Protocol No.: KCI.VERAFLO.2018.02

NCT#: NCT05902793

A prospective, multi-center, randomized, open label, parallel-group controlled, non-inferiority trial evaluating the efficacy and safety of the V.A.C. VERAFLO™ Dressing Kit for wound bed preparation in open wounds with extensive soft tissue damage

Name of the Investigational Device:	V.A.C. VERAFLO™ Dressing Kit
Model and Specification:	ULTVFL05SM/NSP ULTVFL05MD/NSP ULTVFL05LG/NSP ULTLNK0500 ULTDUO0500
Class Ⅲ Medical Device Requiring Approval for Clinical Trials	Yes☐ No☒
Protocol Version No. and Date:	2.0, 23-Aug-2022
Leading Institution:	The Second Affiliated Hospital of Zhejiang University School of Medicine
Coordinating Investigator:	
Sponsor:	KCI USA, Inc.
Agent:	上海铠唏尔医疗器械贸易有限公司

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List of Abbreviations

Abbreviations	Meaning
ADE	Adverse Device Effect
AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
ANCOVA	Analysis of Covariance
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electric Data Capture
FAS	Full Analysis Set
FDA	U.S Food and Drug Administration
GCP	Good Clinical Practice for Medical Device
ICF	Informed Consent Form
IFU	Instructions for Use
INR	International Normalized Ratio
MOA	Mechanisms of Action
NMPA	National Medical Products Administration
NPWT	Negative Pressure Wound Therapy
NPWTi-d	NPWT and Solution Instillation with a Dwell Time
PD	Protocol Deviation
PI	Principle Investigator
PPS	Per-Protocol Set
PT	Prothrombin Time
OR	Operating Room
RBC	Red Blood Cell
WBC	White Blood Cell
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCI	Spinal Cord Injury
SD	Standard Deviation
SMV	Site Monitoring Visit
SOP	Standard Operating Procedure
SS	Safety Set

1 Sponsor Information

1.1 Name of Sponsor

KCI USA, Inc.

1.2 Address of Sponsor

12930 IH 10 West, San Antonio, Texas 78249 USA

1.3 Contact Information of Sponsor

Name:

Telephone:

E-mail:

1.4 Qualifications of Sponsor

ISO 13485 Certificate, 510K Certificate, please see **Appendix 1** for details.

1.5 Agent Information

1.5.1 Name

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1.5.4 Qualifications

Business license information,

License#:05000002202012220005

2 List for All Sites and Principal Investigators of Multicenter Trial

See **Appendix 2.**

3 Background Information of Clinical Trial

3.1 Research and Development Background

3.1.1 Treatment Field Background

3.1.1.1 Wound Management

The management of wounds represents a significant challenge in healthcare. There are many considerations necessary in developing the optimal treatment plan for achieving wound care goals. It is recognized that effective wound management requires a comprehensive assessment of both the patient and the wound to determine the optimal treatment plan for achieving wound care goals. Numerous wound and patient risk factors are known to potentially complicate wound healing and increase health care costs[1, 2]. Wounds at risk for delayed healing include those with extensive tissue loss, critical colonization and/or infection, high levels of exudate or exposed critical structures. Historical factors, including the duration the wound has been open, the number of times it has been open and previous attempts to close the wound, help define the timeline until closure.

Wounds heal either by primary, secondary or tertiary intention. Closure by primary intention occurs if there is no loss of tissue, or when the wound is surgically closed immediately following the injury by direct approximation of the wound margins or by graft or flap. Typically, this type of wound is closed within 6 hours of injury. Secondary intention (or closure by secondary intent) refers to healing without surgical intervention of a wound that is intentionally left open because of the presence of infection, excessive trauma or loss of tissue with separated edges of the wound. Closure occurs when wound edges come together via granulation tissue formation and subsequent epithelialization[3]. Tertiary intention occurs when a wound is initially left open after removal of all non-viable tissue. Wound edges are surgically brought together after a period of open observation, when the wound appears clean and well vascularized. Tertiary intention can also refer to subsequent surgical repair of a wound initially left open or not previously treated. This method is indicated for infected or unhealthy wounds with high

bacterial content, wounds with a lengthy time lapse since injury or wounds with a severe crush component with significant tissue devitalization [4].

3.1.1.2 Standard Treatment of Wound

Current standard treatment of wound in the management of wounds may involve clinical assessment, debridement, antibiotic treatment and local application of antiseptics or antimicrobials, and drainage. Delayed primary closure (when necessary), use of drains and repeated wound cleansing are fundamental concepts in caring for these at-risk wounds. Critical to the process of wound healing, wound irrigation is to instill the steady flow of a solution across an open wound surface to achieve wound hydration, remove deep debris and assist with visual examination. The irrigation solution is meant to remove cellular debris, wound exudate and metabolic wastes to help create an optimal wound healing environment[5, 6].

Wound bed preparation is the critical issue for delayed primary wounds healing. Wound bed preparation is defined as the comprehensive management of the wound to accelerate endogenous healing by eliminating negative factors that prevent wound healing[7-9]. Wound bed preparation is most important for wounds with excessive tissue loss, when the strategy is to close the wound by secondary intention, or when wounds need to be prepared for grafts, such as split-thickness and epidermal skin grafts. This process often involves management of necrotic tissue, infection/ inflammation and moisture balance for wound healing. A method as part of an active wound closure strategy involves consideration of therapy goals, such as wound cleansing, wound granulation tissue formation and a combination of both, prior to delayed primary or secondary wound closure.

Table 3-1 Goals of wound bed preparation[10]

cleanse	granulate
· Remove contamination/infectious materials · Dilute and solubilize/devitalized tissue · Decrease exudate	· Increase granulation preparation · Promote wound fill · Cover exposed structures

3.1.2 Negative Pressure Wound Therapy

Choice of therapeutic modality is one of many important decisions. Over time wound care has progressed from use of products such as dry gauze to advanced moist wound therapies and further to active wound healing therapies. One of such advanced wound healing therapies is negative pressure wound therapy (NPWT), which was developed in the 1990s[11]. NPWT is a technology that is currently used widely in wound care and is promoted for use on complex wounds (open wounds)[12].

NPWT consists in applying topical sub-atmospheric pressure to a wound that is sealed off by a specially designed dressing (reticulated open-cell foam) and connected by a tube to a suction pump and drainage collection system. The amount of pressure applied using the therapy can vary and there is no single protocol for use, however, pressure being delivered ranges from -75 mmHg to -150 mmHg, with -125 mmHg being commonly used[13].

The place of NPWT in the treatment pathway and the rationale for its use vary based on different types of traumatic wound and local treatment protocols. For open fracture wounds that have been debrided but are still waiting for soft tissue cover, NPWT is considered as an intermediate wound dressing prior to further surgical intervention.

For more general soft tissue trauma wounds, the use of NPWT can vary: the treatment may be used on open wounds with the aim of promoting healing by secondary intention. Many studies used NPWT following surgical debridement until wounds were ready for coverage or closure surgery. And NPWT has been shown to speed up wound closure rates compared with standard wound care dressings[14-16]. Arti et al. used NPWT on debrided open wounds for 10 to 14 days with the aim of reducing wound size and promoting granulation to allow either change to a conventional dressing or further surgery for skin grafting or flap closure[17].

3.1.2.1 Mechanisms of Action

The mechanisms of action (MOA) for NPWT are well established and include both mechanical (macrostrain) and biological (microstrain) tissue responses[18-21]. The

therapy delivers mechanical stress to the tissue and cells by stretching them as the tissue is pulled up into the open pores of the foam. Mechanical forces draw wound edges together (macrostrain) and stretch cells (microstrain). Cell stretch triggers mitosis, resulting in proliferation and ultimately granulation tissue formation.[19] Porcine studies have shown that NPWT increased local blood flow and the rate of granulation tissue formation[22-24]. Removal of high volumes of wound exudate, containing enzymes and other proteins involved in inflammation, may prevent further tissue damage. Removal of this fluid also reduces the frequency of dressing changes by keeping the surrounding skin dry, particularly around anatomically challenging wounds.

3.1.2.2 Negative Pressure Wound Therapy with Instillation

The therapy of NPWT and solution instillation with a dwell time (NPWTi-d) to adjunctively treat high-risk wounds that would benefit from vacuum-assisted drainage and controlled repeated delivery of topical wound solutions, such as normal saline and wound cleansers. Recent evidences suggest that normal saline[25, 26] is effective and is readily available. Normal saline solution is physiologically compatible and non-toxic and, thus, can maintain cell viability. Normal saline does not damage tissue, cause allergies or sensitization or alter the normal flora of the skin; therefore, it does not interfere with the normal healing process[27].

NPWTi-d is a tool primarily suited for wounds that are being prepared for delayed primary closure by either surgical or non-surgical closure, depending on goal of therapy: cleansing (e.g. removal of infectious material and other wound debris) and/or granulation tissue formation.

Combining NPWT with topical wound instillation provides further advantages for wound healing. Instillation and dwell of a topical wound solution allows thorough coverage of the wound bed, thereby cleansing the wound. The topical wound solution that is allowed to dwell over the wound bed also has the potential to dilute and solubilize infectious materials, devitalized tissue and slough.

Currently, wound cleansing is often achieved through lavage, a procedure in which the

wound is irrigated under pressure with one of several widely used solutions. NPWTi-d differs from irrigation and lavage in that the instilled fluid is slowly introduced into the wound and remains in the wound bed for a defined period of time before being removed by applying negative pressure. Automated instillation creates a controlled, protected environment for flushing and cleansing wounds by the proposed mechanism of loosening soluble contaminants in the wound bed followed by subsequent removal during NPWT. As a result, the planktonic bacterial burden can be decreased, contaminants removed, and the wound thus cleansed, without manual intervention. In addition, instillation with NPWT can also lower wound fluid viscosity, which in turn facilitates more efficient removal of exudates and infectious material through the foam and into the canister[28-30].

Enhanced granulation tissue production has been reported with use of NPWTi-d with saline instillation versus conventional NPWT in several comparative studies [25, 26]. Kim et al. reported fewer operative visits, shorter time to final surgical procedure, shorter hospital length of stay and greater percentage of wounds closed before discharge with NPWTi-d with polyhexanide instillation versus NPWT[31]. Easier and less painful dressing changes with NPWTi-d versus NPWT have also been noted[32].

3.1.3 V.A.C. VERAFLO™ Dressing Kit

Since the introduction of NPWT, a variety of new therapies and dressings have been developed in order to better meet the needs of patients with wounds. In 1998, Fleischmann et al described the coupling of NPWT with timed, intermittent, gravity fed delivery of a topical solution[33]. KCI® later developed and commercialized this technology as the V.A.C Instill® Wound Therapy System in 2003[34]. The latest development in V.A.C® technology is the V.A.C. UTLA™ Therapy System which integrates both V.A.C® Therapy and instillation into one therapy unit. The V.A.C. ULTA™ Therapy System consists of a new programmable therapy pump and a specialized dressing system (V.A.C. VERAFLO™ Dressing Kit).

V.A.C. VERAFLO™ Dressing Kit, which is the investigational device, is a reticulated

open-cell foam polyurethane ester dressing that is designed to be hydrophobic to deliver the various compatible topical wound instillation solution(s) to the wound site for therapy[32]. The V.A.C. VERALFO™ Dressing Kit is a 510(k) -cleared, Class II device (K100657), which was approval in July 2010 by FDA. V.A.C. VERAFLO™ Dressing Kit with V.A.C. ULTA™ Therapy System is intended to create an environment that promotes wound healing by secondary or tertiary (delayed primary) intention by preparing the wound bed for closure, reducing edema, promoting granulation tissue formation and perfusion, and by removing exudates and infectious material. The instillation option is indicated for patients who would benefit from vacuum assisted drainage and controlled delivery of topical wound treatment solutions and suspensions over the wound bed.

In at least two clinical studies [25, 26], enhanced granulation tissue formation has been observed using V.A.C. VERAFLO™ Dressing with saline instillation. This has been corroborated in one porcine study[35].

3.1.3.1 Summary of Animal, in Vitro Studies and Clinical Trials

While there is broad acceptance and a large body of evidence that supports NPWTi-d (with V.A.C. VERAFLO™ Dressing Kit) as an important tool in aiding wound healing. Most evidence include animal studies, expert opinion, case reports, case series and involving prospective treatment groups compared with control.

In 2012, Anthony et al,[30] compared continuous and periodic wound instillation in conjunction with negative pressure wound therapy using an agar-based model. Continuous instillation at a rate of 30 cc/hour with negative pressure showed isolated exposure of instillation fluid to wound beds in agar wound models with and without undermining and tunneling. In contrast, periodic instillation illustrated uniform exposure of the additive to the entire wound bed including undermined and tunnel areas, with increased staining with each instillation cycle. These findings suggest that periodic instillation facilitates more uniform exposure throughout the wound, including tunnels and undermining, to instillation solutions, thereby providing therapy consistent with the

clinician-ordered treatment.

In 2013, Lessing et al,[35] found that a greater reduction in wound area and perimeter in NPWTi-d wounds compared to all NPWT wounds ($P < .05$) by 3D images Analysis on porcine excisional wounds.

In 2011, a post marketing study using VAC. VERAFLO™ Dressing in operatively debrided wounds, the results showed that there was no statistically significant difference in the time to wound deemed ready or closure or coverage between NPWTi-d (n=71) and NPWT(n=66) subjects (mean 6.8 vs 6.3 days, median 6 vs 5 days, respectively; $p = 0.7105$) in the Per-Protocol Population (NCT01867580).

