Clinical Investigation Plan (CIP)

PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence - an unblinded, randomized-controlled, superiority trial (BALPIC Trial)

Type of investigation:	Clinical investigation concerning medical devices (MD).
Categorisation:	Risk category A1
Registration:	Clinicaltrials.gov und HumRes
Identifier:	D 2025-D0043, BALPIC
Sponsor-Investigator:	Prof. Dr. med. Ilker Uçkay; Head Infectiology, Clinical Research Balgrist University Hospital Forchstrasse 340 8008 Zürich 044 386 1111 ilker.uckay@balgrist.ch
Medical Device:	PICO 7 Set (donated by Smith and Nephew)
CIP Version and Date:	Version 3.0, 14 November 2025

Signature Page(s)

ID number of the investigation:	
Title:	PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence - an unblinded, randomized-controlled, superiority trial (BALPIC Trial)

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 1.0, 24 January 2025, and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm [current version/2024], ICH-GCP as far as applicable, and the local legally applicable requirements.

The Investigator has received the ICF and consider it appropriate for use.

Sponsor Investigator: Prof. Dr. med. Ilker Uçkay

Zürich, 14 November 2025	Signature
Place/Date	

Statistician: Prof. Dr. med Ilker Uçkay

Zürich, 14 November 2025	Signature
Place/Date	

Principal Investigator at the local investigational site*:

I have read and understood this CIP version 1.0 (24/01/2025) and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm [current version/2024], ICH-GCP as far as applicable, and the local legally applicable requirements. I have received the ICF and consider it appropriate for use.

Site:	Universitätsklinik Balgrist
Principal investigator at the local investigational site:	Prof. Dr. med. Ilker Uçkay

Zurich, 14 November 2025	Signature
Place/Date	

*Note: In multicentre investigations, this page must be individually signed by all participating Local Principal Investigators.

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SYNOPSIS

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor / Sponsor-Investigator	Prof. Dr. med. Ilker Uçkay, Head Infectiology and Infection Control, Balgrist University Hospital, Zürich
Title:	PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence - an unblinded, randomized-controlled, superiority trial (BALPIC Trial)
Short title / Investigation ID:	The BALPIC Study
Clinical Investigation Plan, version and date:	Version 3.0; 14 November 2025
Registration:	Human Research Switzerland (HumRes) and the international registry ClinicalTrials.gov. Publication of the protocol in the Journal "Trials" or an alternative journal specialized in medical research protocols.
Category and its rationale:	Category A clinical investigation: The PICO 7 device has already been placed on the Swiss market and is freely available by everyone. We test a concept, not the device.
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	SMITH & NEPHEW MEDICAL LTD. PICO 7 15CM X 20CM; NEGATIVE PRESSURE WOUND THERAPY POWERED SUCTION PUMP Unique Device Identification (UDI) 04582111156419. PICO devices (including complete equipment) by Smith & Nephew. Standard negative pressure with – 80 mmHg. In use for 7 to 42 days in the study. Minimally, PICO device should remain for 7 days with dressing changes as necessary based on clinical necessity, with a device change at day 7 if continued therapy is required. PICO can be used for up to a total of 42 days if deemed clinically necessary, with the goal of achieving 90% wound closure by day 42Likewise, the professional debridement can also continue up to 42 days in case of clinical necessity. The device is available on the market and is daily used in Switzerland.
Stage of development:	The device is already on the Swiss Market. We use it to test a concept, not the device. We use the PICO 7 system as a choice, but could have used another alternative negative-pressure system as well. The BALPIC study is a postmarketing test of a clinical therapeutics wound concept

Background and rationale:	Acute, postoperative dehiscent wounds and acute foot ulcers of any origin are a frequent problem among adult orthopedic patients; worldwide. The treatment can be surgical (revision surgery with closure) or conservative (debridement, wound care with and without the use of negative pressure wound therapy.[1-15]According to our local unpublished data, dehiscent wounds after elective orthopedic surgery are frequent, and occur up to 2-5% after elective surgery (depending of the type of surgery, the patient, co-morbidities, and obesity), while approximately half of the diabetic foot patients will reveal (chronic) ulcers. A quarter of these DFU probably get infected. From a surgical point of view, infected wounds are always debrided in the operating theatre, Hence, they are closed during the intervention (unless there is an abundance of pus). In contrast, the non-infected wound can be treated conservatively. As most non-infected wounds will also close by secondary closure, it is a matter of patience if the surgeons would like to close it. "Active closures" include negative-pressure therapy, stiches, or surgical revisions in the operating theatre. However, and usually, the surgeons give a chance of approximatively 1-2 weeks to an active, but "conservative" therapy, before going to the operating theatre for revision. We have the impression that a negative-pressure therapy leads to more success in terms of wound closure, and also leads to a more rapid wound closure than other conservative techniques without the use of negative-pressure. Especially, the PICO system appears as very promising. In Zurich Kanton, many nurses in and outside of the hospital setting, regularly use this PICO technique. The PICO therapy is elegant to reducing the wound size and promote wound closure by suction and in-duction of secondary closure. Moreover, the advanced PICO technology (PICO Single Use Negative Pressure Wound Therapy System) is completely portable, inexpensive and clinically effective in the treatment of surgical, chronic and acute wounds and may help to reduce the length of hospital stay, the associated costs and to prevent unnecessary surgical wound revisions in the operating theatre. Despite worldwide experience among surgeons, prospective-randomized trials are very scarce; especially in terms of orthopedic surgery and DFU's. We intend to close these gaps a to provide a better, less ex-pensive and a more convenient wound care to our patients. In this interventional, stratified (DFU's and uninfected postoperative orthopedic wound dehiscence, we randomize adult orthopedic patients between a standard wound care (including local antiseptic agents if needed) without vacuum-assisted devices or immediate closure surgery to a patient population using PICO for up to 42 days . The wounds, and their clinical evolution, are documented using tape measures and photographs. We will treat a maximum of two (biggest) wounds in a given patient, and all patients can only participate once in this trial. Importantly, the wound therapy, including the PICO use, will be per-formed by specialized wound nurses during the hospitalization period and in the outpatient setting. The study duration will be two years and will be monitored by external experts. The British and international corporation Smith + Nephew (Donator) will support the BALPIC-Study with a grant/donation, with scientific information and the necessary PICO material for the trials. The Balgrist University Hospital will keep the academic freedom of publication, but will provide the Donator with anatomized data and will submit the final graft, before publication, for critical review, to the Donator. The Balgrist will organize the insurance and monitoring for these

