Body Temperature
Skin preparation	Alcoholism	Pain
Site, duration and complexity of surgery	Chronic renal failure	etc.
Presence of suture or foreign body	Jaundice	
Suturing quality	Obesity	
Prophylactic antibiotics	Advanced age	
Haematoma	Poor physical condition	
Mechanical stress on wound	Medication	
	Previous radio-or chemotherapy	

These factors are typically interrelated, complex in nature, and often difficult to prevent or treat successfully.

The most common postoperative wound healing impairments are seroma or haematoma, necrosis of wound margins or adjacent soft tissue, and infections, all with potential to cause dehiscence of the primarily closed wound.

Wound dehiscence

Wound dehiscence in general signals the inability of a wound margin to adequately heal after surgical closure. After surgical wound dehiscence, a defect can extend from partial up to full thickness depending on the layers of the abdominal wall involved. According to which wound layers are dehisced, these wounds can be classified into incomplete (open skin, with fascia and peritoneal suture intact), complete (all layers involved), or inapparent (skin suture intact, dehiscence of fascia and peritoneal suture) wound dehiscence. After laparotomy, wounds are endangered by a massively expanded abdomen (atony of the bowel or ileus, mesenteric edema, ascites) and postoperative coughing. Wound infections, including abscesses, are one of the major causes of abdominal and other types of wound dehiscence.

Seroma or Hematoma

Seroma and haematoma involve an accumulation of lymph or blood, respectively, in a preformed cavity or resulting space. Additionally, subcutaneous bleeding (ecchymosis) can lead to haematoma if there is no possibility for drainage. The resulting pressure leads to poor perfusion and delayed wound healing. Furthermore, these fluids are an ideal matrix for bacterial colonization. Reasons for the development of seroma and haematoma are tissue damage, insufficient hemostasis, constrained blood clotting, coagulation disorders, antiplatelets and anticoagulants, loss of coagulation factors, cirrhosis of the liver, thrombocytopenia, or protein deficiency. Seroma are caused by lymphatic disruption after dissection, partial reabsorbed haematoma, and inflammation.

Clinically, these disorders present as pressure pain (ie, tenderness), tenseness, and redness. Often secretion extravasates from the wound; in some instances of haematoma, coloration of the wound area appears.

Necrosis of Wound Margins or Adjacent Soft Tissue

Necrosis is typically caused by diminished or absent perfusion of the related area, which usually originates from damage of a blood vessel or stasis within it. This can

be caused by contusion of tissue prior to or during surgery, use of electrocoagulation, unfavorable performance of incision, too heavy tension on wound clamps during surgery, or a suture placed too tightly. Pre-existing diseases with micro- and macroangiopathia, such as diabetes mellitus and arteriosclerosis, have been shown to play an important role in this condition. Even seroma and hematoma can lead to decreased perfusion of the affected areas within the wound and further enhance tissue necrosis.

Soft tissue necrosis that originates from surgical procedures or trauma is often limited to small areas or margins of the wound and can become healthy; it is most amenable to wound healing after debridement. In contrast, soft tissue necrosis caused by angiopathy represents a serious problem. Minimally perfused areas are spread diffusely and surrounded by hypoperfused or already necrotic tissue, resulting in delayed healing and increasing the risks of developing wound infection. Therefore, extensive soft tissue damage is a frequent reason for early infection after surgery. When tissue necrosis post-surgery occurs, there is a heightened danger for aerogenic bacterial colonization and subsequent tissue infection.

Wound Infections

The risk for wound infection depends on relative size of the incision, degree of contamination of the incision, reason and duration of surgery, nature of surgery (emergency or planned intervention), the use of perioperative antibiotics, and various patient-related risk factors, such as age, immunosuppression, malnutrition, hypalbuminemia, and obesity.

About two-thirds of surgical-site infections (SSIs) of the abdominal wall are superficial.[1] The other one-third is associated with deep tissue wound infections, including abscesses, which are most often associated with abdominal wound dehiscence.

The determination of SSI can be made following the criteria outlined in the CDC's guideline for prevention of surgical site infection. [7]

Clinically, if a wound is infected, wound secretions often appear around the third postoperative day, typically of predominantly serous or bloody serous character, accompanied by recurrent pain, redness, and tenderness in the wound area.

Postoperatively, early recognition and optimal treatment of these complications and wound-healing disorders may prevent major wound infection, more serious complications, and their sequelae.

2.3 Wound Closure after Surgical Wound-Healing Impairment

Surgical wounds may be closed by primary intention, delayed primary intention, or by secondary intention. (Table 2)

Table 2: Types of wound closure and their definition

Type of Healing	Definition
Primary Closure	Closure of a wound within hours of its creation
Secondary Closure	No formal wound closure; the wound closes spontaneously by contraction, granulation, and re-epithelialization
Delayed Primary Closure (Tertiary closure)	Surgical closing of a wound several days after the injury due to an inability to close the wound at the time of excision and debridement

Closure by primary intention

Surgical wounds are usually closed within hours of their creation by primary intention, where the wound edges are brought together (apposed) and then held in place by mechanical means (adhesive strips, staples, or sutures), allowing the wound time to heal and develop enough strength to withstand stress without support.

The goal of surgery is to achieve healing by such means with minimal oedema, no serous discharge or infection, without separation of the wound edges, and with minimal scar formation.

Closure by delayed primary intention (Tertiary closure)

If a wound is purposely left open after surgery, has to be reopened because of wound healing impairment, or dehisces spontaneously after primary closure was performed, this wound can be closed after interim treatment and promotion of secondary healing by delayed primary intent.

This method is often used after traumatic injury or dirty surgery. In cases of wound healing impairment, the technique of a delayed primary closure after reopening of the irritated wound is an option for achieving healing. A temporal, open-wound treatment provides time for optimal preparation of the wound bed and margins. An extensive debridement and thorough lavage of the wound to remove necrotic debris and clots are essential prior to closure of the wound.

Delayed primary closure, also known as tertiary wound closure, typically involves initial debridement of the wound for an extended period and subsequent formal closure by direct suturing (secondary suture) or by other closing techniques, after successfully apposing of the wound borders. Grafts and flaps also serve as alternative tertiary closure techniques to surgically close large, open abdominal wounds that are not amenable to direct suturing.

Closure by secondary intention

During wound closure by secondary intent, wound edges come together naturally by means of granulation and contraction. Typically, when open abdominal wounds are not amenable to either type of delayed primary closure, small and shallow, or are chronically infected, they are left to close by secondary intent. Secondary closure involves no formal wound closure; the wound closes spontaneously by contraction, granulation, and re-epithelialization.

2.4 Vacuum-assisted wound closure (V.A.C.®)

V.A.C.® is generally well tolerated and, with few contraindications or complications, is fast becoming a mainstay of current wound care.[8] V.A.C.® Therapy has been successfully integrated in the management of post-laparotomy wound dehiscence in patients with compromised wound healing and has been well documented in the peer-reviewed literature. In this setting, V.A.C.® Therapy has been shown to successfully provide wound stabilization, followed by accelerated healing and resulting in faster wound closure. Although there are reported uses of V.A.C.® Therapy in treating these wound types in the acute care setting, there is a consensus that there is insufficient clinical data based on the systematic evaluation of V.A.C.® Therapy for these wounds in the post-acute environment.

Healing of these types of wounds often extends beyond the initial hospitalization period and frequently requires further wound care treatment outside the hospital environment, either in home care or outpatient clinic settings. Therefore, it is important to understand the relative effect and benefit of using V.A.C.® Therapy versus standard conventional wound therapy (SCWT) in the treatment of these wounds across all relevant care settings.

Over 700 peer-reviewed articles (including 22 RCTs, 18 of which involved at least 1 endpoint associated with wound healing) provide a growing body of evidence regarding the clinical results and mechanisms of action of this integrated wound care system. The literature provides evidence with regards to V.A.C.® Therapy's effectiveness in diabetic foot wounds, chronic wounds such as pressure ulcers and lower extremity ulcers. Additionally to that V.A.C.® Therapy is used in the treatment of a variety of acute wounds, including abdominal wounds [9], surgical and dehisced wounds [9-11], grafts and flaps [12, 13], deep sternal wounds [14-16] and partial thickness burns [17, 18]. In a 2006 study, Yang et al showed that the use of V.A.C.® Therapy reduces healing time by 58% in patients with fasciotomy wounds for traumatic compartment syndrome (6.7 days vs. 16.1 days, $p<0.05$). In a 2000 study, Avery et al showed the use of V.A.C.® Therapy to manage split thickness skin grafts over forearm donor sites had a 100% graft uptake at 5 days. In a 2005 study, Sjogren et al showed that V.A.C.® Therapy when compared to conventional treatment, significantly reduced the 90-day mortality rate in patients with deep sternal wound infections from 15% mortality in the conventional treatment group to 0% mortality in the V.A.C.® Therapy group ($p<0.01$). In a 2005 study, Agarwal et al concluded that V.A.C.® Therapy is a safe and effective first-line therapy in the management of sternal wound infections due to its efficacy in reducing wound edema, ability to decrease time to definitive closure, and ability to reduce wound bacterial colony counts. In a 2006 study, Leininger et al demonstrated that U.S. military hospital infections decreased from 80% (anecdotal) to 0% (documented) as shown in a retrospective analysis of 88 patients when V.A.C.® Therapy was employed.

2.5 Recent History

When compared to SCWT, most of the published literature confirms the advantage of negative pressure wound therapy (NPWT), also called vacuum assisted wound

closure, but sufficient proof of effectiveness and efficacy is lacking [19, 20]. The Federal Joint Committee (G-BA) of the German Health Care System faced this situation by commissioning a report on effectiveness and efficacy of NPWT by the Institute for Quality and Efficiency in Health Care (IQWiG). The final IQWiG-Reports [21, 22] concluded that, in spite of some indications that NPWT may improve wound healing, the methodological quality of the so far performed trials is unsatisfactory and thus the body of evidence available is insufficient, more specifically in the post-acute care setting.

3 STUDY OBJECTIVES AND PURPOSE

3.1 Purpose

This RCT was designed to collect data that would address areas thought to have insufficient evidence. Moreover, this trial seeks to evaluate the use of V.A.C.® Therapy in the acute to post-acute environment, particularly because wound healing occurs across the continuum of care and often continues after a patient is released from hospital to homecare or other community-based care. Thus, there is a need to identify the outcomes and benefits of V.A.C.® Therapy when compared to SCWT, when used across these care settings.

This trial is designed to comply with all quality requirements of IQWiG and G-BA as well as other European authorities.

Wounds with healing impairment after abdominal surgery and intact fascia were chosen as the target study population because they are considered to be a fair representation of open wound types and also are frequently associated with the types of comorbidities observed with other types of open wounds.

3.2 Hypothesis

This study's hypothesis is that the use of the V.A.C.® Therapy System, when compared to SCWT in the management of post-surgical abdominal wound healing impairments with intact fascia, will result in a decrease in the time to achieve complete wound closure with confirmation after subsequent 14 days.

Using V.A.C.® Therapy is an effective and safe treatment option for hospitals as well as for outpatient care for treatment of subcutaneous abdominal wounds with wound healing impairment in the postoperative course.

We postulate that V.A.C.® Therapy will demonstrate statistically significant clinical and health economics benefits when compared to SCWT in the management of human participants with postoperative dehisced abdominal wounds.

3.3 Primary and secondary objectives

The primary objective of this multicenter, parallel design, prospective, randomized clinical trial is to compare the clinical, safety, and economic outcomes of V.A.C.®

Therapy and SCWT in postsurgical abdominal wound healing impairments without fascial dehiscence.

The primary outcome to be observed in this study is time to complete abdominal wound closure where closure is observed at or before Day 42 and is confirmed to have been sustained for a period of at least 14 consecutive days. This study design also will allow detailed description of specific covariates to determine their effect on response variables (healing).

Secondary endpoints to be analyzed in this study will consider the effect of treatment on several quantitative factors for establishing efficacy, safety, quality of life, and resource utilization.

4 STUDY DESIGN

This study is designed as a multinational, multicentre, randomized controlled, clinical superiority trial, with blinded photographic analysis of the primary endpoint. The trial will be performed in Austria, Belgium, Germany, the Netherlands and United Kingdom.