In 2013, Brinkert et al,[25] collected 131 patients treated with V.A.C. VERAFLO™ Dressing. Mean duration of NPWTi-d was 12~19 days. 98% of the cases, the wounds were closed after debridement and following the use of NPWTi-d.

3.2 Basic Product Information of Investigational Medical Device

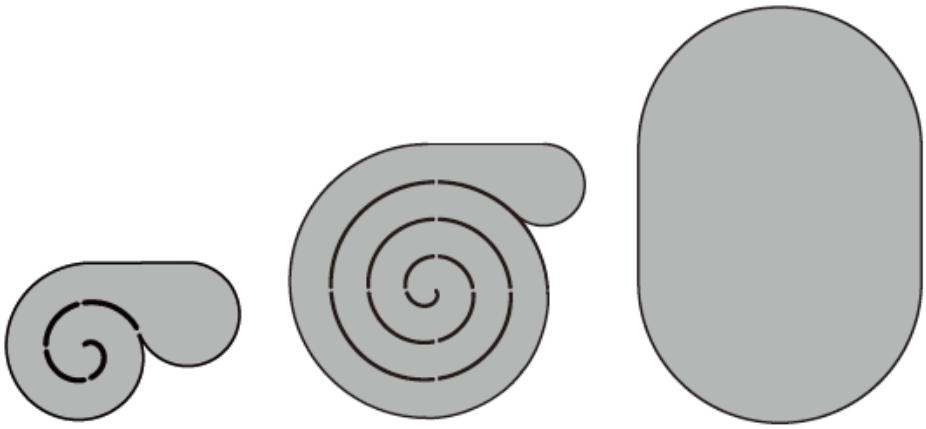
3.2.1 Features

The V.A.C. VERAFLO™ Dressing is designed to be used with instillation therapy. the V.A.C. VERAFLO ™ Dressing is more hydrophilic for improved wetting of the foam during instillation of wound treatment solutions and suspensions. Open wound therapy that alternates cycles of NPWT with cycles of soaking the wound bed with topical wound treatment solutions and suspensions. It allows the clinician to customize cycles of instillation, with a suitable solution to a wound.

3.2.2 Structure and Component

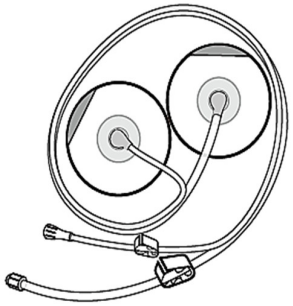
The V.A.C. VERAFLO™ Therapy consists of V.A.C. VERAFLO™ Dressings Kit (small / medium / large), V.A.C. VERALINK™ Cassette, and an optional accessory, V.A.C. VERAT.R.A.C. DUO™ Tube Set. The V.A.C. VERAFLO™ Dressings Kit consists of Black Foam (small, medium, large), V.A.C. VERA T.R.A.C.™ Tube (in small and medium package) or V.A.C.VERAT.R.A.C. DUO™ Tube Set (in large package), V.A.C.® Advanced Drape (sticky sealing film) and V.A.C.® Ruler.

Model	Description	Composition
ULTVFL05SM/NSP	V.A.C. VERAFLO™ Dressing, 5-pack, Small	VERAFLO™ Dressing Drape Tube Ruler
ULTVFL05MD/NSP	V.A.C. VERAFLO™ Dressing, 5-pack, Medium	VERAFLO™ Dressing Drape Tube Ruler
ULTVFL05LG/NSP	V.A.C. VERAFLO™ Dressing, 5-pack, Large	VERAFLO™ Dressing Drape Tube set Ruler
ULTLNK0500	V.A.C. ULTA VERALINK, 5−pack	VERALINK™ Cassette
ULTDUO0500	V.A.C. VERAT.R.A.C. DUO™ Tube Set, 5-pack	VERAT.R.A.C. DUO™ Tube Set

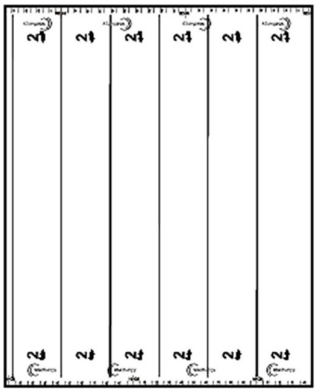


V.A.C. VERAFLO™ Dressings (Small, Medium, Large)

V.A.C. VeraT.R.A.C.™ Tube

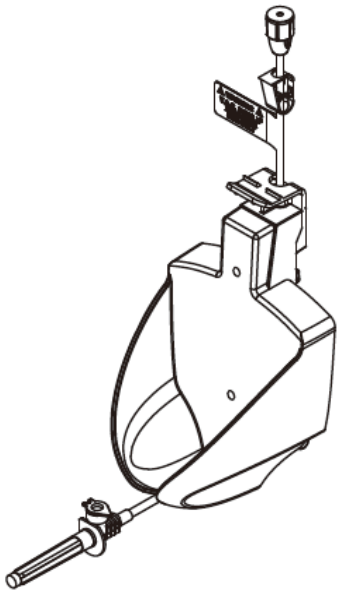


V.A.C. VeraT.R.A.C.Duo™ Tube Set



V.A.C.® Advanced Drape

V.A.C.® Ruler



V.A.C. VeraLink™ Cassette

Figure 3-1 Product structure diagram

3.2.3 Working Principle

NPWT consists in applying topical sub-atmospheric pressure to a wound that is covered with V.A.C. VERAFLO™ Dressing, sealed with drape and connected by a tube to a suction pump and drainage collection system. Instillation and dwell of a topical wound solution allows thorough coverage of the wound bed, thereby cleansing the wound. The topical wound solution that is allowed to dwell over the wound bed also has the potential to dilute and solubilize infectious materials, devitalized tissue and slough. Soaking the dressing with solution prior to removal, thus promoting granulation tissue formation.

3.2.4 Mechanism of Action

The therapy delivers mechanical stress to the tissue and cells by stretching them as the tissue is pulled up into the open pores of the foam. Mechanical forces draw wound edges together and stretch cells. Cell stretch triggers mitosis, resulting in proliferation and ultimately granulation tissue formation[19]. Porcine studies have shown that NPWT increased local blood flow and the rate of granulation tissue formation[22-24].

3.2.5 Scope of Trial

This trial will be conducted in subjects with open wounds that have extensive soft tissue damage using V.A.C. VERAFLO™ Dressing for wound bed preparation. The model (small / medium / large) selection of the dressing will be made based on the wound volume.

3.3 Indications, Contraindications and Precautions of Investigational Device

3.3.1 Indications

V.A.C. VERAFLO™ Dressing Kit is indicated for patients with chronic, acute, traumatic, sub-acute and dehisced wounds, partial-thickness burns, ulcers (such as diabetic, pressure and venous insufficiency), flaps and grafts.

3.3.2 Contraindications

(1) Do not place foam dressings directly in contact with exposed blood vessels, anastomotic sites, organs, or nerves.

(2) Malignancy in the wound.

(3) Untreated osteomyelitis.

(4) Non-enteric and unexplored fistulas.

(5) Necrotic tissue with eschar present.

(6) Do not use Dressings with Octenisept®, hydrogen peroxide or solutions that are alcohol-based or contain alcohol.

(7) Do not deliver fluids to the thoracic or abdominal cavity due to the potential risk to alter core body temperature and the potential for fluid retention within the cavity.

(8) Do not use V.A.C. VERAFLO™ Therapy unless the wound has been thoroughly explored due to the potential for inadvertent instillation of topical wound solutions to adjacent body cavities.

3.3.3 Precautions

(1) Standard Precautions: To reduce the risk of transmission of blood borne pathogens, apply standard precautions for infection control with all patients, per institutional protocol, regardless of their diagnosis or presumed infection status. In addition to gloves, use gown and goggles if exposure to body fluids is likely.

(2) Patient Size and Weight: The size and weight of the patient should be considered when prescribing V.A.C.® Therapy or V.A.C. VERAFLO™ Therapy. Infants, children, certain small adults and elderly patients should be closely monitored for fluid loss and dehydration. Also, patients with highly exudative wounds or large wounds in relation to the patient size and weight should be closely monitored, as they have a risk of excessive fluid loss and dehydration. When monitoring fluid output, consider the volume of fluid in both the tubing and canister.

(3) Spinal Cord Injury (SCI): In the event an SCI patient experiences autonomic dysreflexia (sudden changes in blood pressure or heart rate in response to stimulation of the sympathetic nervous system), discontinue V.A.C.® Therapy or V.A.C. VERAFLO™ Therapy to help minimize sensory stimulation and seek immediate medical assistance.

(4) Bradycardia: To minimize the risk of bradycardia, V.A.C.® Therapy and V.A.C. VERAFLO™ Therapy must not be placed in proximity to the vagus nerve.

(5) Enteric Fistulas: Wounds with enteric fistulas require special precautions to optimize V.A.C.® Therapy. Refer to V.A.C.® Therapy Clinical Guidelines for more detail. V.A.C.® Therapy is not recommended if enteric fistula effluent management or containment is the sole goal of therapy.

(6) Protect Periwound Skin: Consider use of a skin preparation product to protect periwound skin. Do not allow foam to overlap onto intact skin. Protect fragile / friable periwound skin with additional drape, skin protectant, hydrocolloid, or other transparent film. Multiple layers of the drape may decrease the moisture vapor transmission rate, which may increase the risk of maceration. If any signs of irritation or sensitivity to the drape, foam, or tubing assembly appear, discontinue use and consult a physician. To avoid trauma to the periwound skin, do not pull or stretch the drape over the foam dressing during drape application. Extra caution should be used for patients with neuropathic etiologies or circulatory compromise.

(7) Circumferential Dressing Application: Avoid use of circumferential dressings except in the presence of anasarca or excessively weeping extremities, where a circumferential drape technique may be necessary to establish and maintain a seal. Consider using multiple small pieces of drape rather than one continuous piece to minimize the risk of decreased distal circulation. Extreme care should be taken not to stretch or pull the drape when securing it, but let it attach loosely and stabilize the edges with an elastic wrap, if necessary. When using circumferential drape applications, it is crucial to systematically and recurrently palpate distal pulses, and assess distal circulatory status. If circulatory compromise is suspected, discontinue therapy, remove dressing, and contact a physician.

(8) Pressure Points: Periodically assess and monitor the location of tubing connectors, caps, clamps or other rigid components to ensure they do not create inadvertent pressure points in relation to patient position.

(9) V.A.C. ULTA™ Therapy Unit Pressure Excursions: In rare instances, tubing blockages with the V.A.C. ULTA™ Therapy Unit may result in brief vacuum excursions to more than 250 mmHg negative pressure. Resolve alarm conditions immediately. Refer to the V.A.C. ULTA™ Therapy System User Manual or contact your KCI Representative for additional information.

(10) Suitable Solutions: V.A.C. VERAFLO™ Therapy is intended for use with V.A.C. VERAFLO™ Therapy disposables and topical wound treatment solutions and suspensions.

(11) Canister Changes: Monitor fluid level in canisters frequently during use of the V.A.C. VERAFLO™ Therapy. Frequent canister changes may be necessary depending on volume of fluid instilled and wound exudates. At a minimum the canister should be changed weekly and disposed of according to institutional protocol.

4 Study Objectives

The objectives are to evaluate the efficacy and safety of the V.A.C. VERAFLO™ Dressing Kit for wound bed preparation in open wounds with extensive soft tissue damage in this trial.

4.1 Primary Objective

The primary objective is to demonstrate non-inferiority in the wound volume reduction rate of investigational group versus control group patients with open wounds that have extensive soft tissue damage.

4.2 Secondary Objectives

The secondary objectives are to compare the differences of time to completion of wound bed preparation, wound area reduction rate, wound clinical assessments, incidence of adverse events (AEs) / serious adverse events (SAEs) and device deficiencies in investigational group versus control group.

5 Study Design

5.1 Overall Study Design and Rationales

5.1.1 Overall Study Design

This is a prospective, multicenter, randomized (1:1), open-label, parallel controlled, non-inferiority trial evaluating the efficacy and safety of V.A.C. VERAFLO™ Dressing Kit versus Negative Pressure Wound Drainage Material (Guangdong Shuangling Pharmaceuticals Co., Ltd.) for wound bed preparation in open wounds with extensive soft tissue damage. This is a pre-marketing trial of V.A.C. VERAFLO™ Dressing Kit in China for National Medical Products Administration (NMPA) registration. It is anticipated that the primary efficacy endpoint (wound volume reduction rate) of investigational group is non-inferior to that of control group. Up to 170 subjects who meet the eligibility criteria will be randomized to the investigational group or control group at the ratio 1:1.

Debridement is not permitted during study treatment. Therefore, subjects will only be enrolled following definitive surgical debridement (if serial debridement performed) of the target wound. The target wound for each subject in both groups will be treated for up to 14 days or until deemed ready for closure by the investigator (whichever occurs first). Following study treatment, the wound may be treated with any standard therapy selected by the physician, and then accepted secondary intervention for wound closure according to the wound bed preparation situation. The planned study period consists of the following visits: Screening (Day -3 to 0), Day of randomization (Day0), Dressing change visit(s), End of treatment visit. The following data in both groups will be recorded and collected: wound volume reduction rate, time to completion of wound bed preparation, wound area reduction rate, incidence of AEs / SAEs and device deficiencies. The efficacy and safety of V.A.C. VERAFLO™ Dressing Kit in treating open wounds that have extensive soft tissue damage will be evaluated according above data.