	trials and will perform all the correspondence with the regulatory authorizes in Switzerland. Of note, in the BALPIC Trial, we scientifically evaluate the concept of the use of a negative-pressure therapy for open wounds versus professional wound debridement alone. We do not evaluate different available devices, or very similar, techniques of a negative-pressure therapy in the head-to-head comparison which would rather switch to a marketing study and require enormous resources and much larger sample sizes.
Objective(s):	Primary objective(s) To determine if a PICO use during and/or after hospitalization and in the outpatient management of acute uninfected wounds will achieve significantly better, and a more rapid, closure results than standard wound care among adult orthopaedic patients.
Outcome(s):	Primary Outcome: Wound closure without surgical revision at Day 42 (+/- 7 days). Secondary outcomes: - Rapidity of wound closure, adverse events of wound therapy, length of hospital stay, overall costs of hospitalization - Wound closure without surgical revision at Day 7 and 14 - Wound closure without surgical wound revision for foot ulcers only (stratified analysis) Definitions: Wound Closure: Reduction of wound size of a minimum of 90% within 42 days Wound Failure: Persistent wound after 42 days; or surgical wound revision during a period up to 42 days.
Design:	Prospective-randomized, controlled, unblinded, superiority trial in favour of PICO use. Power 80%.
Inclusion / exclusion criteria:	Inclusion criteria: Patient of orthopedic surgery or of the (Diabetic) Foot Polyclinic at the Balgrist Presence of an acute, dehiscent, clinically uninfected wound requiring additional measures First episode of wound treatment for the actual wound (no recurrences) in the last 12 months Wound measuring >=0.5 cm in wide, length or depth Age ≥ 18 years Able to consent Exclusion criteria: Patient's individual refusal to participate Patient already treated with any vacuum-assisted wound device for any wound in the last 12 months; independently of therapy success, the hospital or the localization of the prior wound Underlying liquor leak (spine surgery) Visually active bleeding from the wound Wound size >10 cm in any dimension (area and volume) Anticipated active clinical follow-up of less than 42 days Other wound treatments besides PICO and debridement (e.g. hyperbaric oxygen therapy, other negative-pressure devices, local antibiotics, local antibiotic dressing) (however, local antiseptics and dressing changes remain allowed) Immediate surgical wound revision in the operating theatre for closure Planned plastic or reconstructive surgery already at inclusion Actual Wound / Surgical Site Infection (superficial or deep space) at the time of randomization

Intervention:	Brief Description (text): At enrollment, the patients will be randomized in the ratio 1:1 (PICO vs. no PICO with professional wound care) and followed-up to 42 days for any acute, dehiscent wound and/or ulcer problem. We will measure the wounds and their timely evolution by tape measures and photographs. The entire medical, surgical and nursing teams follow the standard of care that remains stable throughout the study period (control arms). The intensity of the wound debridement, its extent, and the use of the dressing or antiseptic solution, lies at the discretion of the individual professional wound nurse; and will be recorded. The use of antiseptic solution is a possible eventuality in clinically dirty or contaminated wounds (nit infected wounds), but the antiseptic solution is not part of a fix treatment protocol in either randomization arm. A wound healing, defined by the primary endpoint prior to 42 days, will be documented on clinical examination (closed or not) by the professional wound nurses and the study investigators. The timely evolution of the wound size (are and volume) will be documented by measurement by the professional wound nurses and expressed as percentages in relation to the index size at randomization. The teams of the wound nurses will not change during the treatment of the individual patient. The intervention arms will only use the additional PICO which are donated for the study; and will not take any negative-pressure devices from the hospital's regularly equipment. During hospitalization, the wound controls (without PICO removal) will be performed daily (or every second day on week-end) assessing any eventual adverse events of PICO or of the general therapy, and the success of treatment at 7, 14 days, and ultimately, at 42 days. Only in case of dysfunction, the PICO will be changed prematurely. During hospitalization, PICOs' will be changed routinely every 7 days. During an eventual outpatient period, wound evaluation will be once or twice a week, and PICO change once a week. If the PICO is discontinued for any reason (e.g. wound closure), the frequency of the clinical visits is performed only on the individual clinical decision until Day 42. Therapy and study will be supervised by the Sponsor-Investigator and the Specialist Wound Nurses of the Balgrist University Hospital (local Study Team). If the wound becomes infected during the treatment and study conduct, the study investigators will note this new information as an outcome (Serious Adverse Events; SAE). The patient's data are censored at the day of diagnosis, but remain in the dataset until the event of wound infection. We will not collect data on the therapy of infection in the frame of the BALPIC trial. Clinically, we will not use an antimicrobial solution to the PICOs (e.g. Acticoat) for patients who were in the PICO-arm. From a therapeutic point of view, all eventual negative-pressure treatment will end, and the future treatment of infection is at the entire discretion of the responsible clinicians (surgeons, nurses, and infectious diseases specialists) who might, or not, be part of the study investigators. In contrast, systemic antibiotic use for preventive (prophylactic purposes, e.g. dentists' visits; another surgical intervention), or very short antibiotic treatment with no potentially important microbiologic influence on the wound (e.g. urinary tract infection in women) allowed during the BALPIC trial and will be noted. Similarly, if healed wound reopens during the study period, this