4.1 Phase and Classification of the Trial

The trial is classified as an examination of the clinical application of a CE-marked medical device with risk category 2 b.

4.2 Treatments

This study is designed to evaluate treatment effects of a medical device in comparison to control therapy.

Trial intervention is wound treatment with V.A.C.® using the basic principle of NPWT.

Control therapy is defined as any SCWT according to actual guidelines or local clinical standards. Standard therapy is defined as the currently accepted and widely used treatment for the respective wound type, based on the results of past research. Therapy options for standard wound care are treatments that experts agree to be appropriate, accepted, and widely used. Health care providers are obligated to provide patients with best practice and standard of care.

For more information about treatments see chapter 6 TRIAL THERAPY.

4.3 Randomisation

Randomisation to treatment arms will be performed at a 1:1 ratio. Randomisation will be performed via a centralized system with an internet-based tool. Every user will receive access to register and then later to log into the system in order to receive a randomisation number and treatment assignment for a given participant. Participant randomisation will be stratified within centre by wound size.

Patients will be randomised dynamically. The permuted block sizes will randomly vary between 2, 4, and 6.

4.4 Stratification

Stratification will take place by study centre and then also subsequently by wound size (cm^3) within study centre. Wound size categories or strata to be considered will be the following:

Wounds ≤ 60 cm^3

Wounds > 60 cm^3

4.5 Primary Endpoint

The primary endpoint of this trial is defined as time (number of days) to achieve complete wound closure in study participants where closure was observed on or before Day 42 and was confirmed to have been sustained for a minimum of 14 subsequent days.

Complete wound closure is defined as:

- ✓ 100% Epithelialization
- ✓ No drainage from the wound
- ✓ No need for adjuvant therapy or dressing
- ✓ No presence of sutures

Complete wound closure has to be confirmed after a minimum of 14 consecutive days (14 days -0 / + 3).

The clinically determined closure of the wound has to be documented by photos.

Wound closure can be achieved by delayed primary intention (secondary suture, skin flap, skin graft) or secondary intention according to requirements of the participant and wound in the estimation of the attending physician. Optimal care for the participant has to be ensured.

Independent from type of closure, criteria for wound closure have to be reached within a maximum time frame of 42 days and wound closure has to be confirmed for a minimum of 14 consecutive days (14 days -0 / + 3).

4.6 Secondary Endpoints

Incidence of wound closures within 42 days

The incidence of wound closure achieved within each treatment arm will be evaluated after a maximum study observation/treatment period of 42 days. These wound closures have to be confirmed to sustain for a minimum of 14 subsequent days. This will be conducted via blinded photographic analysis.

Recurrence

Recurrence of wound opening after initial closure and confirmed wound closure will be assessed and compared between the treatment groups.

Reduction of wound size over time

Reduction of wound size over time will be evaluated using the following methods: reduction in wound volume over time and reduction in wound surface area over time.

4.7 Verification of wound closure and wound size

For the purposes of this trial a web-based photo documentation platform for wound photographs of study participants will be established. Wound photographs will be uploaded by study sites for each trial visit. The Wound Healing Analyzing Tool (W.H.A.T.) will be integrated within the platform. A centralized wound analysis of anonymized photographs (blinded assessment of wound photos) will be performed, which facilitates the objective evaluation of wound healing processes.

The clinically determined primary endpoint will be verified through blinded assessment of wound photos by observers that are independent from the clinical trial.

Secondary endpoints (numerical parameters) like circumference (mm), area (mm^2), maximum length (mm), and height (mm) will be calculated from the wound image using W.H.A.T., whereas the application of the system also will be performed by blinded independent assessors.

4.8 Safety Endpoints

Incidence of serious adverse events (SAEs) including mortality of any cause within 132 days from the time ofrandomisation, incidence of device-related events (ADEs),

wound-related adverse events (AEs) and incidence of unsustained closure within the study treatment time of 42 days are considered to be safety endpoints of this trial.

4.9 Patient Reported Outcome

Patient-reported outcome (PRO) is an umbrella term that covers different types of measurements to record unbiased self-reports by the participant. Instruments and assessments used for measurement of PRO of the SAWHI-V.A.C.®trial focus on the constructs “Quality of life” (QoL) and “Reports and Ratings of health care” (Patient Satisfaction).

Quality of Life

Healing of the wound is directly associated with patient well-being. QoL is an adequate measurement for a comparison of the treatment options. QoL is measured by using a multidimensional questionnaire assessing a combination of aspects of impairments and disability and reflects a patient’s health status.

QoL questionnaires are multidimensional, generic instruments for the measurement of health related QoL that consider health effects and physical restrictions as well as background information about daily activities and emotional response to restrictions. An innovative treatment option has the ability to cause earlier return to daily activities, improvement of functioning, direct or indirect reduction of emotional distress, and social reintegration. QoL will be measured using the SF-36v2 questionnaire at day 42 (end of maximum treatment time) or at wound closure visit, hospital discharge, and at the general follow-up visit.

Pain

In evaluating pain associated with wound healing and wound healing treatments, the total burden of pain must be considered. Therefore, during study visits, participants will be asked to provide their assessments of pain with an 11-point Likert Scale (Visual Analogue Scale). Participants will be asked to provide an estimate of their wound-associated pain of the last 24 hours.

The holistic treatment of patients with wound healing disorders calls for adequate pain therapy according to existing guidelines during disease-specific treatment time. Therefore, the documentation of therapy-caused pain medication is considered.

Wound related AEs, ADEs and SAEs are part of the safety assessment and will be documented.

Patient Satisfaction

This item covers a structured participant self-report and a valuation of the disease-specific healthcare [23]. Furthermore, this point includes participants' valuation of the treatment result with regard to scarring and the cosmetic result. The Participant should be asked about the general estimation of therapy progression and detailed treatment satisfaction.

This item will be evaluated by using a self-constructed questionnaire on the basis of specific scales of the Cologne Patient Questionnaire [24]. The Cologne Patient Questionnaire has formerly been used to develop a theory-based and empirically tested instrument for measuring patient-reported "psychosocial care by physicians" [25] and represents an ideal basis for development of a specific questionnaire for participant satisfaction of this trial.

Patient Satisfaction will be evaluated during General Follow Up Visit.

4.10 Health Economic Endpoints

Additionally to the evaluation of clinical treatment effectiveness, a prospective assessment of health economic issues will be performed.

This evaluation includes the assessment of parameters relevant for inpatient and outpatient resource use (resource utilization). A detailed baseline data acquisition regarding underlying disease and intervention will create the basis for further assessments of health development and resource use. Participants' co-morbidities will be documented using a separate, standardized case report form (CRF) sheet.

Direct medical resource use

Resource use that results directly from wound treatment or disease-specific therapy is considered as direct resource use.

The category **direct medical resource use** (direct medical costs) includes the resource use that is an immediate consequence of the disease pattern:

- ✓ general and specific clinical diagnostics
- ✓ medication (in particular analgesics and antibiotics)
- ✓ specific wound therapy
- ✓ number and type of debridements
- ✓ residential treatment and medical attendance
- ✓ outpatient treatment and medical attendance
- ✓ reinterventions
- ✓ rehospitalizations

Surgical reinterventions and rehospitalizations are especially a burden for health care and will be evaluated during the study. Reasons for these resource utilization parameters of particular interest will be documented explicitly within the CRF.

Indirect resource use

Resource use (cost) that is not directly associated with disease treatment is considered as indirect resource use (cost):

- ✓ restrictions of productivity besides absence from the workplace (activities of daily living)
- ✓ nonproductive time for those who are gainfully employed

4.11 Blinding

Due to the physical differences between the treatment regimens (eg, V.A.C.® Therapy versus SCWT), it is not possible to blind either Participant or physician to the treatment. Nevertheless, the Federal Joint Committee of the German Health Care System and International Conference on Harmonisation (ICH) GCP guidelines demand blinding procedures within RCTs whenever possible.

To address issues of blinding, wound photo documentation will be obtained during the trial and confirmation of wound closure will be assessed via blinded assessment of photos by independent observers, which will serve as the method of primary endpoint analysis.

4.12 Cross-sectoral patient treatment

Due to the scope of the trial to evaluate outcomes and benefits of V.A.C.® Therapy when compared to SCWT, when used across these care settings, all patients at the time point of randomization or during the active treatment period of 42 days that are eligible for outpatient care and have reasonable access to it, have to be transferred

to outpatient care.The transfer of appropriate patients to outpatient care will be monitored and a missing transition that is not due to medical condition of the patient or is due to provide the optimal treatment will be considered to be a protocol violation.

5 PATIENT SELECTION AND RECRUITMENT

This multicentre study will be conducted in hospital departments with the required manpower as well as structural and scientific qualifications. Study therapy will be started in ambulatory care or in-hospital and may be continued in ambulatory care. Study sites and investigators will be listed in a separate document.

Only patients meeting all Inclusion Criteria and no Exclusion Criteria should be included in the study. No deviation will be granted for waiver of Inclusion Criteria and/or Exclusion Criteria.

5.1 Diagnosis

There are 2 categories of wound patients with distinct post-surgical open abdominal wound diagnoses that will qualify for this study:

⇒ Patients with primarily closed post-surgical abdominal wounds without fascial dehiscence that develop a spontaneous wound dehiscence or require an active reopening of the wound by the treating physician

⇒ Patients with open post-surgical abdominal wounds without fascial dehiscence that cannot be closed by primary intention and require further treatment to achieve permanent closure

5.2 Inclusion Criteria

Only patients meeting all of the following characteristics will be eligible for clinical trial enrolment.

- *Written informed consent*

  Participant is willing and able to provide written informed consent.

- *Diagnosis of post-surgical subcutaneous abdominal wound healing impairment*

  Participant must have post-surgical abdominal wound with intact fascia (see definition of diagnosis).

- *Minimum wound size eligible for the application of the randomized treatment*

  Minimum wound size must be eligible for both possible study treatment options according to the therapeutical requirements of the respective randomized treatment arm.

- *Inclusion, randomisation, and start of therapy*

  Inclusion, randomization, adequate wound pre-treatment (debridement) and start of therapy must be completed within 48 hours after reopening of the wound, diagnosis for non-closable wound or in case of spontaneous wound dehiscence

5.3 Exclusion Criteria

Patients with any of the following characteristics are not eligible for clinical trial enrollment.

- *Age <18 years*

  Patients younger than 18 years are not allowed to be included in the trial.

- *Noncompliance with study procedures, visit schedule, or follow-up*

  A patient unable or unwilling to comply with the protocol and study-related requirements, to sign the Informed Consent Form, or to have their legally authorized representative act as a surrogate will be excluded from study participation. If a potential study patient, in the estimation of the Clinical Investigator, is unable to comply, the patient must be excluded from participation.

- *Pregnancy*

  Female candidates have to be asked about pregnancy. If a pregnancy is present, the patient must be excluded from participation.

- *Present or nonclosable defect of the abdominal fascia*

  If the defect of the abdominal fascia is present at the timepoint of initial diagnosis or reopening of the wound but can be closed before randomization but within the timeframe of 48 hours, participants may be included in the study.

- *Any pre-existing or ongoing organ system failure, that cannot be stabilized or solved by appropriate medical treatment*

- *Necrotic tissue with eschar present*

- *Non-enteric and unexplored fistulas*
- *Malignancy of the wound*
- *Use of any other device based on the principle of negative pressure wound therapy on the study wound within ≤ 8 days prior to screening*
- *Competing therapy and procedures*

  Any concomitant therapies or procedures deviating from the clinical standard wound treatment or with investigational character (eg, use of hyperbaric oxygen therapy [HBO]) are not allowed ≤ 30 days prior to screening or during the course of the trial.

  The need for concomitant therapies or procedures that, in the opinion of the treating physician, would directly affect wound healing or the ability to observe wound healing is an exclusion criterion for trial participation.

- *Other clinical trials*

  Concurrent participation in another trial that interferes directly or in the foreseeable future with study procedures, patient's compliance, wound healing or targeted endpoints is not allowed for participants of this trial.

5.4 Enrolment

A non-enrolled/ineligible potential-participant log (including reasons for non-enrolment/ineligibility) will be monitored for any potential selection bias of enrolled participants that may occur.

5.5 Description and justification for duration of treatment

For both treatment arms, a maximum treatment time of 42 days to achieve complete wound closure shall be provided to cover 80% of participants whether healing occurs by secondary or delayed primary closure [4].