5.1.2 Rationale

5.1.2.1 Rationale of Study Design

A prospective, multicenter, randomized, open-label, parallel group controlled, non-inferiority clinical trial design is adopted in this clinical trial, according to *Helsinki Declaration*, *Administrative Measures for the Registration and Filing of Medical Devices (2021), Good Clinical Practice for Medical Device (GCP) (2022)*, and *Guideline for Clinical Trial Design of Medical Devices (2018)* released by NMPA and other appropriate regulations or guidelines.

5.1.2.2 Rationale of Control Group Selection

According to the *Guideline for Clinical Trial Design of Medical Devices (2018)*, for therapeutic devices, when *selecting* positive control, an approved equivalent product should be given priority, and the efficacy and safety of which have been clinical accreditation. If an equivalent product cannot be selected on the China market for reasonable reasons, a product that is as similar as possible can be used as positive control. Secondly, the standard treatment method can be considered.

Nowadays, there is no approved dressing with solution instillation namely the NPWTi-d therapy in China market. So, a NPWT therapy will be selected in the trial. A Negative pressure wound drainage material manufactured by Guangdong Shuangling Pharmaceutical Co., Ltd. is selected as the control group treatment device, which can apply the NPWT therapy with wall suction. This control device is widely used in clinical institutions in China to deliver NPWT.

5.1.2.3 Rationale of Target Wound Selection

Open wound with extensive soft tissue damage may refer to skin, muscle, tendon, nerves, blood vessels, etc. In damaged wound beds, cell necrosis, exudate secretion, and bacterial proliferation increase the chance of infection. Effective daily drainage of necrosis and timely use of anti-infective treatment can accelerate wound healing. Most patients with extensive soft tissue damage are not suitable for primary skin grafting or skin flap repair, but they need to treat soft tissue trauma first to promote granulation

tissue formation, and then proceed with secondary intervention according to the preparation of wound bed. Conventional procedure requires a longer treatment cycle and recovery time to be able to have secondary intervention. While using of NPWT insulates the air and sucks out the exudate and necrotic tissue in the wound bed through negative pressure, reducing infection at the wound, helping to shorten wound healing time and improve treatment effect. It is considered that NPWT for this kind of wound has potential therapeutic advantages. Also, the target wounds of subjects belong to the scope of indications for the investigational device.

5.1.2.4 Rationale of Blinding Selection

This trial is set as open label, since the inconsistent packaging appearance of the devices between the two groups, the investigators and the subjects could not be blinded.

In this trial, independent assessors will be blinded to reduce measurement bias from outcome indicator measurers. 3D images collected from each site will be aggregated into a single database. The aggregated images will be analyzed / measured by the independent assessor so as to achieve the blinding of independent assessors.

5.1.2.5 Rationale of Primary Endpoint Selection

In general, change in wound area or wound closure rate is the primary endpoint in certain wound therapy. But the purpose of using NPWT is to prepare wound bed, promote formation of granulation tissue, reduce the wound and take advantage of the subsequent secondary intervention. If the change in wound area is to evaluate wound improvement for a large area of soft tissue damage, not a superficial wound, the situation is difficult to reflect the improvement in the depth dimension of the wound. Because this type of wound requires a second intervention, the wound is not completely closed after using of the investigational device and the wound closure rate is not suitable. Therefore, change in wound volume is used to reflect the improvement of the wound after NPWT treatment. The endpoint is better for the indication and can reflect the clinical condition of the investigational device performance; many previous studies have used this endpoint for wound evaluation [36, 37]. In addition, the wound volume will

be measured by a 3D Wound Imaging System, and the acquired data are objective, which can reduce bias by operators and other factors.

5.1.2.6 Rationale of Treatment Duration Selection

In general, the duration to prepare the wound bed for the treatment of wounds in the target population using NPWT is generally no more than 2 weeks[38-40], and the subsequent intervention will be followed by other methods for secondary intervention. In combination with this clinical trial, just the performance of the investigational device is observed, so the longest treatment duration is chosen to be 14 days.

5.1.3 Total Anticipated Duration of Clinical Trial and Rationale

Total Anticipated Duration: It is anticipated that the trial duration will be 51 months, i.e. Aug 2019 to Nov 2023.

Rationale: The duration includes all sites initiation, subject recruitment, treatment and follow-up; as well as collection, statistical analysis of study data, and clinical study report development.

5.2 Selection of Subjects

5.2.1 Inclusion Criteria

Only adult subjects meeting all of the following criteria to be considered for participation:

(1) Subject voluntarily participate in the trial and sign the informed consent form, and is willing to comply with protocol and all visits
(2) Is anticipated to be an inpatient for a minimum of 6 days
(3) Age: between 18 years and 70 years
(4) Patient with open wounds from various etiologies with extensive soft tissue damage after definitive surgical debridement and appropriate for NPWT
(5) The minimum size of the wound as measured by 3D wound imaging prior to entry into the study is 8cm (in any dimension), minimum 1cm in width and 0.8cm in depth. i.e. the minimum wound size is 8cm×1cm×0.8cm. Only one wound per subject will be included in the study, regardless of how many wounds the subject

has.

(6) Female subjects of reproductive potential must have a negative pregnancy test result and must not be lactating at the screening visit.

(7) Subject must be willing and able to use a highly effective contraception method during study participation.

5.2.2 Exclusion Criteria

Subject who meets any of the following criteria will be excluded from participation in the study:

(1) Subject undergoing chemotherapy

(2) Subject with known immunodeficiency

(3) Subject with serious complications or serious systemic infection

(4) Known bleeding disorder or has received or is planning to receive long-term anticoagulation therapy

(5) Known allergic reactions/hypersensitivity to any of the study treatment dressings components

(6) Target wound is a burn wound

(7) A wound open for 6 months or more

(8) The subject's targeted traumatic wound injury is a craniofacial wound

(9) There is implant (such as cardiac pacemaker, bone nail, bone lamella, artificial joint, artificial bone) visible in the targeted wound.

(10) If undermining or tunneling represents approximately 15% or more of the wound.

(11) A wound with enteric fistulas.

(12) Subject's targeted wound that is contraindicated with investigational device including:

a) Malignancy in the wound

b) Untreated osteomyelitis

c) Non-enteric or unexplored fistulas

d) Necrotic tissue with eschar remaining in the wound after surgical debridement

(once necrotic tissue or eschar is removed from the wound bed, subjects may be included)

e) Unprotected, exposed blood vessel, anastomotic sites, organs, or nerves in direct contact with foam

f) Thoracic or abdominal cavities

g) Unexplored wounds that may communicate with adjacent body cavities

(13) Subject's targeted wound that is contraindicated with the control group device and not suitable for participating in the trial judged by investigator

(14) Participation in another device or drug study within the past 30 days before screening or during study participation

(15) Other subjects who are not suitable for participating in the trial judged by investigator.

(16) Wounds that require more than 2 images in order to capture the entire wound. NOTE: each image must not exceed 20 cm in any one direction.

(17) Wound presents on greater than 50% of the circumference of any part of the body (e.g. wound that wraps around >50% of a leg or arm).

5.2.3 Criteria and Procedures for Subject Withdrawal

1) Dropout Criteria

Definition: A subject in the clinical trial who for any reasons fails to continue in the study until the last visit required of him/her by the study protocol.

If meet the following situations:

- Lost to follow-up.
- Subjects withdraw their informed consent and voluntarily withdraw from the trial: Subjects could withdraw from the trial voluntarily if they could not endure the AE, think the treatment is not effective, and want to take other treatments or without any reason.
- When the investigator judged that the risk is greater than the benefit if subject continues to participate in the trial, or the subject cannot continue the clinical trial

in the following conditions, for example a subject has abnormal organ dysfunction, allergic reaction, poor compliance, exacerbations, or a SAE needed to stop the trial treatment, and the subject should withdraw from the trial.

- The subject's target wound needs other treatment and should withdraw from the trial.
- If the target wound condition worsens (such as infection aggravated, anaerobic bacteria infection, etc.) in the use of investigational dressing or control dressing during the process of NPWT, after the investigator's evaluation of wound and treatment result, and if the surgical debridement is needed again, the NPWT will be stopped, the end of study assessments completed and the subject withdrawn from the study, then the target wound will be opened and debrided repeatedly, until the next intervention (such as delayed healing, surgical closure, graft et al) can be carried out.

Subjects have the right to withdraw from the trial at any time without any reason.

For all subjects terminate the trial in advance, the investigator should make every effort to obtain the reasons of withdrawal, e.g. AEs, unsuccessful correction therapy, withdrawing from the trial based on the investigator's judgment or other reasons, which should be recorded on the source documents. Subjects withdrawing from treatment in the trial should complete withdraw visit according to the schedule of visit procedure.

Disposal of drop-out cases: trial conclusion form and reasons of dropout should be completed in the related document for all dropout cases. The investigator should make every effort to contact subjects to ensure compliance, obtain reasons for subject dropping out, record complications and AEs and try to complete required evaluations.

2) Criteria for Trial/Trial Treatment discontinuation

Trial termination is defined as the trial discontinued without planned assessments of all subjects completed.

- The trial should be terminated when the device is found with no clinical significance during the trial;

- Major mistake of protocol is found during the trial resulting in difficulty to evaluate the efficacy and safety of the device;
- The trial should be terminated when major deviation occurs during the conduct of the trial resulting in difficulty to evaluate the efficacy and safety of the device if the trial continues;
- Requirement from sponsor (e.g. financial problem, administration problems. etc.);
- The administration department terminates the trial for some reasons;
- The ethics committee (EC) terminates the trial for protecting the rights and benefits of subjects;

When the trial is discontinued, new subjects will not be enrolled and enrolled subjects who have not completed the trial will be treated and visited according to the result of discussion of sponsor and the investigator.

5.2.4 Time Point of Enrollment

Before study specific screening assessments are performed, signed informed consent forms (ICF) must be obtained from subjects, then appropriate screening procedures will be conducted; and subjects will be taken to receive the 3D-wound imaging procedure of their wounds following the definitive surgical debridement performed (if applicable). At the end of the procedure, subjects who continue to meet all inclusion and no exclusion criteria will be included and randomized. The randomization point will be the time point of enrollment for subjects.

5.2.5 Expected Duration of Each Subject's Participation

The participation duration of each subject is defined as the duration from the time of subject to be enrolled in the trial to the last visit. For each subject, it is estimated that the screening duration is up to 3 days, anticipated treatment i.e. wound bed preparation duration is up to 14 days. In total, expected duration of each subject's participation is up to 17 days. During the period, all patients will have the initial dressing placement and a minimum of 2 dressing changes.

5.3 Evaluation Method

5.3.1 Evaluation of Efficacy

5.3.1.1 Primary Endpoint

(1) Wound Volume Reduction Rate (unit: %)

Define: wound volume change over 14 days or until deemed ready for closure by investigator (whichever occurred first).

Formula: wound volume reduction rate = (wound volume before initial study treatment – wound volume after study treatment 14 days or deemed ready for closure before 14 days) ÷ wound volume before initial study treatment × 100%.

Measurement: 3D Wound Imaging System, digital photos and three-dimensional photographs will be taken of the wound (without dressing) by assigned staff for all subjects.

Three-dimensional wound images will be captured for randomization visit, dressing change visit (s), and end of treatment visit using a specialized imaging system. Imaging guidelines, equipment, and supplies will be provided to the investigational sites by KCI. The 3D images collected from each site will be aggregated into a single database. The aggregated images will be analyzed /measured by the independent assessor. The independent assessor will determine and plot the wound perimeter, the clean, healthy viable tissue, and other tissue types for each image. The imaging software will be used to calculate wound length, width, depth, surface area, and wound volume. The values of these parameters/assessments will be used for calculations of the primary endpoint and the secondary endpoints. The 3D wound images should not be used to guide patient treatment.

Evaluation time point: Day of Randomization (Day 0), Dressing Change Visit (s), and End of Treatment Visit.

Statistical method: the difference of wound volume reduction rate between investigational group and control group will be evaluated to determine whether the primary endpoint of the investigational group is non-inferior to that of control group.

Rationale: please see Section 5.1.2.5.

5.3.1.2 Secondary Endpoints

(1) Time to Completion of Wound Bed Preparation (unit: day)

Define: duration from the randomization until target wound ready for closure by secondary intervention judged by investigator.

Evaluation time point: Day of Randomization (Day 0) and End of Treatment Visit

Measurement: the date deemed ready for closure by secondary intervention - the date of the randomization + 1.

Statistical method: the difference between investigational group and control group will be assessed.

(2) Wound Area Reduction Rate (unit: %)

Define: wound area change over 14 days or until deemed ready for closure by investigator (whichever occurred first).

Formula: wound area reduction rate = (wound area before study treatment –wound area after study treatment 14 days or deemed ready for closure before 14 days) ÷ wound area before study treatment×100%.

Measurement: 3D Wound Imaging System, the value for area can be collected from the 3D wound imaging system report directly.

Evaluation time point: Day of Randomization (Day 0), Dressing Change Visit (s), and End of Treatment Visit

Statistical method: the difference between investigational group and control group will be assessed.