occurrence will be noted as a Failure and SAE'. The individual study data will be censored at the time of this SAE and the patient cannot further participate in the interventional part of the BALPIC study.

Study visits

One or at maximum two PICO devices will used over the wound for 7 or 14 days, but can be clinically expanded after the main study up to 42 days. One PICO device should remain for the full 7 days. Daily visits during hospitalization or outpatient professional wound care.

The treatment period includes the following daily study visits:

Visit 1 – Enrollment (Day 1)

Assessment of the basic study variables (clinical and laboratory), randomization, wound care. Overall, there might up to six visits before the Test-of-Cure Visit, if the PICO or a wound treatment are needed for up to 42 days. In the PICO arm, one PICO device should remain for 7 days. PICO use might be repeated every week until wound closure or latest to the TOC visit at Day 42. The minimum duration of PICO use is 7 days. In the non-PICO, arm, a wound control is equally needed one a week, and minimally for one week. Each of the following weekly Visits 2 to 6 can formally represent the EOT-Visit (End of Treatment), whereas the Test-of-Cure Visit is always at Day 42 (+/- 7 days) for both randomization arms. If the wound is (prematurely closed), these additional Visits have no longer a therapeutic intervention and can be skipped until Day 42. Hence, in prematurely closed wounds, the Visits 3 to 5 are allowed not to take place (only for control purposes), if not they are not theoretically indicated. Formally, lacking of all control visits (in case of premature success) will not represent a protocol failure in the BALPIC Study.

Visit 2 - or - End-of-treatment visit (EOT) – Day 7 (+/- 2 days)

Wound assessment, decision to continue the PICO for another week; or not. with a device change at Visit 2 if continued therapy is required,

We will stop PICO use if the primary outcomes (or, inversely, any formal exclusion criteria) are achieved. If not, PICO use (or the control management) will continue until Day 14 for the study (but may be prolonged clinically, by the clinical teams, up to 42 days; as the professional wound debridement might also be prolonged to 42 days).

Visit 3 - or - End-of-treatment visit (EOT) – Day 14 (+/- 2 days)

Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events. The PICO can be continued, for clinical reasons and indications, once weekly up to 42 days. Equally, the professional wound debridement in the control arm can clinically continue up to 42 days. Wound debridement will be performed as clinically necessary in both wound

Visit 4 - or - End-of-treatment visit (EOT) – Day 21 (+/- 2 days)

Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events. device deficiencies.

	Visit 5 - or - End-of-treatment visit (EOT) – Day 28 (+/- 2 days) Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, device deficiencies Visit 6 - or - End-of-treatment visit (EOT) – Day 35 (+/- 2 days) Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, deficiencies Test-of-cure visit (TOC) – Day 42 (+/- 7 days). Wound assessment, adverse eventsdevice deficiencies .
Control intervention (if applicable):	Individualized professional wound care according to clinical indications and measures
Number of subjects with rationale:	We perform at least 7000 orthopedic procedures per year at the Balgrist, and see 200-300 acute dehiscent wounds per year. We manage approximatively 80 (diabetic) foot ulcers per year. The frequency of PICO use (without the study) per year is 50 PICOs (mostly rent for outpatient use).The calculated sample size is 2 x 134 treatment episodes of moderate to severe wound problems, i.e. 2 x 150 (300 episodes in 300 different patients targeted). This includes the stratum of (diabetic) foot ulcers. This stratified sample size would be 2 x 58 ulcers, i.e. 116 (diabetic) foot ulcers in total. We expect 10% more conservative resolution of wound problems in favor of the PICO use (85% success with PICO treatment vs. 70% with standard care), leaving only 15% for ultimate surgical revision. We target an overall superiority analysis including all kind of orthopedic surgery with an established moder-ate or severe wound problem (5% of all orthopedic patients and 30% of patients with diabetic foot ulcerations). Randomization 1:1, power 80%. We formally need 2 x 134 treatment episodes of clinically important wound problems. These are a total of 268 patients. With an additional reserve of 32 episodes (=12% of the official sample size), we stand at 2 x 150 episodes to compensate for the losses during the trial. We think that 80% of all eligible patients will sign for the trials, because this is our experience with a similar population in other trails running. This targeted sample size is sufficient, because with at least 7000 orthopedic procedures per year in the hospital, and assuming that 20% of the patients may eventually renounce on a randomized trial, we would approximatively need two years to complete this RCT (7000 episodes, 200-300 wounds per year).
Statistical considerations:	Group comparisons with the Pearson-Chi2-test or the Wilcoxon-ranksum-test, as appropriate. Multivariate adjustments on the primary outcomes using a cluster-controlled Cox regression analyses (with clustering on the individual patient's lev-el. Stratified analyses according to the type of orthopedic surgery and patients. We will analyze both, ITT (Intention-to-Treat) and PP (Per-Protocol) populations. One interim analysis will be performed one year (+/- three months) after study start. If the PICO is significantly more efficacious than the standard treatment in any of these futility analyses, we will stop the trials. The final decision will be made by an independent supervision committee.