5.6 Description and justification for follow-up

All participants will be followed up for 90 days (3 months) after the maximum treatment time of 42 days, independent from whether a wound closure was achieved or not or at which time point within the maximum time frame for active treatment the wound closure was achieved. Thus, a general follow-up date for all study participants will be at day 132.

A follow-up period of 3 months after the active treatment period allows for an assessment of recurrence of the wound dehiscence or impairment as well as an adequate assessment of health economic relevant issues.

Participants who have not achieved wound closure after 42 days will be seen at 45 days (6 weeks) after the end of active treatment time (Day 87). This timeframe allows for a complete assessment of wound progression after study treatment and an assessment of wound closure that is achieved later than day 42.

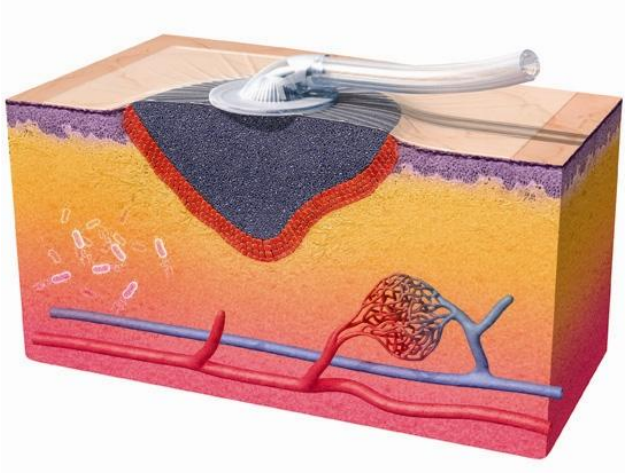
6 TRIAL THERAPY

6.1 Description of Intervention

6.1.1 General information

The V.A.C.® Therapy System is a non-invasive wound therapy system that uses controlled, localized negative (ie, subatmospheric) pressure to create an environment that promotes wound healing in chronic and acute wounds.

Picture 1: Vacuum Assisted Closure (V.A.C. ®)



The V.A.C.® Therapy System label is on the market since 1995 and bears the CE mark and includes the trade name and address of the manufacturer, the batch code, and all other essential information according to European Union (EU) Directive 1993/42/EEC.

The V.A.C.® Therapy System promotes wound healing through optimization of blood flow, decreasing local tissue edema, and removing excessive fluid from the wound bed. These physiologic changes facilitate the removal of bacteria from the wound. Additionally, the cyclical application of subatmospheric pressure alters the cytoskeleton of the cells in the wound bed through microstrain, triggering a cascade of intracellular signals that increases the rate of cell division and subsequent formation of granulation tissue. Moreover, this system has been shown to also cause macrostrain, bringing the edges of the wound closer and also stimulating wound bed granulation. Further, V.A.C.® Therapy has proven beneficial in reconstruction of wounds by allowing elective planning of the definitive reconstructive surgery without significantly jeopardizing the wound or outcome. It has been shown to significantly

increase the success rate of skin graft uptake when used as a bolster over the freshly grafted wound. V.A.C.® Therapy is generally well tolerated and, with few well-known contraindications and a limited number of AEs, is fast becoming a mainstay of current open-wound care.

6.1.2 Composition and functionality

The V.A.C.® Therapy System employs medical grade polyurethane or polyvinyl alcohol foam dressing that is fitted at the bedside to the appropriate size for each Participant wound and then covered with an adhesive drape to create an occlusive dressing seal.

The V.A.C.® Therapy devices that will be used in this study include the ActiV.A.C.®, InfoV.A.C.®, V.A.C. Freedom®, V.A.C. Via® and V.A.C Ulta®.

There are 3 types of wound dressings, available in different sizes, typically used in the treatment of open wounds with the V.A.C.® Therapy System.

The V.A.C.® GranuFoam™ Dressing has reticulated or open pores and is considered effective at stimulating granulation tissue while aiding in wound contraction. It is hydrophobic (or moisture repelling), which enhances exudate removal.

The V.A.C.® WhiteFoam Dressing is dense foam with a higher tensile strength. It is hydrophilic (or moisture maintaining) and is premoistened with sterile water. The dressing possesses overall nonadherent properties and is generally recommended for situations where the growth of granulation tissue into the foam needs to be more controlled or when the Participant cannot tolerate the V.A.C.® GranuFoam™ dressing due to pain. Due to the higher density of the V.A.C.® WhiteFoam Dressing, higher negative pressures (–125 mm Hg to –175 mm Hg) must be utilized in order to provide adequate NPWT distribution throughout the wound.

The V.A.C. GranuFoam Silver® Dressing has reticulated or open pores with microbonded metallic silver uniformly distributed throughout the dressing, providing continuous delivery of silver. The silver is an effective barrier to bacterial penetration and may help reduce infection. The V.A.C. GranuFoam Silver® Dressing is considered effective at stimulating granulation tissue while aiding in wound contraction. The dressing is hydrophobic, which enhances exudate removal.

A hole is cut in the adhesive drape and the T.R.A.C.™ Pad or SensaT.R.A.C.™ opening is placed directly over the hole. The tubing attached to the T.R.A.C.™ Pad or SensaT.R.A.C.™ Pad is then connected to a fluid collection canister contained within a portable computer-controlled vacuum pump. V.A.C.® Therapy devices create controlled subatmospheric (negative) pressure. The SensaT.R.A.C.™ Pad (used with ActiV.A.C.®, InfoV.A.C.®, V.A.C. Freedom® , V.A.C. Via® and V.A.C Ulta®.) reliably maintain the target pressure at the wound site to help provide safe, controlled therapy.

V.A.C.® Therapy delivers continuous or intermittent negative pressure, providing a range of negative pressure options to optimize fluid removal, tissue tension, capillary flow, and enhanced vascular perfusion through vessels previously compressed by excess fluid pressure. Negative pressure settings may range from –50 mm Hg and –200 mm Hg, where –125 mm Hg is typically used for wound healing. Dressing changes are recommended to be performed no less than 3 times per week. Dressing changes for infected wounds may need to be performed more frequently (every 12–24 hours).

6.1.3 Contraindications and Precautions for Use of V.A.C.® Therapy

There are several contraindications and precautions for the use of V.A.C.® Therapy. These are shown in Table 3.

Table 3: V.A.C.® -Therapy Contraindications and Precautions

V.A.C.® Therapy Contraindications and Precautions	
Contraindications for patients with:	• Malignancy in the wound • Non-enteric and unexplored fistula • Untreated osteomyelitis • Necrotic tissue with eschar present • Exposed blood vessels or organs

Precautions for patients with:	• Active bleeding • Difficult wound hemostasis • Anticoagulants • When placing a V.A.C.® Dressing in close proximity to blood vessels or organs, take care to ensure that all vessels are adequately protected with overlying fascia, tissue, or other protective barriers • Greater care should be taken with respect to weakened, irradiated, or sutured blood vessels or organs • Bone fragments or sharp edges could puncture protective barriers, vessels, or organs • Wounds with enteric fistula require special precautions to optimize V.A.C.® Therapy • Follow universal precautions

6.1.4 Use within the trial

The V.A.C.® Therapy devices that will be used in this study include the ActiV.A.C.® Therapy System, InfoV.A.C.® Therapy System, V.A.C. Freedom® ,V.A.C. Via® and V.A.C Ulta® Therapy Systems. All V.A.C.® Therapy devices to be utilized in this study bear the CE mark and will be operated within normal conditions of use. In addition, all dressings to be used in the treatment group (V.A.C.® Therapy) bear the CE mark and will be used according to clinical guidelines. The use of the allocated V.A.C.® Therapy System should be performed according to the clinical guidelines released by KCI. Instructions for use (User Manuals) will be provided for every study centre. The standard patient labelling will be provided with products. Product labelling will be indemnified by the manufacturer (KCI) according to local requirements.

In this trial, V.A.C.® Therapy should be used with any of the following dressings: black GranuFoam™ Dressing, V.A.C. GranuFoam Silver® Dressing, or V.A.C.® WhiteFoam Dressing as indicated by the treating physician.

Dressing changes have to be performed every 48–72 hours, no fewer than 3 times per week, with frequency adjusted by the clinician as appropriate. In particular, the first dressing change should be performed carefully and with moistened dressing to ensure that the foam can be removed easily. During dressing changes, if any analgesics or local anesthetics are used to provide an optimal pain management, their amounts and types should be recorded in the CRF. At each visit, the wound will be examined. In case of formation of excess granulation tissue and necrotic areas, a repeated debridement may be necessary to assure optimal conditions for wound healing and surgical closure.

Infected wounds detected by the wound contamination measurements post-op or during the follow-up visits must be monitored often and very closely. For these wounds, dressings may need to be changed more often than 48–72 hours; the dressing change intervals should be based on a continuing evaluation of wound condition and the Participant's clinical presentation.

Participants randomized to receive V.A.C.® Therapy may receive only V.A.C.® Therapy or V.A.C.® Therapy plus SCWT when the treating physician prescribes it in order to achieve wound closure by secondary intent; epithelialization may only occur with SCWT. V.A.C.® Therapy is indicated for granulation and preparation of an abdominal wound bed. In general, all participants receiving V.A.C.® Therapy should receive it only to the point where the treating physician believes the Participant has achieved maximum benefits from it. After that point, participants should be treated with SCWT to achieve final closure.

These are important fundamentals of V.A.C.® Therapy, as it is intended to promote granulation and wound bed preparation but not epithelialization.

Table 4: V.A.C.® Treatment Recommendation

Treatment cycle	**Target negative pressure**			**Dressing change interval**
	V.A.C.® Granufoam® (black)	***V.A.C.® Granufoam® Silver®***	***V.A.C.® WhiteFoam®***	
Continuous	125 mmHg	125 mmHg	125-175 mmHg Titrate up for more drainage	Every 48-72 hours Or more frequent if clinically indicated (no less than 3 times a week)

6.1.5 Operating Conditions of V.A.C.® Therapy Systems and disposables within the trial

The V.A.C.® Therapy System carries the CE mark and is a commercially available product. All V.A.C.® Therapy units and disposables will be used in clinical routine according to local regulations.

Purchasing, storage and dispense of the devices will follow the usual practices of the institutions performing the study and applicable regulatory requirements. The therapy unit and dressing are to be stored in a dry location at controlled room temperature away from direct sun exposure. If significant temperature deviations are noted, the study site should ensure that storage conditions be brought into compliance.

It is the CI's responsibility to ensure that an accurate record of each Participant's exposure to the device is maintained. The clear assignment of the medical device to the trial participant will be recorded in the medical device log. The CRA shall ensure that a copy of the medical device form is kept in each Investigator Study File and is to review by the CRA during routine monitoring visits.

The CRA shall document inadequate device-using practices, discuss them with the CI, and report them to IFOM. A pattern of deviation from the manufacturer's specifications is considered grounds for terminating the site's participation in the study.

6.2 Description of Control Therapy: Standard Conventional Wound Therapy

Given the objective to determine the superiority of V.A.C.® Therapy to standard of care practices, it is important to ensure that the comparator arm of this study reflects optimal outcomes (wound closure) achievable without the use of V.A.C.® Therapy. As wounds have different barriers to healing, and various clinical presentations that will evolve over time, this study allows the use of all commonly used wound care dressings such that the physician can, based upon the wound and the Participant's needs, deliver optimum wound care.

For the purposes of this study, SCWT is the control therapy. It will be considered standard of care in the current healthcare system and will be performed within the context of the clinical wounds delineated within this protocol. SCWT constitutes a range of simple (i.e. gauze) to advanced dressings and other pertinent products that

demonstrate benefit through the facilitation of a moist wound environment, which is known to promote faster relative wound healing compared to wounds exposed to air.

SCWT constitutes a myriad of products that are used alone or in combination to achieve wound healing.

SCWT in treatment of open abdominal wounds without fascial dehiscence includes a multitude of products and may be performed according to the clinical standards determined by the treating physician.

The choice of dressing type, rinsing solution, and topical treatments used should be determined based on the wound type and the best expected clinical outcome and should be applied as often as necessary. The therapy used will be recorded in the CRF.