(3) Wound Clinical Assessments

Define: Wound depth, edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount of target wound after therapy will be evaluated.

Measurement: Wound depth, edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount will be evaluated according to

table below.

Wound Depth	1 = non-blanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis and/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; and/or mixed partial and full thickness and/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures	
Edges	1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred or hyperkeratotic	
Necrotic tissue type	1 = None visible 2 = White/grey non-viable tissue and/or non-adherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar	
Necrotic tissue amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered	
Granulation Tissue	% change in granulation tissue from baseline utilizing 3D Wound Imaging System and clinical judgement	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled and/or tissue overgrowth 3 = Bright, beefy red; < 75% and > 25% of wound filled 4 = Pink, and/or dull, dusky red and/or fills ~ 25% of wound 5 = No granulation tissue present
Undermining	1 = None present 2 = Undermining < 2 cm in any area 3 = Undermining 2-4 cm involving s 50% wound margins 4 = Undermining 2-4 cm involving> 50% wound margins 5 = Undermining> 4 cm or Tunneling in any area	
Exudate type	1 = None	

	2 = Bloody 3 = Serosanguinous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor
Exudate amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large

Evaluation time point: Day of Randomization (Day 0), Dressing Change Visit (s), End of Treatment Visit.

Statistical method: the difference between investigational group and control group will be assessed.

5.3.2 Evaluation of Safety

(1) Incidence of AEs (unit: %)

Define: an AE is any untoward medical occurrence in the course of a trial, whether or not related to the investigational device.

Evaluation: type, incidence, seriousness and relatedness of AEs/Adverse device effects (ADEs), and laboratory abnormalities will be reported.

Formula: incidence of AEs/ADEs = sum of subject who occurred AEs/ADs ÷ sum of subjects for each group × 100%.

Statistical method: the difference between investigational group and control group will be assessed.

Note: especially focus on the systemic reactions and local skin/tissue irritation (such conditions as wound secretions and swelling, pain, and local skin color change, etc.)

(2) Incidence of SAEs (unit: %)

Define: see relevant subsections of Section 12.2.1.

Evaluation: incidence, and relatedness of SAEs/Serious adverse device effects (SADEs) will be reported.

Formula: incidence of SAEs/SADEs = sum of subject who occurred SAEs/SADEs ÷ sum of subjects for each group × 100%.

Statistical method: The difference between investigational group the control group will be assessed.

(3) Incidence of Device Deficiencies (unit: %)

Define: see relevant subsections of Section 12.3.1.

Formula: incidence of Device deficiencies = sum of subjects experienced device deficiency ÷ sum of subjects for each group × 100%.

Statistical method: The difference between investigational group the control group will be assessed.

5.4 Diagnosis and Treatment of the Investigational and Control Group

5.4.1 Diagnosis and Treatment of the Investigational Group

- Investigational device: V.A.C. VERAFLO™ Dressing Kit
- Negative pressure Unit: V.A.C. ULTA™ Therapy Unit (Registration No.: 国械注进 20152543887)
- Instillation solution: Normal saline
- Instructions: see the details in Instructions for Use (IFU) of V.A.C. VERAFLO™ Dressing Kit (see **Appendix 3**).

Note: Other information for investigational device could be seen in Section 3.

5.4.2 Diagnosis and Treatment of the Control Group

- Dressing Name: Negative pressure wound drainage material
- Indications: Drainage for wounds with more secretions and exudates
- Component: Negative pressure wound drainage material consists of 5 parts: sponge block, medical surgical film, drainage catheter, clamp and external fixing film of catheter pad.
- Storage

  This product is stored in a dry, light-proof and heat-proof place.
- Manufacturer: Guangdong Shuangling Pharmaceutical Co., Ltd.
- Registration No.: 国械注准 20173664628.
- Negative pressure Unit: Wall Suction.

- Instillation solution: None.
- Instructions: see the details in IFU of Negative pressure wound drainage material (see **Appendix 4**).

5.5 Study Procedure

5.5.1 Schedule of Activities

Schedule of Activities

Procedures	Screening Day -3~ 0	Randomization Day 0	Dressing Change Visit (s)	End of Treatment Visit[1]	Withdrawal or Discontinuation Visit[2]
Informed Consent	X				
Demographics [a]	X				
Medical History	X				
Surgical History	X				
Wound History [b]	X				
Vital Signs [c]	X				
Physical Exam	X	X	X	X	X
Blood Routine Examination [d]	X			X	X
Blood Coagulation Function [e]	X				
Serum Pregnancy Test [f]	X				
Evaluate inclusion/exclusion criteria	X	X			
Wound Clinical Assessments [g]		X	X	X	X
Wound Surgical Debridement		X[3]			
Digital/3D Wound Imaging [h]		X	X	X	X
Randomization		X			
NPWT		X	X		
Dressing Changes			X		
Concomitant Medications	X	X	X	X	X
AEs/SAEs Review and Evaluation	X	X	X	X	X
Device Deficiencies		X	X	X	X

Note:

a: Date of birth, Gender, Race;

b: Wound etiology/type, Duration, Anatomic location;

c: Pulse, Blood pressure, Respiration rate, Body temperature;

d: Red Blood Cell (RBC) count, White Blood Cell (WBC) count, Hemoglobin, Platelet;

e: Fibrinogen, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR);

f: Only for female subjects of reproductive potential;

g: Wound depth, edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount;

h: Wound length, width, depth, area, and volume;

1: The visit will be conducted when subject is deemed ready for closure by investigator or treatment duration up to 14 Days (+/-1 Day).

2: For subjects withdrawing from the trial or discontinuation of trial treatment.

3: Definitive surgical debridement (if applicable)

5.5.2 Visit Time Point

5.5.2.1 Screening (Day-3 to 0)

The investigator will introduce the purpose of this trial and content of ICF to potential subjects. Each potential subject will review the EC approved ICF. The subject and the investigator (or designated medically licensed sub-investigator), must sign and date the ICF before the subject can undergo any clinical investigation-related procedures.

Upon signing the ICF, subjects will be assigned a unique Screening Number. The Screening Number will be a combination of the study site number (2 digits) + sequence of subject screened (3digits begins from 001) at each site. Screened subjects will be entered onto a screening log. Once a number is assigned it cannot to be re-assigned to another subject. In the instance a subject is considered a screen failure, they will keep the screening number assigned to them and the screen failure log will be completed noting the reason(s) for screen failure.

The following data will be collected:

(1) Informed consent obtained.

(2) Demographics

Date of birth, gender and race.

(3) Medical and allergic history: related to the inclusion/exclusion criteria in the past 3 months.

If the subject has diabetes history, the investigator shall evaluate whether he/she has serious diabetes (judged by investigator or fasting blood glucose level is more than 11.1mmol/L) at screening visit.

(4) Surgical history.

(5) Wound history.

The subject's wound will be assessed at screening and a wound history will be captured. The history will include prior wound related surgeries and treatments including but not limited to hyperbaric therapy, use of biologics, whirlpool, debridement, closure, revascularization procedures, prior infection, previous use

of negative pressure therapy, advanced moist wound therapy (including the solution used), which have occurred within the past 30 days. For subjects who present with multiple wounds, all wounds will be assessed at screening. The study appropriate wound with the greatest volume will be selected for the study and a wound history will be recorded.

The history will also document wound etiology/type, onset and chronicity of the wound, and anatomic location.

(6) Vital signs

Pulse, blood pressure, respiration rate, body temperature.

(7) Physical exam: Skin Assessment

A skin exam will be performed and documented as part of screening procedures. The exam should be skin focused and include observation and documentation of any pertinent findings such as skin infections (local and remote to the wound), scars (including keloids or other hypertrophic scarring), erythema/cellulitis, wounds and drainage etc.

(8) Laboratory Assessment*

- Blood routine examination

  Red Blood Cell (RBC) count, White Blood Cell (WBC) count, Hemoglobin, Platelet.

- Blood coagulation function

  Fibrinogen, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR).

- Serum pregnancy test

  Only for female subjects of reproductive potential.

***Note:** the date of laboratory assessment performed within 72 hours before screening can be collected.

(9) Evaluate inclusion/exclusion criteria.

(10) Concomitant medications

All medications the subject is taking at screening visit.

(11) Collect and assess AEs/SAEs.

5.5.2.2 Day of Randomization (Day 0)

The following data will be collected:

(1) Physical exam.

(2) Wound clinical assessments

Wound depth, Edges, necrotic tissue type and amount, granulation tissue, undermining, exudate type and exudate amount will be evaluated.

For subjects who present with multiple wounds suitable for the trial, the wound with the greatest volume will be randomized.

(3) Definitive surgical debridement (if applicable).

(4) Digital/3D wound imaging

Digital photos and three-dimensional photographs will be taken of the wound (without dressing) for all subjects, and target wound length, width, depth, surface area and volume will be measured and reported.

When a wound extends over a convex/curved surface, such as a limb, the imaging will be taken so that each part of the wound is photographed (max. 2 photos) in a way that the photographed surface is as flat as possible in relation to the camera lens.

(5) Evaluation of inclusion/exclusion criteria again.

(6) Randomization

Subjects who continue to meet all inclusion and no exclusion criteria will be randomized in a 1:1 ratio stratified by wounds surface area ($<15cm^2$, 15-30cm^2, and $>30cm^2$) to be treated with either investigational group [V.A.C. VERAFLO™ Dressing Kit with ULTA™ Therapy Unit (instillation)] or control group [Negative pressure wound drainage material with Wall suction (without instillation)].

(7) Administer assigned NPWT treatment

Date, time, condition and settings of NPWT treatment need to be recorded.

(8) Concomitant medications

All medications the subject is taking during the study.

(9) Collect and assess AEs/SAEs.

(10) Device deficiencies.

5.5.2.3 Dressing Change Visits

The following data for each dressing change visit will be collected:

(1) Physical exam.

(2) Wound clinical assessments.

(3) Digital/3D wound imaging.

(4) Dressing changes (several times)

Date and time need to be recorded.

(5) NPWT treatment

Record the condition and settings of NPWT treatment.

(6) Concomitant medications

All medications the subject is taking during the study.

(7) Collect and assess AEs/SAEs.

(8) Device deficiencies.

Note: The specific frequency of dressing change is determined by the investigator based on the wound condition and clinical experience while following the IFU for the assigned study product and the frequencies of the investigational and control devices are the same.

5.5.2.4 End of Treatment Visit

The following data will be collected before any subsequent treatment:

(1) Physical exam.

(2) Blood routine examination

RBC count, WBC count, Hemoglobin, Platelet.

(3) Wound clinical assessments.

(4) Stop study treatment and remove NPWT dressing.

(5) Digital/3D wound imaging (prior to commencing any subsequent treatment).

(6) Concomitant medications

All medications the subject is taking during the study.

(7) Collect and assess AEs/SAEs.

(8) Device deficiencies.

Note: Visit will be conducted when subject's target wound is deemed ready for closure by investigator or treatment duration up to 14 Days (+/-1 Day). If the target wound can be closed judged by investigator within 14 days since initial treatment, the closure date and method are to be recorded.

5.5.2.5 Withdrawal or Discontinuation Visit

If the subject withdraws from the trial or discontinues the trial treatment, the following data will be collected before any subsequent treatment:

(1) Physical exam.

(2) Blood routine examination.

(3) Wound clinical assessments.

(4) Digital/3D wound imaging (prior to any subsequent treatment).

(5) Concomitant medications

All medications the subject is taking during the study.

(6) Collect and assess AEs/SAEs.

(7) Device deficiencies.

5.5.3 Specification Direction for Use of Device

(1) For subjects with multiple wounds, the target wound can only be treated with the randomly assigned device and the other wounds will receive the standard wound treatment in the institution.

(2) Placing the dressings in the target wound directly following the definitive surgical debridement (if applicable) according to the investigational or control device IFU.

(3) During the subject's hospital admission, subjects will receive their assigned study

treatment without interruption until the wound is deemed ready for closure or up to 14 days (whichever occurred first).

(4) For the investigational group, instillation solution (only normal saline) will be refilled by related staff as often as required. Canister changes for each group will be performed by related staff as often as required.

(5) Dressing change frequency will be determined by the investigator based on the wound condition and clinical experience, and the frequencies of investigational and control group devices are the same (48-72h one change).

(6) If the wound has been deemed ready for closure, study treatment will stop and subjects will then transition to receive institutional standard wound treatment at the discretion of the investigator.

(7) If the secondary intervention condition of the target wound is not met after 14 days of treatment with the investigational device, the patient will receive further clinical treatment judged by the investigator re-evaluation according to the standard wound treatment in the institution.

5.5.4 Management of Investigational Medical Device

(1) Investigational medical devices will be labelled and numbered uniformly and be noted “for clinical trial use only”.

(2) Investigational medical devices will be transported to each investigational site by person designated by sponsor. The investigational sites and sponsor should establish a complete handover procedure, and the handover and receipt information including device name, model, specification, batch number and date shall be well recorded.

(3) Each investigational site will designate a specific location for the storage of investigational device.

(4) Each investigational site will establish strict management system for investigational device managed by designated person and create specific *Record for Use of Investigational Medical Device*. The administrator will complete the record according to the sequence of enrollment of each subject with the subject’s screen number, date of

use, device number and signature of the designated person. The administrator should record the device number on the accountability log timely and truthfully. All unused investigational V.A.C. VERAFLO™ Dressing Kits and all V.A.C. ULTA™ Therapy Units must be returned to sponsor collectively after the completion of the trial.