<table>
<tr><td>Investigation schedule:</td><td>January 2026 of First- subject –In (planned)
December 2027 of Last- subject –Out (planned)</td></tr>
<tr><td>Investigator(s):</td><td>Daniela Richner, WN, Cristina Damiano, WN, Regina Sauer, Head Nurse, Felix Waibel, MD, Ilker Uçkay, MD, Anita Hasler, MD, Lucienne Gauthier, MD; Team of Wound Nurses Balgrist
Authors of the ultimate scientific publication: Daniela Richner, Cristina Damiano, Regina Sauer, Head Nurse, Felix Waibel, MD, Anita Hasler, MD, Lucienne Gauthier, MD, Ilker Uçkay, MD</td></tr>
<tr><td>Investigational Site(s):</td><td>Single centric investigation: Universitätsklinik Balgrist</td></tr>
<tr><td>Compliance statement:</td><td>This investigation will be conducted in full compliance with the CIP, the current version of the Declaration of Helsinki, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.</td></tr>
<tr><td>Budget</td><td>
<table>
<tr><td>Costs without PICO</td><td>Total</td><td>Start, 1st Year</td><td>2nd Year</td></tr>
<tr><td>a. Ethical Committee</td><td>3,000</td><td>3,000</td><td>0</td></tr>
<tr><td>b. Monitoring</td><td>10,000</td><td>5,000</td><td>5,000</td></tr>
<tr><td>c. Study Nurse 50%</td><td>95,000</td><td>47,500</td><td>47,500</td></tr>
<tr><td>Securities study nurse</td><td>14,250</td><td>7,125</td><td>7,125</td></tr>
<tr><td>d. Outpatient PICO use</td><td>19.000</td><td>9,500</td><td>9,500</td></tr>
<tr><td>e. Transportations</td><td>8,000</td><td>4,000</td><td>4,000</td></tr>
<tr><td>f. Supervision time and activity</td><td>10,000</td><td>5,000</td><td>5,000</td></tr>
<tr><td>g. Miscellaneous</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Swiss Frans (CHF)</td><td>159,250</td><td>81,125</td><td>78,125</td></tr>
</table>
</td></tr>
<tr><td>Payment of donation</td><td>Smith & Nephew provides an academically-unconditional grant (donation) to perform the BALPIC study with a cumulative sum of 159,250 CHF (VAT included), to be paid in six instalments. Additionally, the study team will receive up to 900 study PICO’s, for free, to be used in the BALPIC Study.</td></tr>
<tr><td>Insurance</td><td>The Trial is covered by the research insurance of the Balgrist.</td></tr>
<tr><td>Monitoring</td><td>The Sponsor Investigator will assign and pay an independent, external Monitor. The Monitoring is scheduled for at least twice: after the inclusion of the first ten patients; and at the study end (close-up visit). The Monitoring will base on the recommendations of the SCTO regarding a risk-based monitoring (sctoplatforms risk-based-monitorlng-guidelines feb22 v3.pdf).</td></tr>
<tr><td>Storage of data and of PICOs</td><td>All health-related patient data will be stored and archived in the data capture software REDCap™. Operational study log files and recruitments lists can be written at Excel sheets. Patient-source data will be registered using subject identifiers. After full data analysis, all subject identifiers will be erased.
The PICOs provided by Smith & Nephew will be stored for the study period, and discharged after the analysis via the regular way of discharging of medical devices. They will not be returned to the British headquarters of Smith & Nephew.</td></tr>
<tr><td>Jurisdiction</td><td>The place of jurisdiction is the Canton Zürich, Switzerland. The Donator and the Institution of the Sponsor will make a separate agreement document concerning jurisdiction issues.</td></tr>
</table>

Donation	Smith & Nephew unconditionally supports this scientific project -with a donation of approximatively 160,000 (one-hundred-sixty thousand) Swiss Francs including for Social Security) for a period of 24 months (salaries of study nurses; donation in three tranches, supervision, monitoring, outpatient parts); independently of the number of study sites, the third years' follow-up and the number of orthopedic disciplines involved -by borrowing / providing the Smith & Nephew PICO devices for the study -1 PICO is used for 1 week. We need a minimum of 150 and a maximum of 900 PICOs PICO device should remain for the full 7 days with dressing changes as necessary based on clinical levels, with a device change at day 7 if continued therapy is required. After 14 days of PICO use, its use can continue for clinical reasons up to 42 days (6x7 days of PICO use after each 7 days).

ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ASA	American Society of Anesthesiologists
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
CRP	Serum C-reactive protein
DD	Device Deficiency
EOT	End of treatment
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
HumRes	Human Research Switzerland *(in German: Humanforschung Schweiz)*
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IMM	Institut für Medizinische Mikrobiologie
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device

MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
USADE	Unanticipated Serious Adverse Device Effect
VAC	Vacuum-assisted negative pressure
ZLZ	Zentral Labor Zürich

STUDY BACKGROUND AND AIMS IN LOCAL LANGUAGE

Akute (postoperative) Wundkomplikationen, sowie schwer zu verschließenden Wunden, sind Alltag auf orthopädischen Abteilungen. Nebst professioneller Wundbehandlung, gibt es grundsätzlich weitere Aspekte des Wundmanagements. Eine Option ist die Hilfe von Unterdruck, welche die Wundflüssigkeit aufsaugt und theoretisch zu schnelleren Wundverschlüssen führt als mit reinem Debridement alleine. Vorgänger dieser Technologie heißen im englischen Sprachraum „Vacuum-Assisted Closure Systems“ und sind unter dem Kürzel VAC mittlerweile auch in der Allgemeinbevölkerung bekannt. Eine Weiterentwicklung sind PICOs. Das PICO besteht aus einer kleinen, tragbaren Pumpe mit einer Betriebsdauer von bis zu 7 Tagen; erneuerbar für weitere 7 Tage im Rahmen der Studien, und rein klinisch weiterführbar bis zu 42 Tagen. Die Unterdrucktechnik allgemein ist eine Option für die Wundbehandlung. Sie entspricht nicht festgeschrieben internationalen, nationalem oder lokalen (wie zum Beispiel) Empfehlungen. In der Fachwelt wird dessen Nicht-Anwendung nicht als Behandlungsfehler angesehen, weil eventuelle Nachteile für den Patienten und ihre/seine Wunden nicht klar ersichtlich sind. Generell, und aus Vorsicht, wird die Unterdrucktherapie nicht über eitrigen Wunden angewendet, damit der Eiter frei nach aussen frei drainieren soll (und nicht durch das Gerät dabei gehindert werden soll). Diese Vorsichtsmassnahme beruht aber nicht auf starker wissenschaftlicher Evidenz.

Die PICO-Pumpe erzeugt einen effektiven Unterdruck von -80 mm Hg und ist so klein, dass sie diskret in einem Beutel aufbewahrt werden kann und sich für ambulante Therapien sehr gut eignet. Hin-gegen ist der Nutzen des PICO im chirurgisch orthopädischen Spitalalltag erstaunlicherweise wenig untersucht, vor allem nicht im prospektivem Direktvergleich zum professionellen Debridement. Wir möchten eine prospektive-randomisierte Studie durchführen. Operationell wird es von professionellen Wundpflegerinnen durchgeführt werden unter Mithilfe von orthopädischen Chirurgen und Infektiologen mit langjähriger Erfahrung im Wundbereich. Es ist auch eine Pflegestudie. Die anfallenden Kosten werden von der Firma Smith & Nephew mit einer Spende über 159‘000 CHF sowie einer Spende von 900 PICO-Sets unterstützt. Das Monitoring ist extern. In dieser Studie testen wir ein Konzept, und nicht eine neue Indikation oder ein Gerät, welches bereits seit Jahren auf dem Markt erhältlich ist. Die Spende hat keinen Einfluss auf die Durchführung und Publikation der Studie

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change

INVESTIGATION SCHEDULE

Study Periods	Screening / Baseline*	Visit 1* Enrolment	Visit 2, potential End-of-Treatment	Visits 3 to 6potential End-of-Treatment	Test-of-Cure
Time	Day -30 to 0	Enrolment, Day 0 or 1	Day 7 (+/- 2 days).	Day 14, 21, 28, or 35 (+/- 2 days).	Day 42 (+/- 7 days)
In-/ Exclusion criteria	X				
Patient information	X				
Informed consent	X				
Demographics	X	X			
Co-morbidities	X	X			
Concomitant medication		X	X	X	X
Wound closure			X	X	X
Randomization	X				
Handing out of the PICO's		X	X		
Compliance		X	X	X	X
Adverse Events		X	X	X	X
Device Deficiencies	X	X	X	X	X
Study End				X	X

We assess:

- Patient's general characteristics (age, sex, body mass index, co-morbidities , anticoagulation) and in addition: the indication of surgery, presence of osteo-synthesis material, diabetes and eventual other immune suppression, local ischemia, first serum CRP (C-reactive protein) upon diagnosis of a wound problem: wound size, wound discharge, seroma, hematoma, surgical

site infection, number and types of surgical lavages and professional debridement, wound closure or wound failure, ad-verse events of wound therapy and their durations, total costs of hospitalization, length of hospital stay, off-loading techniques, number of dressing changes and debridement, antiseptic use, and duration of PICO use.

- The wound(s) will be photographed, measured and noted at enrolment and during the study visits in all three dimensions (height (defined as the dimension in vertical body axis), length (defined as the maximal dimension of horizontal axis), maximal depth from body surface level) in centimetres. We will note eventual subjective wound notes written by professional wound nurses but do not de-mand to comment the subjective aspects such as the colour of wound discharge, its amount or smell. Regarding the individual PICO used, we will note eventual device deficiencies.
- Of note, we will not demand for further wound-related laboratory analysis (e.g. serum albumin), histology, wound-related radiological exams or the nutrition status of the patients. However, we will incorporate this information prospectively, if it is available in the medical and/or nursing files.