At each visit, the wound will be examined, and in case of formation of excess granulation tissue and necrotic debris, the open areas will be curetted and debrided to remove this tissue and debris. All such processes should be documented in the CRF.

Most of the products discussed above have been reported as being used in conjunction with either V.A.C.® Therapy or SCWT. For the purpose of this study, SCWT includes non-V.A.C.® Therapy moist/advanced wound care dressings that are appropriate and applicable for treating the wounds according to the physician's treatment intent. Further, their use with either therapy and between dressing changes will be allowed at the discretion of the treating physician.

6.2.1 Operating Conditions of SCWT-material within the trial

All SCWT supplies will be used in clinical routine according to local regulations.

Logging, storage and dispense is the responsibility of the study site and is based on the manufacturers guidance as well as in accordance with applicable regulatory requirements.

6.3 Wound Care Principles and Practices

The challenges associated with the management of wound healing, especially in light of complications, are multifactorial and thus effective therapy is multifaceted. Given that the goal of this study is to compare V.A.C.® Therapy with SCWT, it is important to apply key non-wound-dressing-related interventions such as debridement, infection management, and nutritional support consistently and in alignment with established clinical standards. For the purposes of this study, the following principles and practices should be applied as medically indicated in the judgment of the treating physician, irrespective of randomized treatment assignment within the clinical trial.

6.3.1 Wound Debridement

Effective wound debridement is a foundation for timely healing of complex abdominal wounds. All participants will have undergone appropriate debridement of necrotic and nonviable tissue from the wound (if medically indicated) before randomisation and treatment start. The CI will assess the need for debridement during each subsequent visit and perform such wound debridement as medically indicated, irrespective of randomized treatment assignment. Debridement may occur by surgical or sharps debridement, pulsatile lavage, or enzymatic means. Given the impact of debridement on the size, appearance, and state of the wound, wound examination will be performed both pre- and post-debridement. Microorganisms identified within laboratory cultures from samples taken during debridement should be documented and, if indicated, the wound should undergo appropriate infection management.

6.3.2 Wound Cleansing

Wound cleansing, as a premise of good wound care, should occur within this study as is clinically indicated by the general appearance of the wound, irrespective of randomized treatment assignment. Established standards of wound care indicate that washing of the wound with a nontoxic agent (such as normal saline) is acceptable for all wounds to remove debris and infectious materials. It is expected that the use of other antiseptic/antimicrobial skin cleansers or wound irrigants will be reserved for situations where there is a clinical indication to address wound bioburden or infection.

6.3.3 Wound Infection Management

As a premise of good wound care, sources of wound infection must be readily identified and appropriately treated to facilitate wound healing. It is assumed that all participants included in the study will have undergone appropriate debridement and removal of nonviable tissue as an initial step to addressing wound infection (where indicated). All participants having clinical signs and symptoms of infection at any point during the study should receive medically indicated antibiotic and topical wound therapies consistent with standard of care within the respective treatment facility, irrespective of randomized treatment assignment. All antibiotics and topical therapies administered for the treatment of infection should be documented under the study's concomitant medications.

Some participants enrolled in this study will have an active diagnosis of wound infection that resulted in the wound dehiscence or inability to primarily close the wound. This information is relevant and should be captured on the initial wound assessment (examination) and medical history in the CRF. In such participants, the initial infection would not be considered an AE unless that infection worsened or deteriorated after initiation of randomized study treatment. Infections that occur after the initiation of study-randomized treatment will be considered an AE and should be documented and reported as such.

6.3.4 Wound Pain Management

Each person's experience of wound pain is complex and is influenced by a wide range of factors specific to the individual. Wound pain can be persistent, greatly affecting individuals' quality of life and having a significant impact on the lives of those around them. For others, the pain experienced is specifically related to, and often exacerbated by, wound dressing-related procedures. It is also important to recognise that emotional components, including anxiety and previous experience, can compound a person's perception of pain and may negatively affect the patient/practitioner relationship. Thus, a sufficient pain treatment concept is required for study participants, regardless of the randomised treatment arm. Pain management for study participants should be performed according to clinical

standards and will be documented during treatment time (pain medication and assessment). Pain treatment is recommended to be performed in a sufficient manner according to local guidelines [26-28].

6.3.5 Treatment Compliance

Monitoring will be performed to ensure compliance by the CIs to the protocol. The Steering Committee or its designees, CRAs, IFOM representatives, and KCI representatives may visit participating centres to control adherence to the protocol. Wound healing documentation may be evaluated by the Steering Committee, the IDMC, qualified personnel (assigned by either of these committees), CRAs, IFOM representatives, and KCI representatives by visit or by using photographs. Compliance to follow-up will be enforced by reminders.

6.4 Training on Study Products and Procedures

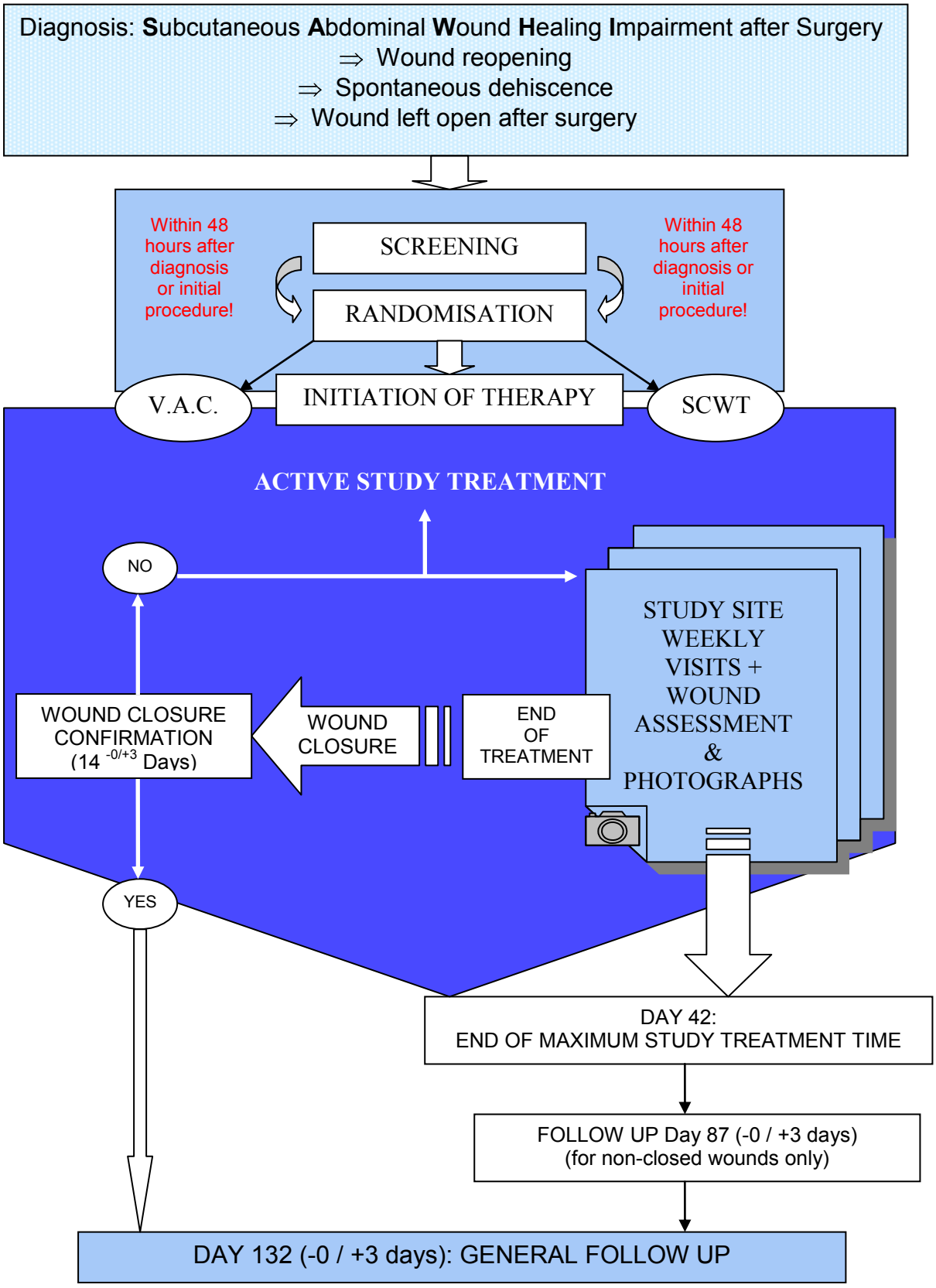
The CI and site staff will be trained on the study as a whole, the investigational device, if applicable, and any specialized procedures prior to and/or during the site initiation visit.

IFOM and KCI will ensure that clinical support to site staff is provided for any questions or concerns related to treatment plans; however, IFOM and KCI will not have any influence on participants' care.

7 STUDY PLAN

7.1 Study Flow Chart

Picture 2: Study Flow Chart



7.2 Description of Study Visits

The following section describes the planned visits and information to be collected. The following procedures and assessments are to be performed and documented. An overview of study visits can be found in APPENDIX Schedule of Visits.

7.2.1 Screening

- Written informed consent (to be performed before other procedures start)
- Review of Inclusion Criteria and Exclusion Criteria
- Demographics
- Relevant medical and surgical history
- Concomitant medications taken routinely and within the last 3 days before screening. Medications given during anaesthesia should not be collected.
- Baseline health economic parameters
  - ⇒ Working status and standard job
  - ⇒ Location prior to hospitalization
  - ⇒ Hospitalization time prior to screening
  - ⇒ Reason for hospitalization
  - ⇒ Date of, location of, and reason for initial surgery
  - ⇒ Type of surgical procedure performed
- Wound examination: Location, status of wound and surrounding area
- Wound measurement, including depth, wound surface area,
- Digital wound photographs (pre- or post-debridement, as applicable) (Appendix)
- Wound pain assessment
- Laboratory parameters (Blood count, C-Reactive Protein [CRP], Coagulation: Quick, Partial Thromboplastin Time [PTT]): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care

7.2.2 Randomisation and Initiation of Therapy

Randomisation, wound pre-treatment, and initiation of therapy have to be performed within 48 hours after wound reopening, spontaneous dehiscence, or decision for wound to be left open.

- Randomisation of participant to either the treatment group (V.A.C.® Therapy) or control group (SCWT)
- Time point of post-surgery initiation of wound care (V.A.C.® Therapy or SCWT)
- Performance and documentation of wound pre-treatment
- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Documentation of wound treatment (V.A.C.® Therapy or SCWT)
- Concomitant medications wound pain assessment
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.3 Weekly wound visits until wound closure or end of active treatment period

Beginning at Day 6-8 (Week 1), weekly wound visits will be performed until wound closure or end of maximum treatment time. A maximum of 6 visits will be performed within the maximum treatment time of 42 days.

Weekly visits should be planned and scheduled to take place during dressing changes in the V.A.C. Therapy® arm.

- Treatment continuation
- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Wound pain assessment

- Concomitant medication
- Wound related procedures (localization, time, quality, person)
- Dressing changes/applications between study visits
- Rehospitalisation (reason, time, procedures, length of hospital stay)
- Length of hospital stay
- Resource utilization
- Discharge documentation, if applicable (see visit: Hospital Discharge)
- Wound closure documentation, if applicable (see visit: Wound Closure)
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.4 Hospital Discharge

- Date of discharge
- Disposition
- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Concomitant medication
- Wound pain assessment
- SF-36®
- Description of procedures
- Status of treatment
- Resource utilization
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.5 End of treatment

End of Treatment (EOT) will be reached if an optimal preparation of the wound bed is achieved as determined by the treating physician.

In case of wound closure by secondary suture, skin graft, or flap, the surgical procedure is required to be performed not longer than 72 hours after end of treatment. If the intended surgical procedure cannot be performed within 72 hours after end of therapy, randomised therapy has to be continued until surgery.

- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Concomitant medication
- Wound pain assessment
- Dressing changes/applications between study visits and surgical or local wound treatment procedures
- Description of procedures
- Resource utilization
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.6 Wound closure

Wound closure visit will be performed at any time complete wound closure according to wound closure definitions is achieved within the maximum treatment time of 42 days.

Independent from type of closure, it should be the primary intent of therapy to achieve wound closure in a prompt fashion!