5.6 Bias Control Measures

Multicenter: Subjects from multiple institutions are more representative than that from single institution, which may avoid the bias of trial results due to systematic error of single institution.

Randomization: Randomization allows subjects to have equivalent opportunity to be assigned to the investigational group or the control group without the influence of the subjective will of the investigators and / or subjects. It can make the distribution of various influence factors similar and avoid selection bias and information bias as far as possible. In this trial, randomization method will be used to reduce the trial bias caused by the sampling error. Eligible subjects will be randomized to the investigational group or the control group to receive study treatment after the investigator has verified the inclusion and exclusion criteria. Random number table was generated by biostatistician using PLAN procedure of SAS before first subject enrollment. The detailed randomization method will be documented in the randomization specification.

Parallel Control: Parallel control design will be used in this trial. The investigational group and control group will be carried out at the same period to make factors that may influence the efficacy judgment distribute evenly between two groups.

Training for the Investigator: Before the clinical trial, Clinical Research Associates (CRAs) will coordinate with person in charge of each investigational institution to provide training about study protocol for the investigators to make the investigators understand and be familiar with the investigational medical device, to perform inclusion and exclusion criteria strictly, to complete appropriate examinations according to the requirements of the protocol and to master all new information related to this device found during the clinical trial, thus to reduce interference factors as far as possible.

Monitoring of the Trial: CRAs designated by sponsor create a monitor plan and perform on-site monitor visit regularly at the investigational institutions to make sure all contents in the study protocol are followed strictly, and check data in original source documents to make sure consistency with that in electronic case report form (eCRF).

Blinding of independent assessor: In this trial, independent assessors will be blinded to reduce measurement bias from outcome indicator measurers. The 3D images collected from each site will be aggregated into a single database without any randomization information. The aggregated images will be analyzed /measured by the independent assessor so as to achieve the blinding of independent assessors. Before the clinical trial, independent assessors shall complete the training on 3D wound imaging system. Independent assessors will not participate in randomization processing or patient treatment. The independent assessors will not be allowed to discuss the randomization results with any non-blinding study personnel and have no access to any study documents that may lead to unblinding.

6 Statistical Considerations

6.1 Sample Size Calculation

Up to 170 eligible subjects will be enrolled into the trial.

6.1.1 Total Sample Size

The number of evaluable subjects required for this trial is 128 subjects (64 per treatment arm). To account for a potential 10% drop-out rate, at least 140 subjects (70 per treatment arm) will be randomly assigned in a 1:1 allocation ratio to V.A.C. VERAFLO™ or control group. 140 subjects (70 per study arm) will achieve approximately 80% power to detect a difference with a non-inferiority margin of 20% based on a one-sided t test with a significance level of 0.025 and pooled standard deviation being 40%.

Due to the uncertainty in the actual variability and trying to limit the study size to those strictly needed, a blinded sample size re-estimation will be performed after 50% evaluable subjects per arm (70 evaluable subjects total) have completed End of

Treatment Visit.

This number of subjects is expected to provide a sufficiently precise calculation of the variability in the actual study population. The point estimate for the pooled standard deviation will be used for the sample size re-estimation.

If the re-estimated sample size is greater than 140, the sample size may be increased up to a maximum of 200 subjects to provide sufficient power for this study. If the re-estimated sample size is less than 140, the sample size of the study is still 140.

To account for a higher than initially estimated drop-out rate of 25%, up to 170 subjects (85 per treatment arm) will be randomly assigned in a 1:1 allocation ratio to V.A.C. VERAFLO™ or control group. 170 subjects (85 per study arm) will achieve 80% power to detect a difference with a non-inferiority margin of 20% based on a one-sided t test with a significance level of 0.025 and pooled standard deviation being 40%.

6.1.2 The Level of Significance and the Power of the Clinical Trial

The level of significance is one-side 0.025. The power of the clinical trial is 0.8.

6.1.3 Expected Drop-out Rate

Drop-out includes all conditions that cannot be included in the primary endpoint analysis finally, which refers to major protocol deviations judged by the investigator.

An expected rate of drop-out is about 25%.

6.1.4 Sample Size Allocation

6.1.4.1 Study Numbers for Each Type of Disease and Rationale

Not applicable.

6.1.4.2 Sample Size of Each Institution

No one site can have more than 50% of total subjects enrolled (85 subjects).

6.1.5 Pass/Fail to be Applied to the Primary Endpoint

When lower limit of the 95% confidence interval is greater than -0.20, it will be concluded that the V.A.C. VERAFLO™ Dressing Kit is non-inferior to the control. The -0.20 margin was based on clinical judgement as the minimum difference in the primary endpoint values that can be considered meaningful.

6.2 Analysis Data Set

Full Analysis Set (FAS): including all subjects randomized to receive either V.A.C. VERAFLO™ Dressing Kit or control treatment. It is the secondary analysis set for efficacy evaluation, such as the time to completion of wound bed preparation, rate of wound area reduction, and changes in granulation tissue.

Per Protocol Set (PPS): PPS is the subset of the FAS. It is the primary analysis data set for efficacy evaluation.

Safety Set (SS): including all subjects who have received either V.A.C. VERAFLO™ or control treatment. The data set is used to evaluate the safety of this trial.

6.3 Subject Exclusion Criteria

PPS is a subset of FAS, including subjects who have received the treatment specified in the protocol, the observation data of the primary endpoint are available, and there are no significant protocol deviations affecting the primary efficacy endpoint. The rules for exclusion of subjects from PPS are as follows:

(1) Missing baseline volume measure;

(2) Missing end-of-treatment (EOT) volume measure;

(3) Not completing the study (evaluable subjects will have completed the study if deemed ready for closure by investigator or had a treatment duration of up to 14 days);

(4) Violating wound size inclusion criterion (maximum depth at baseline < 0.8cm or wound dimensions less than 8cm by 1cm) as determined by Independent Assessor (IA);

(5) Baseline or EOT wound volume measures deemed unreliable after image review (i.e. laser line coverage inadequate, or depth unreliable, or poor margin visibility, or entire wound not imaged, or no comparison across time possible);

(6) Major protocol deviations that would impact the primary endpoint as judged by the medical monitor. For example, the occurrence of post-baseline study wound debridement.

6.4 Criteria for the Termination of the Clinical Trial on Statistical Grounds

The interim analysis is not planned for the trial, thus the trial will not be terminated due to statistical reasons.

6.5 Statistical Design, Method and Analytical Procedures

The descriptive statistics of continuous variables include number, mean, standard deviation, median, minimum and maximum. Frequency and percentage will be used in the descriptive statistics for categorical variables. Unless otherwise specified, all statistical tests will be performed at a significance level of 2.5% (one-sided) with 95% confidence interval (CI).

Detailed statistical methods will be further demonstrated in the statistical analysis plan (SAP).

All statistical analyses will be performed using Statistical Analysis System (SAS) 9.2 version or a later version after database locked according to SAP.

6.5.1 Statistical Analysis Method

Primary efficacy endpoint

The statistical hypothesis for testing the treatment group difference for primary efficacy endpoint is presented as follows:

- H_0: $M_T - M_C \leqslant -0.20$ tested against the alternative hypothesis
- H_1: $M_T - M_C > -0.20$

where:

M_C is the means in control group and M_T is the means in to V.A.C. VERAFLO™ group.

A two-sided 95% confidence interval for $M_T - M_C$ will be constructed using the method of ANCOVA with treatment group, site, and treatment-by-site interaction (if the interaction effect is not statistically significant, then it will be removed from the final model) as fixed factors, and wound size ($<15cm^2$, 15-30cm^2 $>30cm^2$) as covariate. If the lower limit of the 95% confidence interval is greater than -0.20, then it will be concluded that the V.A.C. VERAFLO™ Dressing Kit is non-inferior to the approved control dressing in China (Local) + wall suction.

A rejection of the null hypothesis will trigger superiority testing based upon treatment difference. If the lower limit of the CI is greater than zero, V.A.C. VERAFLO™ Dressing Kit is proven to be superior to China (Local) + wall suction.

The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is rejected. There is no alpha adjustment for the second test as a result of the hierarchical testing.

A primary analysis will be conducted on the PPS population, and sensitivity analysis will be conducted on the primary endpoints using the FAS population.

If the treatment-by-site interaction in ANCOVA model is significant, it always reveals that there is the heterogeneity of substantial treatment in different sites. In order to explain the heterogeneity influence for reliability of statistical conclusion, the descriptive statistics will be reported by different site.

Secondary and safety endpoints

For other continuous secondary endpoints, the same analysis procedure will be conducted as above. In addition, Kaplan-Meier and log rank test will be performed for time to completion of wound bed preparation. An analysis of covariance (ANCOVA) model on mean change in wound area reduction rate as dependent variables with treatment group as fixed factors, site, treatment-by-site interaction (present only if interaction effect is significant) and wound size as covariate will be performed. The difference between the two treatment groups and 95% CI will be reported. The Wilcoxon rank-sum test and Wilcoxon signed rank test will be performed for wound clinical assessments.

In addition, all efficacy and safety endpoints will be summarized descriptively for subjects in each treatment group and overall. The continuous data will be summarized by number of subjects, mean, standard deviation (SD), median, minimum and maximum. The categorical data will be summarized by frequency counts along with associated percentages.

Exploratory endpoints

Repeated measure analysis of variance using mixed model on mean change in exploratory endpoints (volume, area and granulation tissue) at each dressing change time point as dependent variables with site, treatment group and treatment-by-site interaction as fixed factors, wound size (wounds surface area, ＜15cm^2, 15-30cm^2, and ＞30cm^2) as covariate, and time point as repeated factor will be performed using mixed model.

6.5.2 Handling of Missing Data

Subjects in the study whose wound volume and area reduction rate at effective visit (after study treatment 14 days or deemed ready for closure before 14 days) is unknown will be imputed. The multiple imputation (MI), and the last observation carried forward (LOCF) method (for missing post-baseline data) and next observation carried back (NOCB) method (for missing baseline data) will be used to impute missing area measures for each subject as a sensitivity analysis. Missing value for other secondary endpoints for example time to wound bed preparation will not be imputed and will be treated as missing. Incomplete data imputation will be further stated in the SAP.

6.5.3 Handling of Unused or Spurious Data

Unused or spurious data in the database will be identified and resolved during the data management process.

6.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

If the analysis methods in this protocol have changed before data lock, they should be recorded in the SAP. If the analysis contents in finalized SAP have changed after data lock, they should be recorded in the statistical analysis report and clinical study report.

6.7 The Exclusion of Particular Information from the Testing of the Hypothesis, if Relevant

None.

7 Monitoring Plan

7.1 Purpose of Monitoring

(1) To ensure that all parties comply with the requirements of *Administrative Measures*

for the Registration and Filing of Medical Devices (2021), *GCP (2022)*, and other local regulations during the conduct of the clinical trial.

(2) The rights of subjects are protected.

(3) To ensure compliance with study clinical trial protocol/procedures and the authenticity, integrity, accuracy of the collected data.

7.2 Content and Plan of Monitoring

This trial will be monitored regularly by qualified monitors in accordance with applicable regulations and Standard Operation Procedures (SOPs). Monitoring procedures will include one or more visits prior to study initiation as well as periodic monitoring visits during the study on a regular basis according to a mutually agreed schedule.

During these visits, the monitor will check for compliance with the protocol and applicable regulations including but not limited to assessing integrity of the source data with the eCRF entries; proper reporting of adverse events; subject eligibility and consent; and proper handling and disposition of the investigational product. In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits.

8 Data Management

8.1 Data Collection

Electronic data capture (EDC) will be used in this trial, and clinical trial data will be entered into eCRF by the investigators or authorized staff at the investigational institutions. The investigators and authorized staff at the investigational institutions will receive appropriate trainings before the initiation of investigational institutions or data entering and appropriate measures will be adopted to protect the safety of data.

The investigators will be responsible for maintaining all source documents and ensure

to be monitored by CRAs at each visit. In addition, the investigators should submit a complete eCRF for every subject participating in the trial, regardless of the duration of participation. The trial number and subject number in all supporting documents (e.g. laboratory records or investigational institution records) submitted with eCRF should be checked carefully and all individual privacy (including the name of subjects) should be deleted or measures should be taken to make it difficult to identify subjects to protect the privacy of subjects.

8.2 Data Entering and Modification

The investigators or designees will be responsible for all entering, correction and modification of data. Any modification on data will be recorded by audit tracking, i.e. the reasons of modification, the name of the operator, time and date of the modification will be recorded. The role and permission of staff who are responsible for entering the data at the investigational institution will be predetermined. CRAs or data management staff will raise queries in EDC for data and the staff at investigational institution will be responsible for handling the queries. EDC system will record the audit tracking of queries, including the name of the investigator, time and date.

8.3 Database Lock

The data manager, PIs, statistical analysis staff, sponsor and monitoring management staff will review the data together and issue any necessary data queries. Then the database will be locked by data manager.

In general, locked database should not be changed.

Subjects will be included in the appropriate analysis sets based on definitions within the Statistical Analysis Plan.

8.4 Data Transfer

The locked database will be transferred to statistical analysis staff for statistical analysis based on SAP. The statistical analysis staff will write the statistical analysis report after completing statistical analysis and submit it to the coordinating -investigator for writing clinical study report.