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Prof Dr. med. Ilker Uçkay, Head of Infectiology, Balgrist University Hospital, Forchstrasse 340, 8008 Zürich

The sponsor is responsible for trial design and management, data handling and record keeping, subject protection, quality management, financing, investigational product management and safety evaluation. He ensures oversight and designates appropriately qualified personnel. The sponsor is going to supervise data collection, management and integrity as well as analysis and interpretation.

1.2 Principal Investigator(s)

Prof Dr. med. Ilker Uçkay, Head Infectiology, Former Head UCAR (Clinical Research in Orthopedic Department).

The PI is responsible for the protocol and GCP-conform conduct of the trial at the site. The PI dele-gates and supervises trial-related duties to qualified staff and ensures medical care of trial subjects. The PI ensures that randomization and informed consent procedures are followed, source and CRF records are accurate and that safety reporting requirements are met.

1.3 Statistician ("Biostatistician")

Statistical analyses will be performed by the investigators (mainly by Prof. Ilker Uçkay) using SPSS™ and/or STATA™ software (Version 18). In case of necessity, other biostatisticians will be consulted.

1.4 Laboratory

The BALPIC Study does not demand for laboratory analyses, but will assess the patient's routine (clinical) laboratory data. Laboratory analysis will be done by ZLZ Zentrallabor Zürich and IMM, in the immediate vicinity of UKB, as part of the regular analysis of the clinical course. Idem for radiology.

1.5 Monitoring institution

The Sponsor Investigator will assign and pay an independent, external Monitor. The Monitoring is scheduled for at least twice: after the inclusion of the first ten patients; and at the study end (close-up visit) (Appendix 2) . The Monitoring will base on the recommendations of the SCTO regarding a risk-based monitoring (sctoplatforms risk-based-monitorlng-guidelines feb22 v3.pdf).

1.6 Data Safety Monitoring Committee

A data safety committee of persons with experience in clinical research and biostatistics who are not part of the investigators or future authors of the scientific publication will monitor the safety of data and of the study; during the interim analyses (approximatively after one into the study).

1.7 Any other relevant Committee, Person, Organisation, Institution

The study takes place at the Balgrist University Hospital, but can be theoretically be expanded to other centres during the study period (after the necessity protocol amendments).

2. ETHICAL AND REGULATORY ASPECTS

There are no major ethical concerns. The PICO device is daily used in the Swiss Market and will be compared to iterative professional wound debridement in wounds, for which a treatment is medically and surgically indicated. The BALPIC Study is only a head-to-head comparison of established treatment concepts and does not use placebo or shame interventions. We are totally concordant with ethical requirements in clinical research (e.g. Emanuel E et al. What makes clinical research ethical? JAMA 2000; 283:2701-2711).

The final positive decision of the CEC and of the CA on the conduct of the investigation will be made and given in writing to the Sponsor before the investigation can start. Additional requirements set by the authorities must be implemented.

2.1 Registration of the investigation

The study will be registered at http://www.clinicaltrials.gov and https://www.humanforschung-schweiz.ch.

2.2 Categorisation of the investigation

Category A1. The investigational products (PICO) used in this study are already authorized in Switzerland for the prevention of surgical sites infections. The indication and the dosage are used in accordance with the product information and international guidelines. There will be no placebo.

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit the investigation to the CEC and obtain ethical committee approval before the start of the investigation. The PI ensures that approval from the CEC is obtained and filed in the Investigator site file before the investigation starts.

2.3.1 Reporting duties to the Competent Ethics Committee

No changes are made to the CIP without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to subjects.

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation. A summary in easily understandable terms must be included with the final report (Art. 37 ClinO-MD).

For safety reporting see Chapter 10.

2.4 Competent Authorities (CA)

CA (*Swissmedic*) approval is only necessary for category B and C studies. Category A studies do not require CA approval.

2.5 Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority's requirements.

2.6 Declaration of interests

No conflict of interest compromises the professional judgement of our investigators and the other involved people in conducting and reviewing this study. Their objectivity is not influenced in any way (e.g. independence, intellectual, financial, proprietary) or through any party.

However, Smith & Nephew supports the BALPIC trial with an unconditional grant (third party funding) to pay a minor part of the salary of the study nurse(s) and will provide the PICO sets free of charge and

for exclusive use in the study. Smith & Nephew may receive the trial data in encrypted form. Smith & Nephew will not interfere with the scientific publication of the final study results according to the terms specified in the contract of the clinical investigation.

2.7 Patient Information and Informed Consent

For the participation in the study, patients will be recruited/preselected by any of the investigators of the study. If patients match the inclusion criteria and do not meet any exclusion criterion, they will be informed by one of the study investigators, about the study, its nature, purpose, procedures involved, expected duration, participating investigators, potential risks and benefits and any potential discomfort the study could entail, during post-surgery visit when an orthopedic infection is diagnosed. Each participant will be informed that the participation in the study is completely voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her medical assistance and treatment in the future. No further screening requirements (other than the in- and exclusion criteria) exist.