The following procedures and assessments are to be performed and documented:

- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Concomitant medication
- Wound pain assessment

- SF 36®
- Dressing changes/applications between study visits and surgical or local wound treatment procedures
- Description of procedures
- Resource utilization
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.7 Wound Closure Confirmation

This visit takes place after a minimum of 14 and a maximum of 17 days after clinical diagnosis of complete wound closure according to wound closure criteria defined in chapter 4.5.

The wound closure has to sustain constantly for a minimum of 14 days after wound closure visit.

If wound closure cannot be confirmed during this visit, wound therapy has to be continued as randomised.

- Wound examination: Status of wound and surrounding area
- Wound status: determination of wound closure
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Concomitant medication
- Wound pain assessment
- Description of procedures
- Dressing changes/applications between study visits and surgical or local wound treatment procedures
- Collection of resource utilization Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.8 End of maximum treatment period

End of Maximum Treatment Time (EOMT) (Day 42) or early termination

In case of a non-closed wound at day 42 an additional follow-up will be performed at day 87.

- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area and volume (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Concomitant medication
- Wound pain assessment
- SF 36®
- Description of procedures
- Dressing changes/applications between study visits and surgical or local wound treatment procedures
- Collection of resource utilization Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.9 Follow-up Visit at Day 87 for non-closed wound at Day 42 (EOMT)

- Wound closures (date and number)
- Recurrences
- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximal width and length, maximum depth)
- Wound pain assessment
- Digital wound photographs
- Type, length and care setting of wound treatment after Day 42
- Collection of resource utilization Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care

- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.2.10 General Follow-up Visit at Day 132

- Wound closures (date and number) and recurrences, if applicable
- Wound examination: Status of wound and surrounding area
- Wound measurement, including wound area (size: area of wound opening, largest distance of wound margins, maximum width and length, maximum depth)
- Digital wound photographs
- Type, length and care setting of wound treatment after Day 42
- Wound pain assessment
- SF36®
- Patient satisfaction
- Collection of resource utilization
- Laboratory parameters (Blood count, CRP, Coagulation: Quick, PTT): to be completed if collected as part of standard of care
- Local wound swab and blood culture, if signs and symptoms of infection are present: to be completed if collected as part of standard of care
- Safety: Wound related adverse events and device-related adverse events (ADEs); all SAEs (including Serious Adverse Device Events (SADEs))

7.3 All Interim Dressing Changes

Wounds being treated with the V.A.C.® Therapy System and with SCWT should be monitored on a regular basis. In a monitored, non-infected wound, V.A.C.® foams should be changed every 48 to 72 hours but no less than 3 times per week, with frequency adjusted by the clinician as appropriate.

If a dressing change is required between scheduled visits, the participant can go to the ambulant department of the study centre (if on V.A.C.® Therapy arm) or to a certified and appropriately trained resident physician or certified, appropriately trained home health care professional. For the SCWT arm, the participant dressing changes will be performed according to standard of care.

If the dressing changes are performed elsewhere than in the study centres, the participant will be given an informational sheet instructing the physician or nurse to refer the participant to the study centre for any AEs and observations of wound closure. The visit documentation will be done at every visit. If a dressing change is required between study visits, the details will be documented in the next regular visit form.

For all dressing changes special data collection forms for participants' bedside or to put into source document like participants' health records will be offered to ensure that all data that need to be collected for the study visits can be filled in properly and completely.

7.4 Wound Assessment (Examination)

A wound assessment (examination) will include:

- Observatory confirmation of wound closure
- Epithelialization and granulation on wound base
- Skin Condition: wound edge, periwound condition, wound appearance and wound base color, presence of necrotic tissue, signs and symptoms of infection, peripheral tissue edema
- Wound drainage: amount, appearance

- Wound measurements will be recorded according to the Schedule of Study Visits (Appendix A). Wound measurements will include:
    - (Volume = Maximum Length × Maximum Width × Maximum Depth)
    - Reduction in wound surface area over time (Area = Maximum Length × Maximum Width)

Photographs will be taken during study visits to document reduction of wound size over time, wound closure and confirmation of closure.

7.5 Wound pain assessment

Wound pain assessment during active treatment time will be performed during study visits. Participants should record an estimation of their average pain of the last 24 hours in the CRF.

7.6 Prior and Concomitant Medication

Medication will be documented for the following categories:

- Anti-diabetics
- Anticancer agents
- Immunomodulators
- Corticosteroids
- Antiinfectives for systemic use
- Antiinflammatories
- Antirheumatics
- Antithrombotics
- Antihemorrhagics
- Analgesics

Medication taken within 3 days prior to randomisation and taken or administered until EOMT will be recorded in the CRF. Concomitant medications will be recorded as per the Schedule of Study Visits.

7.7 Early Termination of Treatment and Trial Participation

If a participant prematurely terminates trial participation, he/she will be offered adequate medical treatment, as necessary. Unless requested by the participant, all

data collected up to termination will be available for database entry and analysis. Participants who terminate the study early will be offered to be followed for safety monitoring for up to 42 days post-intervention.

7.8 Early Study Termination

The IDMC may decide in the interest of healthcare to terminate the study before completion of participant recruitment (eg, if an unacceptably high rate of ADEs is seen in participants or if issues arise that prevent successful completion of the study).

Noncompliance due to unfulfilled contractual and/or financial agreements between KCI and the PCI may lead to early termination of the study, after consultation with the Steering Committee, IDMC, KCI, and IFOM.

Also, unfeasibility for successful completion of the study may lead to premature termination after consulting with the Steering Committee, IDMC, KCI, and IFOM.
Early termination of the study should be based on mutual agreement among the Steering Committee, IDMC, KCI, and IFOM.

7.9 Removal of Participants from Therapy or Assessment

The participating CIs are responsible for adequate treatment of participants following the study protocol. A CI may decide to remove a participant from the therapy or the trial for these reasons:

- Deterioration of the wound that cannot be solved within a temporarily therapy intermission and that medically precludes or contraindicates continuation of randomized study therapy. In such case, the participant may be withdrawn from the active treatment phase of the study and considered to be a treatment failure but followed in the study's follow-up phase for safety, quality of life, and healthcare economics resource utilization.
- New information becomes known that changes the risks and benefits for the participant (this includes conditions of the participant).
- Best medical interest, including safety, of the participant.

Regardless of the underlying reasons, participants have the right to withdraw at any time. Likewise, any relevant medical event as judged by a PCI may lead to the decision to withdraw a participant from the study. All reasons for drop-out of a participant will be documented.

7.10 Closure of Study Centers and Exclusion of Investigators

The Steering Committee or KCI may decide to exclude participating centres and/or CIs from further participation on the basis of fraud or noncompliance with the study protocol (eg, international guidelines for Good Clinical Practice [GCP]) by the participating center or CI. If the Steering Committee makes the decision, this determination can be made only after consulting with the IDMC, KCI, and IFOM. If KCI makes the decision, this determination can be made only after consulting with the IDMC, Steering Committee, and IFOM.

Study centres or CIs may stop recruiting Participants for this study when the CI finds that inclusion of participants into this trial presents problems for ethical, medical, or organizational reasons. If this occurs, the study centre or CI must provide a detailed explanation to the Steering Committee and IDMC for the decision to cease recruitment.

8 DATA

8.1 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified CIs and appropriate study centres, review of protocol procedures with the CI and associated personnel before the study commences, periodic onsite monitoring visits, and any other procedures as deemed appropriate by IFOM and KCI. IFOM and KCI will confirm that the clinical trial will meet International Organization for Standardization (ISO) 14155 guidelines and all applicable regulatory requirements, including ICH-GCP. All evaluation methods used are standard according to current scientific literature.

Guidance for CRF completion will be provided and reviewed with the study personnel before the start of the study.

In order to guarantee the high quality of the study data and data retrieval, all participating centres will be visited on a regular basis onsite by the CRAs according to a predefined monitoring plan. Data protection rights will be respected. Participant files will be monitored on a 100 % basis to control original data and to verify accurate data registration and management (100 % source data verification). The presence of a written Informed Consent Form (ICF) and the correct interpretation of Inclusion Criteria and Exclusion Criteria will be controlled. The IFOM CRAs will review CRFs for accuracy and completeness during on-site monitoring visits and any discrepancies will be resolved with the CI or designee, as appropriate. The CRA also will have regular contact in person, by phone, and/or by email with all participating centres as specified in a predefined monitoring plan. The purpose of the contacts is to monitor the study progression, verify adherence to the study protocol, and discuss problems related to the study. The CRA will particularly concentrate on AEs, the number of drop-outs, and excluded participants. The CIs in the participating centres will support the CRA in his/her activities.

8.2 Data Collection and Documentation

The study CRF is the primary data collection instrument for this study. A paper CRF will be used throughout this study. All data fields on the CRF or on the documentation sheets (for wound assessment, wound related procedures and medical history) which

is supposed to be archived as source data in the patient file should be completed within 24 hours of the Participant's visit. All missing data should be explained in an appropriate comment section. A detailed guideline document for completion of CRFs will be provided to all study sites.

All Participant data, excluding photographs of wounds, are to be considered source data and must be retained in a secure place and made available for review during routine monitoring/audits or on request of IFOM and KCI. The CI must document in the Participant's clinical file that the Participant participated in this study.

The CRF includes all necessary forms, separated according to the anticipated investigation time points. The CI will be responsible for the maintenance of every CRF in an up-to-date manner. The CI is responsible for the quality of all data documented in the CRF. The CI is responsible for the documentation of the study data in the source-data documents and the quality and correct entry of all data documented in the CRF.

Only the CI or qualified personnel authorized by him/her are entitled to enter data into the CRF. All authorized personnel must be identified in the delegation of authority log, which specifies the delegation of responsibilities for the study. Corrections and additions must be signed with initials and dated by qualified study personnel.

Remaining questions or missing data posed either by the monitor or by the data manager (appearing during data entry or additional consistency checks on the data base) will be noted using data clarification forms (DCFs). These queries will be sent to the CI. It is the CI's obligation to complete and return the forms to the data management group within five working days or within 24 hours of database lock. The data management will do the bookkeeping of the queries, ie, requery in case the answer is not sufficient or keep track of the data entry into the database.

Original copies of the CRFs will be sent to IFOM's data management department for data entry into the study database. Copies of the CRFs designated for the CI must be stored together with the study documentation.

CRFs and source data are to be retained and stored in accordance with local applicable regulations or in accordance with the ICH-GCP regulations in effect for the jurisdiction where the clinical trial site is located whichever period is greater. The CI will ensure that a correct assignment of the CRFs to the corresponding Participant files, including all relevant source data, is possible at any time. A separate Participant identification list must be recorded by the CI. Participants' ID lists and medical records will be kept separately at the individual study sites by the CI.

The Participant ICFs designated for the CI are to be kept in the study documentation files at each CI's site. All information on which the entries in the CRF are based must be available in the Participant files (ie, source documentation).

After termination of the study, the CI will enter all relevant information obtained subsequent to the study in a Participant's medical records.

8.3 Data Handling and Management

The infrastructure and personnel for data management will be provided by the Center for Clinical Studies and Innovation (ZKSI) at the University of Witten/Herdecke. The ZKSI will assign qualified personnel for the implementation of data management activities.

IFOM and KCI are responsible for compilation and verification of the study data, retention of the clinical study database, performance of statistical analysis, and preparation of the trial reports. IFOM will perform data management activities in accordance with the study Data Management Plan (DMP).

The setup of the database will be done by IFOM. The design of the database is given by the structure of the study, here a multicentre investigation. The content of the tables and variables in the database is determined by the paper CRF (pCRF) and refers to the study schedule. The pCRF serves as a reference to setup a Meta database describing the structure of the CRF and the variables. This Meta database will be validated against the pCRF. The Meta database serves as a basis to generate the study database. The study database itself will be validated against the Meta database and the pCRF.

The data validation plan contained within the DMP describes the edit and consistency checks for the entered data. The checks are implemented into the study database. The checks will be tested during the validation procedure.

A data management program will be used that is FDA compliant. All protocol-specified data documented on the CRFs will be dually entered into the study database utilizing appropriate data management procedures. After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the database. Queries generated from these edit checks will be sent to the study site for resolution, and the database will be updated to reflect query resolutions as appropriate. All activities associated with entry or alteration of any data will be traceable.