9 Risk Benefit Analysis

9.1 Analysis of Possibility of Success

The trial is conducted in accordance with *Helsinki Declaration*, *Administrative Measures for the Registration and Filing of Medical Devices (2021), GCP (2022)* and other applicable regulations/guidelines. The trial will be conducted after obtaining approval of EC. The subject must sign an informed consent form before participating in the trial to ensure the compliance of the subject. The dropout out rate can be well controlled based on the experience of previous clinical trial of similar devices.

The indications of the investigational device are clear and the composition and technical index are all in accordance with the national industry standard. This investigational device complies with the standard with clear principle and definite efficacy. And the devices are manufactured and examined according to the requirement of V.A.C. VERAFLO™ Therapy Dressing with self-inspection qualified before leaving the factory and have been registered and validated by Medical Device Quality Supervision and Inspection Center of NMPA. The investigational device has met the technical requirement for V.A.C. VERAFLO™ Therapy Dressing with the conclusion of qualified and all performance measurements verified.

The sites participating in the clinical trial have good experience on clinical trial and quality control system and the investigational staff participating in the trial have sufficient clinical experience and skilled operating ability. They also have sufficient subject resource, appropriate investigational group, reasonable clinical trial protocol, unified training for individuals participating in the trial and unified recording procedure and standard of judgment. The investigators participating in the clinical trial will be trained about the knowledge of device and operating procedure by technicians of the investigational device. The investigators should follow the operating procedures strictly and all observations and laboratory results during the clinical trial should be recorded and checked carefully to ensure authenticity and reliability of data and to ensure that all conclusions of the clinical trial are based on source data.

In summary, the clinical trial is very likely to be conducted successfully.

9.2 Analysis of Possibility of Failure

The non-compliance of trial conduct with protocol, operating procedures not been followed strictly, incomplete records of observations and laboratory results during the clinical trial or lack of source data supporting may cause the failure of this trial, but these factors are controllable.

The physicians who have rich experience for clinical trial will be designated as the investigators. The investigators will be trained about the knowledge of device and operating procedures before the trial to ensure the skillfulness of the operators. Each subject participating in the clinical trial will be followed up comprehensively after procedures. The additional supervision may improve the probability of early detection of any AE. The medical records of each subject will be monitored to observe the occurrence of complications closely and create detailed emergency treatment regimen.

In summary, the possibility of failure of clinical trial is small, but also related to the systemic risk operation and the conditions of subjects.

10 Quality Control of Clinical Trial

10.1 Quality Control Measures in Laboratory

The laboratory of participating hospitals should have SOP and quality control procedure for laboratory examination.

10.2 Trainings for the Investigators

The CRA designated by sponsor should provide trainings about clinical trial protocol to the investigators before the clinical trial.

10.3 Measures to Improve the Compliance of Subjects

The informed consent should be performed carefully by the investigators to ensure that subjects have fully understood the requirements of the trial and are compliance with the trial.

10.4 Monitoring of the Clinical Trial

The CRAs designated by sponsor will perform the on-site monitor visits regularly at

the investigational institutions to ensure that all contents in clinical trial protocol are followed strictly and check the source documents to ensure consistency with eCRF.

10.5 Completion of Case Report Form

All data will be entered in English. eCRF should be completed during or after visits as soon as possible and be updated timely to ensure that it will reflect the latest conditions of subjects. The baseline data and all subsequent efficacy and safety data of the same subject will be reviewed by the same investigator as far as possible to avoid discrepancy between the evaluation results by different reviewers. The investigator should review the data to ensure the accuracy and authenticity of all data entered into eCRF. If some assessments are not performed during the trial or some information is unavailable, inapplicable or unknown, they should be recorded in eCRF by the investigator. The investigator should attach the electronic signature to the reviewed data.

10.6 Maintain Source Documents

Source data refers to the original records of clinical findings, observations and other activities in medical device clinical trials and all information in its approved copies, which can be used for reconstruction and evaluation of medical device clinical trials. Source documents refer to printed documents, visual documents or electronic documents containing source data. The source documents of the trial include signed informed consent form, dispensing records of investigational device, laboratory reports, case records and other relevant records.

The essential documents of medical device clinical trials are used to evaluate the sponsors, clinical trial institutions of medical devices and principal investigators whether implementation of clinical trial follow *GCP (2022)* and the relevant requirements of the drug regulatory department. The sponsor and clinical trial institutions should have the place and conditions for the preservation of essential documents, and shall establish rules for maintaining essential documents. The essential documents can be divided into three parts based on the stages of clinical trial: documents during the preparation, documents during the execution and documents after

the termination or completion of the trial. The sponsor and the clinical trial institution shall ensure the integrity of the essential documents of clinical trial during the storage period, and avoid intentional or unintentional changes or losses. The investigators should properly keep the essential documents of clinical trials during the medical device clinical trials. The clinical trial institutions should maintain the essential documents of clinical trial for 10 years after completion or termination of medical device clinical trial. The sponsor should maintain the essential documents of clinical trial until no investigational device is used.

11 Ethical Considerations and Informed Consent of the Clinical Trial

11.1 Ethical Considerations

The clinical trial must be conducted in accordance with *Helsinki Declaration, GCP (2022)*, appropriate regulations and laws about clinical trials in China. The clinical trial protocol should be approved by the EC of leading institution before conducting the trial. The investigators will be responsible for providing paper materials to subjects and (or) their legal representatives to explain the objectives, procedures and possible risks of the trial comprehensively and patiently before each subject is enrolled in the trial. The subjects must be informed that they have the right to withdraw from the trial at any time without providing any reason. A paper informed consent form should be provided to every subject before enrollment. The investigator is responsible for obtaining informed consent before each subject is enrolled in the trial and the informed consent form should be filed as clinical trial documentation.

The investigator needs to submit the clinical trial protocol, informed consent form and other related documents through management department of clinical trial of the hospital to the EC of the leading institution. The clinical trial will be conducted after approved by the EC. Any modification on clinical trial protocol should be approved by the EC before conduction. The serious AEs during the clinical trial must be submitted in writing to the EC within 24 hours after investigator awareness.

The EC of leading institution will be responsible for reviewing the rationality and

scientificity of clinical trial protocol before each clinical trial institution initiating the trial, and the EC of other clinical trial institutions could adopt meeting review or documents review to evaluate the feasibility of the trial at their clinical trial institutions, based on the comments of the EC of leading institution, including the qualification and experience of the investigators, equipment and conditions. In general, no revision will be made to the design of clinical trial protocol, but they are entitled to not approve the trial in the clinical trial institutions.

The EC should track and supervise the clinical trial conducted in their clinical trial institution. They may suspend or terminate the clinical trial in writing at any time when the rights and interests of subjects cannot be guaranteed.

The terminated clinical trial will not be continued without approved by the EC.

The EC shall keep all records of the ethical review until 10 years after the completion or termination of the clinical trial of the medical device.

Within 24 hours after learning about the SAE, investigators shall report to the sponsor, the management department and the EC of the medical devices clinical trial institution. At the same time, investigators shall also follow up the SAE according to the clinical trial protocol and submit a follow-up report of SAE.

Sponsor shall evaluate and report the safety information during medical device clinical trial. Within 7 days after learning that death or life-threatening SAEs related to investigational medical device under clinical trial, and within 15 days after learning that non-death or non-life-threatening SAEs related to investigational medical device under clinical trial or other serious safety risks, the sponsor shall report to other medical device clinical trial institutions, the EC and principal investigators involved in the clinical trial, to the drug regulatory departments in the province, autonomous region or municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions or municipalities directly under the Central Government where the medical device clinical trial institutions are located and take risk

control measures. In case of any information that may affect the safety of subjects and the implementation of clinical trials of medical devices, or change the approval opinions of the EC, the sponsor shall promptly organize the modification of the clinical trial protocol, the ICF and other information provided to the subjects as well as other relevant documents, and submit them to the EC for review.

In case of any SAE on the medical device under clinical trial on a large scale or any other major safety problems, the sponsor shall suspend or terminate clinical trials of medical devices and report to the management department of all medical devices clinical trial institutions, the EC and principal investigators, to the drug regulatory departments in the province, autonomous region and municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions and municipalities directly under the Central Government where all clinical trial institutions of medical devices are located.

11.2 Clinical Trial Protocol Approval

The clinical trial protocol will be approved by the EC, and the clinical trial must be conducted after approved by the EC. During the clinical trial, revised documents such as clinical trial protocol and informed consent form, deviation application, application for continuing the suspended clinical trial should be approved by the EC before conduction.

11.3 Procedure of Informed Consent and Text of Informed Consent Form

The investigators should state the detailed information about the clinical trial to subjects or guardians of subjects without or with limited capacity for civil acts, including known, predictable risks and possible AEs. Subjects or their guardians(if applicable) will sign and date on the informed consent form when the information about the clinical trial are explained to them, and the investigator should also sign and date on the informed consent form. If subjects lack reading ability, an impartial witness shall be designated to witness the whole process of informed consent and sign his/her name and date on the

ICF.

The informed consent form is signed by the investigator and subjects or their guardians (if applicable), or their impartial witnesses (if applicable). A copy of the informed consent form will be saved by two parties.

When the investigator observes unanticipated AEs of investigational medical device during the clinical trial, he/she should modify the corresponding content in the informed consent form with sponsor and submit it to the EC for approval, and the revised informed consent form should be signed by subjects involved, or their guardians (if applicable) and their impartial witnesses (if applicable) again.

12 AE and Device Defect Reporting

12.1 Adverse Event

12.1.1 Definition

An AE is any untoward medical occurrence in the course of a medical device trial, whether or not related to the investigational device.

12.1.2 Severity of Event

AEs' course, severity, dispose and prognosis should be observed closely and be recorded in AE report form. According to following criteria, severity of AE can be categorized as, mild, moderate, and severe.

- Mild – Transient or mild discomfort; no limitation in activity; no medical intervention/ therapy required.
- Moderate – Marked limitation in activity, assistance usually required; medical intervention/ therapy required, possible hospitalization.
- Severe – Extreme limitation in activity, significant assistance required; significant medical intervention/ therapy required hospitalization or probable hospice care. Of note, the term "severe" does not necessarily equate to "serious".

12.1.3 Relationship to Study Intervention

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including

an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other devices or drugs or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigator.

12.1.4 Adverse Device Effect

Any AE related to the use of an investigational device is adverse device effect (ADE).

12.1.5 Anticipated AE

Anticipated AEs with NPWT Therapy/Dressing for this trial are summarized in following table.

Skin and Subcutaneous Tissue Reaction/Allergy	Desiccation/injury Skin rash, irritation, blistering Pruritus/itching Skin excoriation/breakdown Skin stripping Skin scarring if significant skin irritation were to occur Maceration Skin hyper/hypo-pigmentation at and/or around dressing application area Erythema/redness, edema, inflammation, or swelling at and/or around dressing application area
Mild Pain or Discomfort	Tenderness/minor ache at and/or around dressing application area Perspiration associated with wearing dressing Auditory irritation (due to mild buzzing sound of negative pressure unit) Decreased sleep or sleep quality Paresthesia (numbness, tingling, prickling, creeping sensation)
Other	Bleeding Cardiac compromise (vagal response, bradycardia) Pulmonary compromise Accidental instillation in a body cavity Localized infection Autonomic dysreflexia (in subjects with spinal cord injury) Retained foreign debris (e.g. foam) in the wound Impairment of mobility/activity (limitation secondary to weight and attachment of therapy unit) Possible tubing entanglement/trip or slip hazard leading to fracture, tissue damage Incorrect therapy unit settings resulting in incorrect frequency/dosing Tunneling Stalled healing/non-progression of healing Deterioration of the wound Systemic reaction (due to allergic reaction to dressing materials)

	Burn secondary to therapy unit or power cord malfunction

12.1.6 Adverse Event Reporting

Investigators shall record AE identified during clinical trials of medical devices. Investigators deal with AEs with target treatment and follow-up, until symptoms disappear or become stable or otherwise a reasonable explanation.

The investigators shall provide adequate and timely therapy and treatment for the subjects in case of any AE in medical device clinical trial and inform the subjects in time when they need therapy and treatment for complicated diseases.

Within 24 hours after learning about the SAE, investigators shall report to the sponsor, the management department and the EC of the medical devices clinical trial institution . At the same time, investigators shall also follow up the SAE according to the clinical trial protocol and submit a follow-up report of SAE.

Within 7 days after learning that death or life-threatening SAEs related to investigational medical device under clinical trial, and within 15 days after learning that non-death or non-life-threatening SAEs related to investigational medical device under clinical trial or other serious safety risks, the sponsor shall report to other medical device clinical trial institutions, the EC and principal investigators involved in the clinical trial, to the drug regulatory departments in the province, autonomous region or municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions or municipalities directly under the Central Government where the medical device clinical trial institutions are located and take risk control measures.

In case of any information that may affect the safety of subjects and the implementation of medical device clinical trials, or change the approval opinions of the EC, the sponsor shall promptly organize the modification of the clinical trial protocol, the ICF and other information provided to the subjects as well as other relevant documents, and submit them to the EC for review.

In case of any SAE on the medical device under clinical trial on a large scale or any other major safety problems, the sponsor shall suspend or terminate clinical trials of medical devices and report to the management department of all medical devices clinical trial institutions, the EC and principal investigators, to the drug regulatory departments in the province, autonomous region and municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions and municipalities directly under the Central Government where all clinical trial institutions of medical devices are located.