All participants will be provided with a participant information sheet and informed consent form describing the study and entailing sufficient information for the participant to make an informed decision about their willingness to participate in the study. The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The information sheet provides the possibility to read through the study concept again and enables the patient to rethink the study participation without being pressured into deciding. If the participant decides to take part in the study, he/she will be asked to date and sign the informed consent form. The potential participant will be requested to read through the consent form and the information sheet carefully and to clarify any misunderstandings before signing. He/she will have enough time for consideration and the study investigators will answer all his/her questions before consenting. Once the patient dates and sign the informed consent form, one of the investigators will also date and sign the aforementioned document. The participant will be given a copy of the signed document. The original signed informed consent form will be retained as part of the study records.

The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study specific procedures. The inclusion and exclusion criteria undergo a final check (control) after the signature. The randomisation will be performed after the signature. The collection of the general consents for further use of health-related personal data and biological material is a standard at UKB. It is not study-specific.

The PI explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. Enough time is given to the subjects.

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records. All subjects a given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation. The formal consent of a subject, using the consent form approved by the CEC, is obtained before the subject is submitted to any study procedure. The subject should read, understand, and voluntarily agree before signing and dating the informed consent form and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee, when applicable). The subjects are informed, with their approval, that their personal physicians are informed about the subjects' participation in the clinical investigation, when applicable. The signed consent form it is retained as part of the clinical investigation documents. The subject's medical records are clearly marked to indicate that the subject is enrolled in the clinical investigation. The subject is provided with well-defined procedures for possible emergency situations related to the performance study. The PI makes the necessary arrangements for emergency treatment.

Neither the PICO, nor the professional wound debridement in the Control Arm will detect any new incidental findings *per se*. These findings can be detected during the clinical therapy, which, overall, is not a protocolled part of this specific study.

2.8 Subject privacy and confidentiality

The Sponsor-Investigator and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The Sponsor-Investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 5, ClinO-MD).

Individual subject medical information obtained as a result of this investigation is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor, the CA or a CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

2.9 Early termination of the investigation

The Sponsor may terminate the investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient subject recruitment,
- when the safety of the subjects is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of the investigation unwise,
- early evidence of benefit or harm of the experimental intervention, e.g. based on interim analyses

2.10 Clinical investigation plan amendments

The Sponsor-Investigator Prof. Ilker Uçkay is allowed to amend the CIP or to provide suggestions for a CIP amendment.

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD) and, for category C investigations, after approval by the CA also (Art. 20 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC (and for category C investigations without prior approval by the CA). Such deviations shall be documented and reported to the Sponsor and the CEC (and to the CA for category C investigations) within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC annually together with the safety report / general progress report of the clinical investigation (Art. 15 ClinO-MD), and for category C clinical investigations to the CA as soon as possible (Art. 20 ClinO-MD). The report will include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

2.11 Deviation from the Clinical Investigation Plan

In case of deviations from the Clinical Investigation Plan, the patient drops out of the interventional study or is excluded from the PP study population and the patient will be informed accordingly by the Study team. His/her epidemiological data main remain in the descriptive database.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale for the clinical investigation

Acute, postoperative dehiscent wounds and acute foot ulcers of any origin are a frequent problem among adult orthopedic patients; worldwide[1,2]. The treatment can be surgical (revision surgery with closure) or conservative (debridement, wound care with and without the use of negative pressure wound therapy.

According to our local data, dehiscent wounds after elective orthopedic surgery are frequent, and occur up to 2-5% after elective surgery (depending of the type of surgery, the patient, co-morbidities, and obesity)[3], while approximately half of the diabetic foot patients will reveal (chronic) ulcers[4]. A quarter of these DFU probably get infected. From a surgical point of view, infected wounds are always debrided in the operating theatre, Hence, they are closed during the intervention (unless there is an abundance of pus). In contrast, the non-infected wound can be treated conservatively. As most non-infected wounds will also close by secondary closure, it is a matter of patience if the surgeons would like to close it. "Active closures" include negative-pressure therapy, stiches, or surgical revisions in the operating theatre[3]. However, and usually, the surgeons give a chance of approximatively 1-2 weeks to an active, but "conservative" therapy, before going to the operating theatre for revision. We have the impression that a negative-pressure therapy leads to more success in terms of wound closure, and also leads to a more rapid wound closure than other conservative techniques without the use of negative-pressure. Especially, the PICO system appears as very promising. In Zurich Kanton, many nurses in and outside of the hospital setting, regularly use this PICO technique. The PICO can be used preventively[5] or therapeutically[6,7] concerning postoperative wounds. For the subset of DFUs, its use is rather therapeutic[7-10]. Of note, negative-pressure itself is only an option for wound management in the highly individualized wound problem of a given patient and episode It might be mentioned, but is not firmly promoted in international, national or regional guidance[9,13,14]. Its lack is not considered as a breech in quality of case for the individual patient.

In terms of indications, indicated for patients who would benefit from a suction device (negative pressure wound therapy) as it may promote wound healing via removal of low to moderate levels of exudate and infectious materials (Appendix 1). Appropriate wound types include partial-thickness burns, Ulcers (such as diabetic or pressure) Traumatic wounds, and subacute and dehisced wounds. According to the manufacturer, the usual contraindications represent patients with malignancy in the wound bed or margins of the wound (except in palliative care to enhance quality of life), Previously confirmed and untreated osteomyelitis, Non-enteric and unexplored fistulas, Necrotic tissue with eschar present., Exposed arteries, veins, nerves or organs, exposed anastomotic sites.