All incoming CRFs and DCFs will be registered by data management. All registration forms will be checked for completeness, plausibility, and correctness.

Participant ID lists and medical records will be kept separately at the individual study sites.

Further details on implementation of the data management structure can be found in the DMP.

8.4 Record Storage and Retention

Investigator

In accordance with the Investigator Agreement, the CI shall maintain all study documentation in his/her possession and/or control and institute measures to prevent accidental or premature destruction of any data and/or documents related to the study.

After formal discontinuation of the clinical trial, the CI shall retain the clinical trial documentation produced by the CI in accordance with local applicable regulations or in accordance with the ICH-GCP regulations in effect for the jurisdiction where the clinical trial site is located, whichever period is greater.

In accordance with the Investigator Agreement, the CI shall allow KCI and IFOM to have access to the clinical trial documents as defined in the Investigator Agreement.

KCI and IFOM

KCI and IFOM shall maintain all study documentation in their possession and/or control and shall institute measures to prevent accidental or premature destruction of any data and/or documents related to the clinical trial.
Study records will be stored for a minimum of 10 years after trial completion.

After formal discontinuation of the clinical trial, the PCI shall retain the clinical trial documentation produced by the PCI for a minimum of three (3) years or in accordance with the ICH-GCP regulations in effect for the jurisdiction where the clinical trial site is located, whichever period is greater.

8.5 Data Ownership

Rights, duties, and obligations regarding ownership of any ideas, concepts, inventions, or results, whether patentable or not, shall be in accordance with the terms and conditions set forth in the Investigator Agreement by and between the Institution and IFOM. KCI retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this clinical trial, including information set forth in and derived from the CRFs.

In accordance with the Investigator Agreement, all materials, information (oral or written), and unpublished documentation provided to the CIs (or any company/institution acting on their behalf), inclusive of this protocol and the CRFs, are exclusive property of KCI and IFOM and may not be given or disclosed, either in part or in whole, by the CI or by any person under his/her authority to any third party without the prior express consent of KCI.

The CI shall consider all information, results, discoveries, records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without IFOM's and KCI's prior written consent, without comments and with or without analysis, in order to submit data to the health authorities of any country for purposes of regulatory filing and/or submissions.

9 STATISTICAL CONSIDERATIONS

The primary outcome to be observed in this *multicentre, parallel design, prospective, randomized clinical trial* is time to complete open abdominal wound closure by day 42 which is confirmed after 14 (-0 / +3) consecutive days. Secondary endpoints to be analyzed in this study with repeated observations over time will consider the effect of treatment on several quantitative factors for establishing efficacy, safety, Patient-reported outcome, and economic parameters.

The Statistical Analysis Plan (SAP) will include a detailed description of specific covariates that will be evaluated to determine their effect on response variables.

9.1 Determination of Sample Size

The primary efficacy endpoint is the time to achieve confirmed wound closure within 42 days of surgery (ie, wound confirmed closed after 14 consecutive days). Time to confirmed wound closure will be compared between the 2 treatment groups using log-rank test. Sample size estimation has been performed using the expected difference in wound closure rates rather than hazard ratios. Assuming a complete wound closure rate of 50% in the control group, and a minimum difference of 12.5% after a treatment time of 42 days, a number of 246 participants per group would be needed (chi-square test) to achieve 80% power with $\alpha = 0.05$. If $\alpha = 0.048$ due to one interim analysis (see below) sample size per group would increase only marginally (n=249 per group, or n=498 in total). Assuming a maximum loss-to-follow-up rate of 10% for both treatment groups, a total of 550 participants will be required. Up to 600 participants will be enrolled in this study.

The computer program of Dupont and Plummer was used for sample size calculation [29].

One interim analysis will be performed when 250 participants complete the first phase of the study, and type I error rate will be adjusted using O'Brien-Fleming method ($\alpha = 0.005$ for the interim analysis and $\alpha = 0.048$ for the final analysis).

The final analysis is planned to be performed with time-to-event data (survival curves; log-rank test) rather than wound closure rates. However, since this more detailed

approach is able to detect differences more sensitive than event rates, the calculated sample size is considered to be sufficiently large.

9.2 Analysis Populations

The following Participant populations will be considered for analyses for this study:

- **Intention-to-Treat Population (ITT)** – The ITT analysis population will include all randomized participants who have a valid baseline and at least 1 valid post baseline wound assessment (examination). For the ITT analysis population, participants will be assigned to treatment group based on the randomisation schedule, regardless of the treatment actually received.
- **Per-Protocol Population (PP)** – The PP analysis population will include participants in the ITT analysis population set who do not have disqualifying important protocol deviations such as participants who did not satisfy the inclusion/exclusion criteria, participants who received the wrong treatment, or participants who were not compliant with the protocol.
- **Safety Population** – The Safety Population will consist of all enrolled and randomized participants who receive any study-related treatment procedure. Safety analysis will be analyzed **as treated**. All safety results will be presented based on the Safety Population.

9.3 General Considerations and Baseline Parameters

Unless otherwise stated, all statistical tests will be performed using 2-sided tests at the 5% significance level. Baseline is defined as the last observation before the intervention. Continuous demographic parameters, such as the Participant's age at the time of enrollment, will be summarized for the ITT population using descriptive statistics (N, mean, median, standard deviation, minimum and maximum value, and 95% 2-sided confidence limits). Categorical demographic parameters, such as gender, will be summarized as a proportion of the ITT population. Comorbid risk factors will be summarized for the ITT population by treatment assignment and according to the type of variable (categorical, continuous). Kaplan-Meier estimates for the individual time-to-event analyses will be prepared based on the ITT population. The number and proportion of participants who achieve complete closure will be tabulated and summarized using 95% binomial confidence intervals and compared between treatment groups using a Chi-square test.

Separate tables containing Participant counts, percentages, and 95% binomial confidence limits will be prepared based on individual risk factors.

9.4 Efficacy Analysis

9.4.1 Primary Efficacy Analysis (Time to Confirmed Wound Closure)

The primary efficacy variable for this clinical study is time to achieve confirmed wound closure, defined as the number of days from onset of wound reopening, spontaneous dehiscence, or diagnosis for not closable wound until the wound meets the wound closure definition. All participants in the trial should be observed 14 (–0 / +3 days) post first observation of wound closure to determine if the closure has been sustained. Wound closure is defined as 100% epithelialization with no need for drainage or adjuvant therapy or presence of sutures. Wound closure has to be confirmed after a minimum of 14 days.

If a wound was closed but was reopened prior to Day 14 post wound closure, this wound would be considered to not have achieved closure (unsustained closure).

Participants who fail to close during the acute study phase (Baseline to Day 42) will be censored at Day 42.

For the purposes of analyzing time to confirmed wound closure, the time to confirmed wound closure will be derived as: (date of first confirmed wound closure – date of onset of wound dehiscence) + 1 day.

For participants who fail to achieve confirmed wound closure until Day 42, time to confirmed wound closure will be derived as the smallest of: (date of discharge/ discontinuation – date of onset of wound dehiscence) + 1 day, and Day 42; this derived time will be censored.

The time to confirmed wound closure will be compared between treatment groups using a log rank test, and the supportive Kaplan-Meier curves will be generated and presented as well. As supportive analysis, a Cox proportional hazards regression will be performed. Covariates in the Cox regression model will be treatment assignment, study centre, wound size, and other baseline parameters, such as medical history (infection, diabetes, and cardiovascular disease), aetiology of wound, and wound closure method used.

9.4.2 Secondary Efficacy Analysis

Incidence of Confirmed Wound Closure

Confirmed wound closure is defined as in the primary efficacy section. Participants who discontinue the study prior to having achieved confirmed wound closure will be treated as a failure.

Incidence of confirmed wound closure at Day 42 will be analyzed using a Chi-square test comparing the 2 randomized treatment groups.

An additional supportive statistical analysis will include a logistic regression with factors and covariates in the model to include treatment assignment, study centre, and wound size, as well as appropriate baseline parameters, such as medical history (infection, diabetes, and cardiovascular disease), aetiology of wound, and wound closure method used.

Reduction in Wound Volume (cm^3)

The wound volume will be derived from the wound measurements (Length, Width, and Depth) recorded at every visit or time point of interest.

The actual wound volume will be assessed. The actual wound volume reduced at each respective visit will be derived as: actual wound volume – baseline wound volume.

The percentage wound volume reduced also will be assessed. Percentage wound volume reduced at each respective visit will be derived as: (actual wound volume – baseline wound volume) / baseline wound volume × 100.

A 3-factor (treatment group, site, and time) repeated measures (time) analysis of covariance, using the intra-Participant wound volume recorded at baseline as the covariate, will be used to assess the actual reduction, and a similar analysis will be performed for the percentage reduction in wound volume.

Reduction in Wound Surface Area (cm^2)

The wound area will be derived from the wound measurements (Length and Width) recorded at every visit or time point of interest.

The actual wound area reduced at each respective visit will be derived as: wound area – baseline wound area.

The percentage wound area reduced also will be assessed. Percentage wound area reduced at each respective visit will be derived as: (wound area – baseline wound area)/baseline wound area × 100.

A 3-factor (treatment group, site, and time) repeated measures (time) analysis of covariance, using the intra-Participant wound area recorded at baseline as the covariate will be used to assess the actual reduction, and a similar analysis will be performed for the percentage reduction in wound area.

Wound Recurrence

Wound recurrence will have occurred if a wound that had achieved confirmed wound closure is subsequently determined to be reopened at any time during the follow-up phase.

Wound recurrence will be analyzed using a Chi-square test comparing the randomized treatment groups. An additional supportive analysis will be performed using logistic regression analysis.

The population for this endpoint will consist of those participants who achieved confirmed wound closure during the study.

9.4.3 Patient-Reported Outcome

Wound-related Pain

Participants will provide an assessment of pain using an 11-point Likert Scale (Visual Analogue Scale). An estimate of the Participant's wound-associated pain and their worst wound-associated pain of the last 24 hours will be recorded at each study visit. Comparison between treatment groups will be performed using a Wilcoxon's rank sum test. Changes over time within each study group will be assessed with Wilcoxon's signed rank test.

Quality of Life

For each Participant, health-related quality of life (HR-QoL) will be assessed at hospital discharge, at wound closure, or Day 42 (end of study period) in case of non-closed wounds and at general follow up (Day 132). HR-QoL will be assessed using

the self-assessment instrument Medical Outcomes Study 36 Item Short Form Health Survey (SF-36) with 36 items.

The SF-36 will be analysed according to the user manual with 8 subscales and 2 summary scales (physical; psychological). QoL score will be calculated using the scoring manual. Differences in QoL scores between the treatment groups will be assessed using non-parametric rank statistics (Mann-Whitney U). Changes over time within each study group will be assessed with Wilcoxon's Signed Rank test.

Patient satisfaction

Patient satisfaction will include the Participant's evaluation of treatment result in regards to scarring and cosmetic aspects. These data or results will be obtained using specific scales from the Cologne Patient Questionnaire.

Differences between the treatment groups will be assessed using non-parametric rank statistics (Mann-Whitney U).

9.4.4 Health economic parameters

Economic-based outcome measures will include the assessment of parameters relevant for inpatient and outpatient resource use or utilization. This will involve direct medical resource use, and indirect resource use. Differences between the treatment groups will be assessed using non-parametric rank statistics (Mann-Whitney U). Changes over time within each study group will be assessed with Wilcoxon's Signed Rank test.

9.5 Safety Analysis

Safety analyses will be carried out using the Safety population to allow a benefit/risk assessment within the same study population. Safety parameters will include adverse device events (ADEs), serious adverse events (SAEs), and mortality during the duration of the study.

An event will be considered as treatment emergent if the onset is any time on or after randomisation through 30 days after the end of study device treatment. Any event with an onset on the day of randomisation where the time of onset is missing will be assumed to be treatment emergent.

The primary presentation of AE data will be prepared without regard to causality or relationship to study treatment.

Serious AEs and events leading to death will be summarized overall and by body system and preferred term. A life table or other similar analyses to show the relation to time on treatment and assess risk over time may be used.

Unsustained wound closure will be defined as a wound that was closed within the maximum treatment time of 42 days according to the respective criteria, but then subsequently wound closure was not confirmed after a minimum of 14 consecutive days. Incidence of unsustained wound closure will be analyzed using a Chi-square test comparing the randomized treatment groups. An additional supportive analysis will be performed using logistic regression analysis.