12.2 Serious Adverse Event

12.2.1 Definition

An AE that

(1) led to death or

(2) serious deterioration in the health of the subject during medical device clinical trials, including:

- fatal disease or damage; or
- perpetual defects of physical structure or physical function; or
- requires patients' hospitalization or prolonging of hospital stay; or
- requires medical measures to avoid perpetual defects of physical structure or physical function;

(3) fetal distress, fetal death or congenital abnormality and congenital defects.

(4) Other medically significant event.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the clinical investigation plan, without serious deterioration in health is not considered a SAE.

12.2.2 Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of serious adverse event.

12.2.3 Reports of SAEs

When SAE occur in clinical trials of medical devices, investigators shall immediately take appropriate treatment measures for the subjects. Within 24 hours after learning about the SAE, investigators shall report to the sponsor, the management department and the EC of the medical devices clinical trial institution. At the same time, investigators shall also follow up the SAE according to the clinical trial protocol and submit a follow-up report of SAE.

Sponsor shall evaluate and report the safety information during clinical trials of medical devices.

Within 7 days after learning that death or life-threatening serious SAEs related to investigational medical device under clinical trial, and within 15 days after learning that non-death or non-life-threatening SAEs related to investigational medical device under clinical trial or other serious safety risks, the sponsor shall report to other medical device clinical trial institutions, the EC and principal investigators involved in the clinical trial, to the drug regulatory departments in the province, autonomous region or municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions or municipalities directly under the Central Government where the medical device clinical trial institutions are located and take risk control measures.

In case of any information that may affect the safety of subjects and the implementation of medical device clinical trials, or change the approval opinions of the EC, the sponsor shall promptly organize the modification of the clinical trial protocol, the ICF and other information provided to the subjects as well as other relevant documents, and submit them to the EC for review.

In case of any SAE on the medical device under clinical trial on a large scale or any other major safety problems, the sponsor shall suspend or terminate clinical trials of medical devices and report to the management department of all medical devices

clinical trial institutions, the EC and principal investigators, to the drug regulatory departments in the province, autonomous region and municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions and municipalities directly under the Central Government where all clinical trial institutions of medical devices are located.

12.3 Device Deficiency

12.3.1 Definition

Device deficiency refer to any irrational risk in trial, such as tag errors, quality issues, failure, which may threaten subjects' health and safety while investigational device is under normal use.

12.3.2 Recording and Reporting for the Device Deficiency

Investigators should record device deficiency in trial and analyze event cause with the sponsor.

At any stage of trial, both investigators and subjects can lodge complaints on the investigational device or the control device.

12.4 Reporting Procedure and Contact Information

When SAE occur in clinical trials of medical devices, investigators shall immediately take appropriate treatment measures for the subjects. Within 24 hours after learning about the SAE, investigators shall report to the sponsor, the management department and the EC of the medical devices clinical trial institution. At the same time, they shall also follow up the SAE according to the clinical trial protocol and submit a follow-up report of SAE. In this study, CRO Corporation Kun Tuo will report on SAEs on behalf of the sponsor. Report contact: Kun Tuo's clinical safety management department, e-mail: devicesafety@kuntuo.com.

13 Deviations and Amendments to the Protocol

13.1 Deviations

Any act of intentional or unintentional variation of the protocol is defined as protocol

deviation (PD).

13.2 Amendments to the Protocol

After ECs approve the protocol, if there is any modification, “declaration for protocol revision" is required, which should be signed by principal investigators and approved by EC before implementation.

After amendments, revised protocol shall be approved and signed by sponsor firstly.

14 Direct Access to Source Data and Documents

The definition of source data and source documents in *GCP (2022)* is as follows:

Source data refers to the source records of clinical findings, observations and other activities in medical device clinical trials, as well as all information in approved copies, which can be used for medical device clinical trial reconstruction and evaluation.

Source Documents include printed files, visual files, or electronic files which contain source data.

In this trial, the principal investigators and authorized investigators can access, yield and modify inpatient records, ICF, eCRF, any source medical records in Hospital Information Systems (HISs) which support information management and on-line operation in hospital management and medical activities. Laboratory testers and investigators can access and yield testing reports.

Data management personnel can access and yield data-management data; Statistical analysts can access and yield statistical analysis data.

Limits of Authority to access and edit other source data shall be specified by the standard operating procedure (SOP) of the corresponding departments, in accordance with relevant laws, regulations and technical standards in China.

15 Contents of Clinical Study Report

According to *GCP (2022)*, contents of clinical study report should at least include the basic information, implementation, statistical analysis methods, clinical trial results, reports and treatment of AEs and device defect, analysis and discussion of clinical trial results, clinical trial conclusions, ethical description, existing problems and

improvement suggestions of medical devices clinical trial.

16 Confidentiality

The protocol is confidential, which is provided to related medical experts, related personnel such as investigators participate in trial, and related operation authorized agencies such as medical institutions undertaking this trial, ECs and contract research organization. Besides explaining situation to subjects, any content of this protocol shall not be disclosed or leaked to a third party without a prior written agreement from the sponsor.

Contents of the agreement and the clinical trial and all the attached materials are confidential, exclusive to the sponsor, and investigators shall be responsible for the confidentiality.

Including patent application, manufacture process and unpublished data that sponsor provides investigators, etc., investigators shall not be disclosed to any third party unless being agreed by the sponsor, and the confidentiality obligation remains valid after termination or end of this trial.

Investigators and their staff collect subjects' individual data being used in this trial (" trial data"), including date of birth, gender, identity card, home address, photos and physical or mental health data, etc.

All medical records and research materials that can identify subjects will be kept confidential within the scope of law. However, investigators, sponsor and representatives, inspectors (responsible for inspecting trial process and ensure correct information collected) can inspect and copy confidential information which may identify subjects, as well as management institution and EC under certain circumstances.

All personal information in the trial will be handled in accordance with the national and local data protection laws.

Subjects have rights to request investigators and sponsor to protect their information and to correct any inaccurate information in data.

If subjects withdraw informed consent, investigators will no longer use or disclose the

data, and sponsor may still use the data acquired before withdrawing.

The trial results may be published in medical journals and presented at medical conferences.

Subjects will not be identified in any of these publications.

17 Responsibilities for All Parties

17.1 Responsibility for Sponsor

(1) The sponsor of a clinical trial of medical devices shall establish a quality management system covering the whole process of the clinical trial of medical devices to ensure that the clinical trial of medical devices complies with relevant laws and regulations, and protect the rights and interests and safety of the subjects.

(2) Prior to the clinical trials of medical devices, the sponsor shall ask principal investigators to submit the following documents to the Ethics Committee:

- Clinical Trial Protocol;
- Investigator's brochure;
- Text of Informed Consent Form (ICF) and any other written materials provided to subjects;
- Procedural documents for recruitment and promotion of subjects (if applicable);
- Text of Case Report Form (CRF);
- Product test report based on product technical requirements;
- Data related to preclinical study;
- Resume, professional expertise, ability, training and other documents that can prove their qualifications of the principal investigators;
- A Statement That the Investigational Medical Devices are Developed in Accordance with Applicable Requirements Related to Quality Management System of Medical Devices;
- Other documents related to ethical review.

(3) The sponsor shall be responsible for the authenticity and compliance of clinical trials of medical devices. If the sponsor is an overseas institution, an enterprise legal person within the territory of China shall be designated as an agent according to relevant

laws and regulations to assist the sponsor in performing its duties.

(4) The quality management system of the sponsor shall cover the whole process of clinical trials of medical devices, including the selection of clinical trial institutions and principal investigators, the design of clinical trial protocol, the implementation, record, result report and filing of clinical trials of medical devices. The quality management measures taken by the sponsor shall be compatible with the risks of clinical trials.

(5) Before initiating clinical trials of medical devices, the sponsor shall:

- Ensure that the product design has been finalized, and complete the preclinical study of the investigational medical device, including: performance verification and validation, product test report based on product technical requirements, risk benefit analysis, etc.. The results should be able to support the clinical trial of the medical device;
- According to the characteristics of the investigational medical devices, the registered clinical trial institution of medical devices, specialties and principal investigators are selected;
- Responsible for organizing the development of investigator's brochure, clinical trial protocol, ICF, CRF, standard operating procedures and other relevant documents, and providing them to clinical trial institution of medical devices and principal investigators.

(6) The sponsor shall sign a contract with clinical trial institutions of medical devices and principal investigators to define their respective rights and obligations in clinical trials of medical devices.

(7) The sponsor shall file the clinical trial project with the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the sponsor is located after the clinical trial of medical device has passed the ethical review and signed the contract with the clinical trial institution of medical device.

(8) The sponsor shall organize training related to clinical trials of medical devices before the start, such as the rationale, scope of application, product performance, operating method, installation requirements and technical indicators of the

investigational medical device, clinical trial protocol, SOPs, other relevant documents, etc.

(9) The sponsor shall provide investigational medical devices free of charge, which shall meet the following requirements:

- The investigational medical device shall be produced in accordance with the relevant requirements of the Good Manufacturing Practice for Medical Devices with acceptable quality.
- The transportation and storage conditions, storage duration, expiration date, etc. of investigational medical devices shall be clarified;
- The investigational medical devices shall be properly packaged and preserved in accordance with the requirements of the clinical trial protocol. The product information shall be marked on the package label, with the identification of easy identification and correct coding, indicating that it is only used for clinical trials of medical devices.
- After clinical trials of medical devices are approved by the Ethics Committee, the sponsor shall transport investigational medical devices to clinical trial institutions of medical devices under prescribed conditions;
- The sponsor shall keep recovery and disposal records of investigational medical devices recovered from clinical trial institutions of medical devices.

(10) The sponsor shall pay expenses related to clinical trials of medical devices for the subjects. In case of damage or death related to the clinical trial of medical device, the sponsor shall bear the corresponding treatment costs, compensation or indemnity, but excluding the damage caused by the fault of the investigator and the clinical trial institution of medical device as well as the disease progression of the subject.

(11) The sponsor shall evaluate and report the safety information during clinical trials of medical devices:

- Within 7 days after learning that serious adverse events related to death or life-threatening serious adverse events occur on the medical device under clinical trial, and within 15 days after learning that serious adverse events not related to death or non-life-threatening serious adverse events occur on the medical device under clinical trial and the medical device under clinical trial may have

other serious safety risks, the sponsor shall report to other clinical trial institutions of the medical device, the Ethics Committees and principal investigators involved in the clinical trial, to the drug regulatory departments in the province, autonomous region or municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions or municipalities directly under the Central Government where the clinical trial institutions of the medical device are located and take risk control measures. In case of any information that may affect the safety of subjects and the implementation of clinical trials of medical devices, or change the approval opinions of the Ethics Committee, the sponsor shall promptly organize the modification of the clinical trial protocol, the ICF and other information provided to the subjects as well as other relevant documents, and submit them to the Ethics Committee for review;

- In case of any serious adverse events on the medical device under clinical trial on a large scale or any other major safety problems, the sponsor shall suspend or terminate clinical trials of medical devices and report to the regulatory department of all clinical trial institutions of medical devices, the Ethics Committees and principal investigators, to the drug regulatory departments in the province, autonomous region and municipality directly under the Central Government where the sponsor is located, and to the drug regulatory departments and health administration departments in the provinces, autonomous regions and municipalities directly under the Central Government where all clinical trial institutions of medical devices are located.

(12) The sponsor shall undertake the responsibility of clinical trial monitor of medical devices, formulate standard operating procedures for monitoring, and select qualified monitors to perform the monitoring responsibilities:

- The number of monitors and the number of monitoring shall match the complexity of the clinical trials and the number of clinical trial institutions participating in the clinical trials;
- The monitors shall have received corresponding training, be familiar with the GCP and the relevant laws and regulations, have relevant professional background knowledge, be familiar with the relevant study data of the

investigational medical device, clinical information of similar products, clinical trial protocol and relevant documents, and be able to effectively perform the monitor responsibilities;

- The monitors shall follow the standard operating procedures formulated by the sponsor and urge the clinical trials of medical devices to be carried out in accordance with the clinical trial protocol. The contents of the monitor include the compliance of clinical trial institution of medical devices and investigators with clinical trial protocols, the GCP and relevant laws and regulations during the implementation of clinical trials, the signing of ICF, screening, follow-up, rights and security of the subjects, management and use of investigational medical devices and control medical devices (if applicable), management and use of biological samples (if applicable); handling of adverse events and device defects; reporting of safety information, recording of clinical trial data, filling of CRF, etc.

(13) In order to ensure the quality of clinical trials, the sponsor may organize auditors who are independent of the clinical trials of medical devices and have corresponding training and experience to audit the clinical trials and evaluate whether the clinical trials meet the provisions of the clinical trial protocol, the GCP and relevant laws and regulations.

(14) The sponsor shall ensure that the implementation of the clinical trials of medical devices follow the clinical trial protocol. If it is found that the clinical trial institutions and investigators of medical devices do not comply with the clinical trial protocol, the GCP and relevant laws and regulations, the sponsor shall identify and correct them in time. If the situation is serious or not corrected, the clinical trial institution and the investigator shall be terminated to continue to participate in the clinical trial, and a written report shall be submitted to the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the clinical trial institution is located.