9.6 Interim Assessment

One interim analysis will be performed when 250 participants complete the first phase of the study. Both efficacy and safety parameters will be presented in the interim analysis, and the overall type I error rate will be adjusted using the O'Brien-Fleming method Interim data will be used to validate the assumptions made for the sample size calculation, and sample size re-estimation may be performed if warranted.

The trial will be stopped if interim results are able to show a positive effect for V.A.C.®-therapy in comparison with standard therapy at a p-value of <0.001 or if interim data analysis shows a negative effect for V.A.C.®-therapy at a p-value of <0.05.

9.7 Handling of Missing and Spurious Data

Specific algorithms for imputing missing or partially missing data will be discussed in the SAP. Imputed or derived data will be identified in the individual Participant data listings. Imputed data will not be incorporated into the CRF datasets. Imputed data will be used in the preparation of the derived datasets.

10 ETHICAL AND LEGAL ASPECTS

10.1 Ethics Committee

The principle coordinating investigator or in other countries than Germany the CI of every participating study center must submit this protocol to the appropriate EC if requested. As allowed by the EC, submission also may be done by IFOM on behalf of the CI. The CI is required to forward to University Sponsor (IFOM) a copy of the written and dated approval/favourable opinion signed by the Chair, or designee with EC composition. IFOM is required to forward to the KCI a copy of the written and dated approval/favourable opinion signed by the Chair with EC composition.

The study (study number, protocol title, and version number), the documents reviewed, and the date of the review should be clearly stated on the written EC approval/favourable opinion. This approval/favourable opinion will be provided to the ECs of all participating centers together with the CV of the responsible CI to get professional legal advice before enrolment of participants.

Enrolment of participants at a site will not start until a copy of the written and dated approval/favourable opinion has been received by IFOM.

During the clinical trial, any substantial amendment or modification to the protocol must be approved by the EC of the principal coordinating investigator but should also be sent to the participating ECs. The EC also should be informed of any event likely to affect the safety of participants or the conduct of the clinical trial as per local requirements. (see section SAE reporting)

A master ICF will be generated and will be adapted for every participating country as requested by the respective EC and according to local requirements. The ICF used by each CI in local language (as required from the ECs in every country for obtaining the Participant’s informed consent) must be reviewed and approved by IFOM prior to submission to the appropriate EC for approval/favourable opinion.

A progress report will be sent to the EC as per local requirements and a summary of the trial’s outcome will be reported at the end of the clinical trial.

The final study protocol, including the final version of the written ICF, must be approved or given a favourable opinion by the EC responsible for the CI before commencement of the study. The CI is responsible for informing the EC of any substantial amendment to the protocol in accordance with local requirements.

Changes and local modifications in accordance with local requirements have to be approved by IFOM and KCI.

The CI must provide the EC or other authorities with any reports of SAEs from the study as local regulations require. This also may be done by IFOM on behalf of the CI.

10.2 Ethical Conduct of the Study

This study is to be conducted in accordance with the following directives and guidelines:

- ICH Harmonised Tripartite Guidelines for Good Clinical Practice 1996
- EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data as transposed into national law
- EU Medical Device Directive 93/42/EC as amended by Directive 2007/47/EC as amended into national law
- ISO 14155 related to AE definitions
- In the spirit of the Declaration of Helsinki concerning medical research in humans (latest edition)

The CI agrees by signing the protocol to adhere to the instructions and procedures described and to adhere to the above regulatory requirements.

10.3 Regulatory Authority Approvals/Authorizations

Regulatory authority approvals, authorizations, or notifications, where required, will be in place and fully documented in accordance with European and national legislation.

10.4 Participant Information and Consent

Before inclusion (ie, before randomisation or any other study-specific procedure is undertaken) participants will be given written informed consent after receiving full, adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Participants also must be notified that they are free to discontinue their participation in this study at any time without any disadvantages. Participants will be informed that ICH-GCP practices will be maintained throughout

the trial. Participants also will be informed about and agree to having their data captured, monitored, and inspected by qualified personnel or regulatory authorities from inside and outside of the country. Participants will be informed that they may be contacted by phone, fax, mail, or email during the follow-up portion of the study.

Within each center, the CI will be responsible for obtaining written informed consent. The CI can delegate Participant information to a qualified sub-investigator who is informed in full detail about the study. Participants will be given the opportunity to ask questions and allowed time to consider the information provided.

Participant information will be updated if new relevant information becomes available that changes the risk-benefit assessment. Participants already enrolled in the study will be informed by the CI, especially if the Participant's safety is a concern.

The original of the ICF will be kept with the study documentation at the individual study site. Every participating Participant will receive a copy of the Participant information guide and the signed ICF.

During monitoring, ICFs will be checked for each participating Participant by the IFOM CRAs.

The CI will inform a potential Participant of the intention of this clinical trial. The potential Participant and the CI or his/her designated research staff member must sign and date the ICF before the potential Participant can participate in any clinical trial-related activities. The potential Participant will provide a written and signed ICF prior to participating in any clinical trial-related activities using the EC-approved ICF. The Participant will proceed through clinical trial participation as outlined in this section. A clinical trial calendar summarizing the assessments and procedures for this clinical trial is provided in Table 7.

Informed consent will be obtained under the conditions set forth in ICH-GCP guidelines.

- Potential participants must be made aware of the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the ICF.
- Potential participants shall have sufficient opportunity to ask questions and consider participation in the clinical trial.
- Consent forms shall be written in local language that is non technical and understandable to potential participants or a potential Participant's LAR.
- Potential participants cannot be led to believe that they are waiving their legal rights to release the PCIs, CCI, KCI, institution, IFOM, or any of their agents from liability from negligence.
- Potential participants will be asked to sign and date the informed consent, indicating their permission for enrolment in the clinical trial.
- The PCI's responsibilities related to the ICF process include:
    - Screening out potential clinical trial participants who may not be able or willing to comply with the protocol.
    - Assuring that only potential participants fully meeting the Inclusion Criteria and not meeting any Exclusion Criteria are included in the clinical trial.
    - Assuring that participants have signed the ICF prior to being enrolled in the clinical trial.
    - Documenting how informed consent was obtained, including any question(s) asked by the potential Participant or potential Participant's LAR prior to signing the ICF and the corresponding responses. If no questions are asked, this should be recorded.

The case history for each Participant shall document that informed consent was obtained prior to participation in the study.

10.5 Insurance

According to transposition of the (amended) Medical Devices Directive, local insurance shall be applied for. The insurance policy will be referenced in the Participant Information documents.

10.6 Confidentiality

The written ICF will explain that the study data will be stored in a computer database, maintaining confidentiality in accordance with local data legislation and the EU

directive 95/46/EG. Participants in this database will be identified by Participant identifier only. The Participant identifier format will be in accordance with local requirements. The Participant information also will explain that for data verification purposes, authorized representatives of the CIs, a regulatory authority, an EC, IFOM, or KCI may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Anonymity of participants will be assured when presenting the data at scientific meetings or publishing in scientific journals.

In accordance with the Investigator Agreement, all materials, information (oral or written), and unpublished documentation provided to the CIs (or any company/ institution acting on their behalf), including this protocol and the Participant CRFs, are exclusive property of KCI and may not be given or disclosed, either in part or in whole, by the CI or by any person under his/her authority to any third party without the prior express consent of KCI.

The submission of this protocol and other necessary documentation to the EC is expressly permitted. The EC members have the same obligation of confidentiality.

The CI shall consider all information, results, discoveries, and records accumulated, acquired, or deduced in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, and records to any third party without the KCI's prior written consent.

11 SAFETY

Device- and wound-related AEs and all SAEs will be captured after the Participant has signed the ICF. Device- and wound-related AEs will be captured at each study visit during treatment period. All SAEs will be captured at each study visit including all follow-up visits regardless of causality or severity.

11.1 Warnings/Precautions

All described surgical techniques are currently used in general surgical practice. All wound care materials to be used in this trial, in both the V.A.C.® Therapy and SCWT arms, are CE approved or marketed. When any study materials are used in combination with drugs, the drugs must be marked as approved in the country in which they are used.

11.2 Expected Adverse Events

Known risks of V.A.C.® Therapy and SCWT include the following:

- Pain during therapy or dressing changes (especially if tissue grows into wound-dressing material)
- Maceration of the surrounding skin (periwound maceration)
- Desiccation of wound
- Local infection with signs of inflammation
- Dehiscence
- Serious or fatal bleeding from the wound or adjacent blood vessels in participants with weakened or sutured vessels
- Irritation or sensitivity to the drape used to secure dressings (eg, skin rash)
- Pieces of dressing material accidentally left behind in the wound that become embedded in the wound tissue
- Technical problems (eg, leaks, blockage of tubes, breakage of seals)
- Minor bleeding
- Cellulitis

11.3 Potential Risks Associated with Study Participation

Participation in this clinical trial presents risks and benefits to participants in both V.A.C.® Therapy and SCWT treatment arms. Some risks and benefits to participants are generalized, regardless of the treatment arm, while others are specific to the assigned therapy. General risks and benefits are outlined in Table 5.

Table 5: Potential Risks and Benefits Associated with Study Participation

Potential Risks and Benefits Associated with Study Treatment Participation	
Potential Risks	• Wound may not heal by the end of the clinical trial • Pain during debridement • Stinging/burning/pain associated with wound dressing changes
Potential Benefits	• Participants will receive frequent and comprehensive medical treatment for and monitoring of their wounds from a research team comprised of physicians and other health care professionals.

11.4 Potential Risks and Benefits Associated with V.A.C.® Therapy and SCWT

Incidents, complications or adverse reactions have been reported only sporadically while using V.A.C. ® Therapy for treating acute and chronic wounds. (Table 6)

Table 6: Potential Risks and Benefits Associated with V.A.C.® Therapy

V.A.C.® Therapy	
Potential Risks	• Pain during therapy or dressing changes • Maceration • Desiccation • Infection • Rash • Cellulitis • Osteomyelitis • Wound dehiscence • Serious or fatal bleeding from the wound or adjacent blood vessels in participants with weakened or sutured blood vessels • Tissue may attach to the foam if it is left in for too long or if the wound grows aggressively • Irritation or sensitivity to the drape used to secure the dressing • Minor bleeding

Potential Benefits	• Creates an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing wound bed for closure • Reducing edema • Promoting granulation tissue formation and perfusion • Removing exudate and infectious material

The below potential AEs can usually be avoided by complying with the basic rules of vacuum therapy (as detailed in the manufacturer's instructions for use and Guidelines for the use of V.A.C.® Therapy) as well as by the use of specific designed vacuum device systems or can be significantly reduced [30-32].

- Ingrowth of granulation tissue into the sponge

The pull caused by granulation stimulus may lead to an ingrowth of tissue into the sponge, especially if the system was not changed for a long period of time. Descriptive literature on the use of the V.A.C.® Therapy System reported this event almost exclusively if the recommended time course of 2-3 days between 2 dressing changes was exceeded.

The ingrowth of the sponge into underlying and surrounding tissue was predominantly observed in well vascularized, soft tissue with a high tendency for granulation tissue growth [30, 33, 34]. Removal of foam with tissue ingrowth can result in minor tissue trauma or bleeding.

- Pain caused by pull or dressing changes

Wound patients generally suffer from pain, especially during wound dressing changes.

Clinical practitioners should make arrangements for an optimal pain treatment.

An increased pain perception during therapy or during dressing changes was shown to appear in about 2% of the V.A.C.® treated patients [34].

Pain caused by suction on the wound may be reduced by using lower negative pressures between 50-100 mmHg, which still was to be shown to have adequate effects on wound healing. In standard practice, a suction fortitude of 125 mmHg is tolerated by the patients and viewed as painless [35, 36].

- Maceration and pressure damage

Maceration caused by the occlusive foil and the applied pull appear in about 20% of the V.A.C.® treated patients with chronic wounds. Mostly this effect is caused by a fragile surrounding area of the wound or a decreased perfusion in patients suffering from chronic wound healing impairments.

Establishing adequate counteractive measures like exact fitting of the sponge, protection of wound margins with foils or dressings, and elimination of leakages can avoid the appearance of maceration of wound margins or surrounding area [34, 37].