(15) The sponsor shall report in writing to all principal investigators, regulatory departments of clinical trial institutions of medical devices and the Ethics Committee

within 10 working days after the suspension, termination or completion of the clinical trial.The sponsor shall report to the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the sponsor is located within 10 working days after the termination or completion of the clinical trial of medical devices.

(16) The sponsor shall carry out multi-center clinical trials of medical devices according to the following requirements:

- The sponsor shall ensure that all centers participating in the clinical trial of medical devices can comply with the clinical trial protocol;
- The sponsor shall provide the same clinical trial protocol to each center. After the ethical and scientific nature of the clinical trial protocol is reviewed and approved by the Ethics Committee of the leading unit, the Ethics Committee of other clinical trial institutions of medical devices participating in the clinical trial will not propose any modification opinions on the design of the clinical trial protocol under normal circumstances, but has the right not to agree to carry out the trial in their clinical trial institutions of medical devices;
- Each center shall use the same CRF and filling instructions to record the test data obtained in the clinical trials of medical devices;
- Before the clinical trials of medical devices, there should be written documents to clarify the responsibilities of the principal investigators of each center participating in the clinical trials of medical devices;
- The sponsor should ensure the communication among the principal investigators of each center;
- The sponsor is responsible for selecting and determining the coordinating investigator of the clinical trial of medical devices, and the medical institution that the coordinating investigator works for is the leading unit. Coordinating investigators shall undertake the coordination work of each center in multi-center clinical trials.

(17) The sponsor and clinical trial institutions of medical devices shall have the place and conditions for keeping basic documents of clinical trials, and establish a basic document management system. The basic documents of clinical trial of medical device

are divided into three parts according to the clinical trial stage: documents of preparation stage, documents of progress stage and documents after completion or termination.

(18) The sponsor shall ensure the integrity of basic documents of clinical trials during the storage period, and avoid intentional or unintentional alteration or loss. The sponsor shall keep the basic documents of the clinical trial until there is no use of the medical device.

(19) Investigator's brochure, refers to the data compilation provided by the sponsor to help the principal investigator and other investigators participating in the clinical trial better understand and comply with the clinical trial protocol, including but not limited to: basic information of the sponsor, brief description of the investigational medical device, summary and evaluation of the intended use of the investigational medical device and the reasons for the clinical trial design, potential risks, recommended prevention and emergency treatment methods, etc.

(20) If an electronic data acquisition system is used in clinical trials of medical devices, the system shall be subject to reliable verification, have perfect authority management and audit trace, which can be traced back to the creator, creation time or reviser, revision time and revision of the record, and the collected electronic data can be traced back to the source.

(21) The sponsor shall carry out clinical trials of medical devices according to the clinical trial protocol and complete the clinical trial report. The clinical trial report shall reflect the clinical trial results comprehensively, completely and accurately, and the data of safety and effectiveness of the clinical trial report shall be consistent with the source data of the clinical trial.

17.2 Responsibilities for Clinical Trial Institutions

(1) Clinical trial institution of medical devices shall meet the filing conditions, and establish an organizational structure and management system for the management of the clinical trial. Clinical trial institution of medical devices shall have corresponding

clinical trial regulatory departments to undertake the management of clinical trials of medical device.

(2) The regulatory department of the clinical trial institution of medical devices shall be responsible for filling, managing and changing the filing information of clinical trial institution of medical devices in the Management Information System for the Filing of Medical Device Clinical Trial Institutions, including clinical trial specialty and principle investigator information. Be responsible for online submission of the summary report on the clinical trials of medical devices implemented in the previous year in the filing system. Be responsible for organizing and evaluating the qualification of the principal investigators of the clinical trial before the Ethics Committee reviews the clinical trial of medical devices and completing the filing.

(3) Clinical trial institution of medical devices shall establish a quality management system covering the whole process of clinical trial implementation of medical devices, including training and assessment, implementation of clinical trials, management of medical devices, management of biological samples, handling of adverse events and device defects and reporting of safety information, recording, quality control, etc., to ensure that the principal investigators perform their responsibilities related to clinical trials, that the subjects receive proper medical treatment, and ensure the authenticity of the data generated by the trials.

(4) Before accepting clinical trials of medical devices, clinical trial institutions of medical devices shall evaluate relevant resources according to the characteristics of the investigational medical devices, so as to ensure that they have matching qualifications, personnel, facilities, conditions, etc.

(5) Clinical trial institutions of medical devices and investigators shall cooperate with the supervision and inspection organized by the sponsor, as well as the inspection performed by relevant drug regulatory departments and health administration departments.

(6) Clinical trial institutions of medical devices shall properly keep clinical trial

records and basic documents in accordance with relevant laws and regulations and the contract with the sponsor.

(7) Clinical trial institution of medical devices shall report in writing to the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the sponsor is located if the sponsor seriously or continuously violates the GCP, relevant laws and regulations, or requests to change the test data and conclusion.

(8) Each center shall use the same CRF and filling instructions to record the test data obtained in the clinical trials of medical devices.

(9) The clinical trial institutions of medical devices shall have the place and conditions for keeping basic documents of clinical trials, and establish a basic document management system. The basic documents of clinical trial of medical device are divided into three parts according to the clinical trial stage: documents of preparation stage, documents of progress stage and documents after completion or termination.

(10) The clinical trial institutions of medical devices shall ensure the integrity of basic documents of clinical trials during the storage period, and avoid intentional or unintentional alteration or loss. The clinical trial institution of medical device shall keep the basic documents of the clinical trial for 10 years after the completion or termination of the clinical trial.

17.3 Responsibilities for Clinical Trial Investigator

(1) The principal investigators in charge of clinical trials of medical devices shall meet the following requirements:

- Have completed the filing of principal investigators for clinical trials of medical devices;
- Be familiar with the GCP and relevant laws and regulations;
- Have the professional knowledge and experience required for the use of the investigational medical devices, have the experience of clinical trials after the training related to clinical trials, and be familiar with the clinical trial protocol, investigator's brochure and other materials provided by the sponsor;

- Have the ability to coordinate, control and use the personnel and equipment for the clinical trial of medical devices, and have the ability to deal with adverse events and other related events in the clinical trial of medical devices.

(2) Principal investigators shall ensure that clinical trials of medical devices comply with the latest version of the clinical trial protocol approved by the Ethics Committee and carried out within the specified time limit according to the GCP and relevant laws and regulations.

(3) Based on the clinical trial needs of medical devices, principal investigators can authorize the investigators who have participated in training related to clinical trials to organize the following: recruitment, informed consent, screening and follow-up of subjects; management and use of investigational medical devices and control medical devices (if applicable); management and use of biological samples (if applicable); handling of adverse events and device defects; recording of clinical trial data, filling of CRF, etc.

(4) Investigators who participate in clinical trials of medical devices shall:

- Possess the corresponding professional and technical qualifications, training experience and relevant practice in clinical trials of medical devices;
- Participate in the training related to the clinical trial of the medical device organized by the sponsor, and participate in the clinical trial of the medical device within the scope authorized by the principal investigator;
- Be familiar with the principle, scope of application or intended use, product performance, operation method, installation requirements and technical indicators of the investigational medical device, and understand the data related to preclinical study of the investigational medical device;
- Fully understand and comply with the clinical trial protocol, the GCP, relevant laws and regulations, and responsibilities related to clinical trials of medical devices;
- Master the prevention of possible risks in clinical trials and emergency treatment methods.

(5) Investigators shall abide by the ethical codes and relevant ethical requirements of *Helsinki Declaration.* In addition, they shall also meet the following requirements:

- Shall use the latest version of ICF agreed by the Ethics Committee and other information provided to the subjects;
- Before subjects participate in clinical trials, the details of investigational medical devices and clinical trials shall be explained to them. At the same time, they shall also be informed of the possible benefits and known as well as foreseeable risks. After full and detailed explanations, subjects shall sign their names and date on the ICF, and investigators shall also sign their names and date on the ICF;
- If subjects are persons without or with limited capacity for civil conduct, the written informed consent of their guardians shall be obtained according to law. If subjects lack reading ability, an impartial witness shall be designated to witness the whole process of informed consent and sign his/her name and date on the ICF;
- Shall not compel or induce the subject to participate in the clinical trial in any other improper manner;
- After the ICF is updated and approved by the Ethics Committee, all subjects who are involved and have not finished the clinical trial process shall sign the newly revised ICF.

(6) The investigators shall be responsible for the management of the invetigational medical devices and control medical devices (if applicable) provided by the sponsor, and shall ensure that these devices are only used for the subjects participating in the clinical trial of the medical devices, and shall store and keep them according to the requirements during the clinical trial. After the completion or termination of the clinical trial, these devices shall be handled according to the relevant regulations and the contract with the sponsor.

(7) The investigators shall ensure that the collection, treatment, preservation, transportation and destruction of biological samples in the clinical trial of the medical devices comply with the clinical trial protocol and relevant laws and regulations.

(8) The investigators shall provide adequate and timely therapy and treatment for the subjects in case of any adverse events in the clinical trial of the medical devices and inform the subjects in time when they need therapy and treatment for complicated

diseases. Investigators shall record adverse events and device defects identified during clinical trials of medical devices.

(9) Investigators shall promptly report safety information in clinical trials of medical devices:

- When serious adverse events occur in clinical trials of medical devices, investigators shall immediately take appropriate treatment measures for the subjects. Within 24 hours after learning about the serious adverse events, they shall report to the sponsor, the regulatory department of the clinical trial institution of medical devices and the Ethics Committee. At the same time, they shall also follow up the serious adverse events according to the clinical trial protocol and submit a follow-up report of serious adverse events;
- When the risks in clinical trials of medical devices are identified to outweigh the possible benefits and it is indeed necessary to suspend or terminate the clinical trials, principal investigators shall report to the sponsor, the regulatory department of the clinical trial institution of medical devices and the Ethics Committee. In addition to informing the subjects in time, they shall also ensure that the subjects could receive appropriate treatment and follow-up visits.

(10) Principal investigators shall handle the safety information they have received in time:

- When receiving the case with serious adverse events and other safety information related to the investigational medical devices provided by the sponsor, it is necessary to sign in and read them in time, consider whether to make corresponding adjustment to the therapy of the subject, and communicate with the subject as soon as possible when necessary;
- When receiving the notice that the sponsor or Ethics Committee needs to suspend or terminate the clinical trial of medical devices, it shall promptly notify the subjects and ensure that the subjects receive appropriate therapy and follow-up.

(11) Principal investigators shall report the progress of clinical trials of medical devices to the Ethics Committee on time. At the same time, they shall also report the events that may affect the rights and interests and safety of the subjects or any deviation

from the clinical trial protocol in time.

(12) Investigators shall report in writing to the drug regulatory departments of the province, autonomous region or municipality directly under the Central Government where the sponsor is located if the sponsor seriously or continuously violates the *GCP* (2022) relevant laws and regulations, or requests to change the test data and conclusion.

(13) The principal investigators shall carry out clinical trials of medical devices according to the clinical trial protocol and complete the clinical trial report. The clinical trial report shall reflect the clinical trial results comprehensively, completely and accurately, and the data of safety and effectiveness of the clinical trial report shall be consistent with the source data of the clinical trial.

(14) In clinical trials of medical devices, the principal investigators shall ensure that any observations and findings are correctly and completely recorded. For clinical trials with patients as subjects, relevant medical records should be loaded into the outpatient or inpatient medical record.

(15) Principal investigators shall fill in and modify the CRF according to the guidance provided by the sponsor, and ensure that data therein is accurate, complete, clear and timely. The data reported in the CRF should be consistent with the source document. For the revision of the data in the CRF, the initial record shall be clear and identifiable, the revision trace shall be kept, and the reviser shall sign and indicate the date.

(16) Investigators shall appropriately keep basic documents of clinical trials during clinical trials of medical devices.

(17) Clinical trial institutions and investigators should ensure that data, documents and records of clinical trials are true, accurate, complete and traceable.

18 Other Contents Required Description

The details of Finance and Insurance and Publication Policy, please see the contracts with sites.

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Investigator Declaration

I agree:

1. Conduct this clinical trial strictly in accordance with *Helsinki Declaration*, *GCP (2022)*, current Chinese regulations and the requirements of the trial protocol.
2. Accurately copy all required data in eCRF and cooperate to complete the clinical trial report.
3. The investigational devices are only used for this trial. In the process of clinical trial, acceptance and usage situation of the investigational device will be fully and accurately recorded and archive.
4. Allow CRAs, auditors authorized or dispatched by sponsor and regulatory departments to monitoring, audit, or inspection of the clinical trial.
5. Strictly perform the clinical trial contract/agreement signed by all parties.

I have read all the protocol, including above statement, and I agree with all of the above.

Sponsor opinion Signature (stamp) :_____ Date:_____（YYYY/MM/DD）

Investigator opinion Signature: _____ Date:_____（YYYY/MM/DD）

Medical Device Clinical Trial Institution opinion Signature (stamp) :_____ Date: _____（YYYY/MM/DD）

Appendix 1 Qualification Documents (supplied alone)

Relevant qualification documents of sponsor.

Appendix 2 List for All Sites and Principal Investigators

No.	Name of Site	Name of PI	Title	Contact Information
01				
02				
03				
04				

Appendix 3 IFU of V.A.C. VERAFLO™ Dressing Kit (supplied alone)

Appendix 4 IFU of Negative Pressure Wound Drainage Material (supplied alone)