Pressure damages are rarely possible if the T.R.A.C.™ Pad is larger than the wound itself. In this case, wound margins should be protected by a second sponge prior to application of the system [38, 39].

Table7 lists the potential risks and benefits associated with Standard Conventional Wound Therapy (SCWT).

Table 7: Potential Risks and Benefits Associated with SCWT

Standard Conventional Wound Therapy (SCWT)	
Potential Risks	• Risk of bleeding from the wound • Pain during therapy or dressing changes • Maceration • Desiccation • Infection • Rash • Cellulitis • Osteomyelitis • Wound dehiscence • A piece of dressing material may be accidentally left in the wound • Tissue may attach to the foam if it is left in for too long or if the wound grows aggressively • Irritation or sensitivity to the tape used to secure dressing • Minor bleeding

Potential Benefits	• Promotes a moist wound environment • May remove necrotic tissue • Controls exudates • May control infection • Insulates the wound • Minimizes pain • Ease of use • Multiple and versatile dressings available to meet the needs of the wound or wound environment

11.5 Other Study-related Risks

The trial protocol does not include any invasive procedures, such as wound biopsies or additional blood testing beyond routine clinical care. Furthermore, no radiographic examinations are demanded by the study protocol. All wounds will be redressed in certain intervals, but the frequency of wound care visits is not different from routine clinical care.

11.6 Risk-Benefit Analysis

Participation in this trial presents risks and benefits in both V.A.C.® Therapy and SCWT treatment arms. Some risks are generalized regardless of the treatment arm, while others are specific to assigned therapy.

Possible risks that are not related to the treatment arm are wound healing disturbances, pain caused by debridement, pain associated with dressing changes, wound infection, and minor bleeding.

It can be argued that for an individual with an open abdominal wound with intact fascia, trial participation entails only minimal risk because the probability and magnitude of harm or discomfort anticipated in this trial are not greater than those ordinarily encountered in routine clinical care. Patients with an open abdominal wound with intact fascia routinely receive a variety of dressings, including V.A.C.® Therapy and SCWT. To some extent, the choice of dressing depends on medical variables, such as size of wound, but institutional aspects also play a very important role. Therefore, randomisation within this trial only mimics everyday clinical practice, where V.A.C.® Therapy is being tried on some but not all patients. The medical risk

of wound therapy in this trial is not different compared to routine clinical care. Patients with a potentially higher risk (eg, impaired blood coagulation) and vulnerable populations (eg, pregnant women) are identified during the screening process and will not be included in the trial.

Trial participation involves additional follow-up visits and assessment of participative parameters, such as quality-of-life and pain. Nevertheless, this imposes only minimal risk and inconvenience for trial participants.

Trial-related procedures (eg, wound documentation and photograph) do not delay wound therapy in an unduly way. The confidentiality of all documentation is protected. Furthermore, participants will not have to pay any costs related to the trial.

In accordance with national and international clinical trial regulations such as ICH-GCP, ISO 14155, and general ethical principles, no patient will be randomized or receive any trial-related procedure before written informed consent has been obtained and the screening process has been successfully completed. The trial will only be started in a center if the EC responsible for the CI has approved the study. By continuous monitoring of trial safety data and published evidence on wound therapy, the IDMC, CCI, KCI, and IFOM will be responsible for Participant safety issues during the ongoing trial. Based on the incidence of SAEs, the IDMC may recommend terminating the trial or changing the protocol.

Some potential benefits of trial participation may be assumed for individuals who take part in the trial. Most importantly, participants may receive a wound therapy that is better than that when compared to the usual clinical care. This may be the case because V.A.C.® Therapy is not applied routinely to open abdominal wounds with intact fascia, especially on an ambulatory basis. Preliminary evidence suggests beneficial effects of V.A.C.® Therapy on open abdominal wounds with intact fascia.

From a societal perspective, the trial will be able to answer the important question of which of the 2 therapies studied is superior to the other. In addition, because the design of the trial is in accordance with the highest scientific standards, this ensures the likelihood of obtaining the quality of results necessary to answer the hypothesis

that V.A.C.® Therapy is more effective than SCWT on open abdominal wounds with intact fascia. The number of trial participants is based on a sample size calculation. Therefore, trial results are likely to improve medical care of a large group of patients around the globe. In summary, it can be stated that the benefits and risks of this trial are, on balance, favorable, both on an individual level and on a societal level.

11.7 Adverse Event Monitoring

Participants will be monitored regularly during visits for development of AEs, and data on AEs will be collected in both the V.A.C.® Therapy arm and the SCWT arm. The CI or his/her delegate must report to IFOM any SAEs as soon as possible and at the latest within 24 hours of knowledge of occurrence. KCI will be notified by IFOM within 24 hours after knowledge of occurrence of a SAE. IFOM will take care that all SAEs/SADEs will be notified to the authorities as requested by local law and the ECs. IFOM will advise the Clinical Investigator on the applicable reporting requirements. All SAEs will be followed by the CI up to 30 days after last follow-up visit or until resolution/stabilization. After the end of the trial, the CI will be informed about trial participation and responsibilities by a letter of the PCI. IFOM will inform KCI, the ECs and the IDMC according to agreements and law about incidence of SAE/SADEs during and after the trial as per local regulations.

11.8 Safety Monitoring

Participant safety is of the utmost importance in this clinical trial. IFOM and KCI will ensure that all research sites are trained and consequently monitored for adequate safety reporting. The IFOM CRA will review all Participant data to confirm that all SAEs and SADEs are reported accurately and promptly to IFOM. Each participating CI has the responsibility for the safety of the participants under his/her care.

Wound related AEs, SAEs, ADEs, and SADEs in the V.A.C.® Therapy group will be monitored and processed by IFOM until their resolution or stabilization; ADEs and SADEs will be processed in KCI's complaint system and will be reviewed for reporting according to EU vigilance guidelines. Wound related AEs, SAEs, ADEs, and SADEs in the SCWT group will be logged and monitored by IFOM until their resolution or stabilization; resolution for ADEs and SADEs will be the responsibility of the subsequent manufacturer per their vigilance requirements. The specific guidance

on safety reporting responsibilities between IFOM and KCI can be found within the respective safety plan for the trial.

11.9 Adverse Event Definitions

Adverse Event

According to ISO 14155-11, an adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Serious Adverse Event

According to ISO 14155-11, ICH GCP and MEDDEV2.7/3, a serious adverse event is an adverse event that

a. led to a death,
b. led to a serious deterioration in the health of the Participant that
    1 resulted in a life-threatening illness or injury,
    2 resulted in a permanent impairment of a body structure or a body function,
    3 required inpatient hospitalization or prolongation of existing hospitalization,
    4 resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.
c. led to fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned hospitalisation for pre-existing condition, or a procedure required by the study protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

All SAEs should be reported to IFOM as soon as possible and at the latest within 24 hours of knowledge of their occurrence; these will be followed by the CI until stabilization or resolution.

Adverse Device Effect

According to ISO 14155-11,

An adverse device effect is an adverse event related to the use of an investigational medical device

Serious Adverse Device Effect

According to ISO 14155-11, a serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated (Unexpected) Adverse Event

All AEs not consistent with those listed as in section 11.2: “Expected Adverse Events” of the SAWHI study protocol or in the product instructions of the devices used within the study are regarded as unanticipated / unexpected. Adverse Events related to a procedure will be regarded as expected if the event is mentioned in the literature.

11.10 Documentation of Adverse Events

Wound related AEs, ADEs, and all SAEs including a separate documentation of SADEs will be documented in the CRF.

11.11 Reporting of Serious Adverse Events and Incidents

CIs will inform IFOM as soon as possible and at the latest within 24 hours about any SAE or incident.

The PCI will inform IFOM and KCI, IDMC, EC, CIs, and competent authorities about any relevant changes to the risk-benefit ratio.

11.12 Reporting Requirements

The CI has the primary responsibility for safety of individual participants under his or her care. In this function, the CI should routinely monitor each Participant for the occurrence of any AE.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate. CIs will inform IFOM as soon as possible and at the latest within 24 hours about any SAE or incident.

For every SAE and wound and device related AE that occurs, a full description of the event should be recorded including the date of onset, time course, severity, causal relationship to study treatment, and alternate causality if not related to the study treatment, action taken regarding the study treatment, outcome, and the treatment applied if any. Relevant procedures are all measurements to prepare the wound (e.g. debridement), V.A.C.®-installation, V.A.C.®-treatment and dressing changes.

As the event term, the CI should list the specific diagnosis, disease, or syndrome rather than associated signs and symptoms. However, if the CI does not consider an observed or reported sign or symptom a component of a specific disease or syndrome, it should be recorded as a separate AE.

The CI is also responsible for reporting all device malfunctions whether or not they resulted in an AE for the Participant. If a device failure resulted in an SAE/SADE for the Participant, this SAE/SADE must be reported as previously noted.

Reporting of Pregnancies

If a Participant becomes pregnant during the course of the study, she must notify her study doctor immediately. If the Participant becomes pregnant during the study, the Participant can no longer continue in the study. CIs will inform IFOM as soon as possible and at the latest within 24 hours after knowledge about the pregnancy of a Participant and the pregnancy's outcome.

12 REPORTING AND PUBLICATION

12.1 Study Report

Interim Report

An interim assessment report will be done after 250 participants have either completed the study or withdrawn prematurely, as described in section: Determination of Sample Size.

Annual Study Report

The purpose of the Annual Study Report is to meet reporting obligations to the EC. The Annual Study Report will be completed annually and submitted to the EC and other competent authorities, as required.

Final Study Report

The Final Study Report will present the results of the trial, including appropriate tables and figures in the spirit of unbiased objectivity. The PCIs will provide the EC with a summary of the trial's outcome, and if applicable, the regulatory authorities with any reports required. The report or parts of it may be submitted in the form of a summary, a synopsis, published article, or similar document.

Clinical Study Report

The Clinical Study Report (CSR) will be finalized within 1 year of the study's completion.

12.2 Publication

Both positive and negative results of the trial will be disclosed. The results of the trial will be submitted for publication to peer-reviewed scientific journals and/or presented at international scientific congresses. The trial will be registered at a national German as well as at an international WHO approved register.

The Principal Coordinating Investigator and the Steering Committee are responsible for the primary and secondary publications and/or presentations arising from the study. No other publication or presentations of the results of the study are allowed before the primary publication and/or presentation is released. All publications and/or presentations are part of additional requirement more specifically addressed within each institution's clinical trial agreement.

KCI is entitled to examine the manuscript prior to publication and to make comments on it. KCI may delay publication for up to three months after analyzing the research results if it is applying for a patent or other important reasons.
All publications will maintain data protection of Participant data as well as data of the participating Investigators.

The publishing of data from a single study center is permitted after analysis and primary publication of the final results only. Publication of study results or data, including data of a single study center, has to be reviewed and approved by the Steering Committee, IFOM, and KCI.

KCI guarantees IFOM the publication rights for study results. Study results will be prepared for publication according to CONSORT statement. CONSORT, which stands for Consolidated Standards of Reporting Trials, encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials (RCTs) [40].

Every CI who enrolled more than 15 patients into the trial will be offered a Co-authorship for the primary publication. In addition the CI may nominate one of his subinvestigators to be included in the authorlist.

The Steering Committee and IFOM will furnish KCI with a written copy of any proposed publication or presentation of material related to the trial at least 30 days in advance of the submission of any proposed publication (eg, abstract, manuscript) or presentation (eg, poster, seminar) for inclusion at an event (eg, scientific meeting, annual conference).

13 CHANGES IN TRIAL CONDUCT OR PLANNED ANALYSIS

In order to maintain comparable conditions in all study centres and to obtain an objective data analysis, changes to the protocol are not intended. If changes become necessary, they are to be reported as an amendment. The amendment will be agreed upon by the IDMC, Steering Committee, IFOM, and KCI. The amendment will be approved and signed by the same individuals who signed the protocol. The amendment then becomes part of the protocol. An amendment must be approved by each responsible EC and must be submitted to regulatory authorities when appropriate.

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APPENDICES

A Schedule of Visits
B Guideline for Photo Documentation
C Patient Satisfaction Questionnaire
D Documentation sheet for wound assessment
E Documentation sheet for wound-related procedures
F Documentation Sheet for medical history
G SF-36®