By precaution, experts recommend not to use a negative-pressure device over purulent wound in order to let the pus drain freely out of the wound (a discharge that should not be prohibited by the presence of the device on the way out). However, this precaution does not base on strong scientific evidence. Nevertheless, this precaution motivates us to exclude infected wounds from the BALPIC Trial. Moreover, the PICO should not be used for the purpose of concomitant surgical suction (Appendix 1). The PICO 7 pump contains a magnet that can cause other medical devices in close proximity to fail. Therefore, the PICO 7 pump must be positioned at least 4 inches (10cm) away from other medical devices that could be affected by magnetic interference. These include but are not limited to: Implantable Cardioverter-defibrillator (ICD), Pacemakers, Insulin Pumps, Shunt Valves, Neurostimulators, Cochlear Implants. However, the PICO 7 has been tested and found to comply with the limits for medical devices to IEC 60601-1-2. These limits and test levels are intended to provide reasonable safety with regard to electromagnetic disturbances when PICO 7 is used in a typical medical installation and uncontrolled environment like home use. According to the manufacturer, the equipment generates, uses and can radiate radio frequency energy and, if not installed and used in accordance with the instructions, may cause harmful interference to other devices in the vicinityPrecautions should be taken in the following types of patients who are at high risk of bleeding complications (Appendix 1). Inside, or on the human body, the PICO-7 is composed of metal and polyethylene (and associated dressings). These are materials that are widely used in orthopedic surgery since decades.

Conceptually, the PICO system is a Single Use Negative Pressure Wound Therapy (NPWT) System designed to provide NPWT to a closed environment over a wound, it allows exudate to evacuate from the wound site into an absorptive dressing, from which the fluid evaporates through a specialized layer

with a high moisture vapor transpiration rate. The closed environment is created by applying a sterile wound dressing to the wound site and connecting the sealed wound to the suction device. The PICO therapy is elegant to reducing the wound size and promote wound closure by suction and induction of secondary closure. Moreover, the PICO technology (PICO Single Use Negative Pressure Wound Therapy System) is completely portable, inexpensive and clinically effective in the treatment of surgical, chronic and acute wounds and may help to reduce the length of hospital stay, the associated costs and to prevent unnecessary surgical wound revisions in the operating theatre. Despite worldwide experience among surgeons, prospective-randomized trials are very scarce[5,6]; especially in terms of orthopedic surgery and DFU's. We intend to close these gaps a to provide a better, less expensive and a more convenient wound care to our orthopedic patients[11-16,] including for diabetic foot ulcers or wounds.[17]

Technically, the PICO™ 7 is intended for use by or on the direction of a trained and licensed.

physician and healthcare personnel in accordance with these instructions for use(Appendix 1). Specifically, where PICO 7 is used to bolster skin grafts, it is important to visually inspect the system regularly, especially in the first week of treatment to ensure that negative pressure wound therapy is continually applied and a seal is maintained. Where PICO dressings are used on infected wounds, more frequent dressing changes may be required. Regular monitoring of the wound should be maintained to check for signs of infection. If deemed clinically appropriate, care should be taken that the application of a circumferential dressing or the use of negative pressure wound therapy on ischemic limbs does not compromise circulation. The PICO 7 does not contain audible alerts. The pump should be carried so that it is accessible and the patient/healthcare professional can check the status routinely (Appendix 1)..The PICO-dressings should only be applied by a healthcare professional. PICO dressings must only be used on wounds which fit comfortably within the area of the pad, observing precautions on soft port positioning (on intact skin and not extending over the wound) (Appendix 1)In terms of possible adverse reactions, excessive bleeding and the development of an underlying infection are serious risks associated with the application of PICO suction to wounds Carefully monitor the wound and dressing for any evidence of a change in the blood loss status of the patient. Monitor the patient for signs of any sudden or abrupt changes in the volume or the color of exudate (Appendix 1).

Light showering is permissible; however, the PICO 7 pump should be stopped and disconnected and placed in a safe location where it will not get wet. The PICO dressings should not be exposed to a direct spray or submerged in water. While disconnected, ensure the end of the tubing attached to the dressing is facing down so that water does not enter the tube. After showering and bathing the PICO 7 pump should be reconnected to the dressing and restarted (Appendix 1). For this BALPIC Trial, the PICO 7 system has the CE certificate number CE 00356 (Appendix 3). Appendix 4 provides the EUROPEAN DECLARATION OF CONFORMITY for the PICO-7 system of Smith & Nephew.

In this interventional, stratified (DFU's and uninfected postoperative orthopedic wound dehiscence, we randomize adult orthopedic patients between a standard wound care (including local antiseptic agents if needed) without vacuum-assisted devices or immediate closure surgery to a patient population using PICO for 7-14 days. The wounds, and their clinical evolution, are documented using tape measures and photographs. We will treat a maximum of two (biggest) wounds in a given patient, and all patients can only participate once in this trial. Importantly, the wound therapy, including the PICO use, will be performed by specialized wound nurses during the hospitalization period and in the outpatient setting. The study duration will be two years and will be monitored by external experts. We will investigate the therapeutic PICO on open wounds, and will not use it preventively on closed surgical wounds. Of note, in the BALPIC Trial, we scientifically evaluate the concept of the use of a negative-pressure therapy for open wounds versus professional wound debridement alone. We do not evaluate different available devices, or very similar, techniques of a negative-pressure therapy in a head-to-head comparison which would rather switch to a marketing study and require enormous resources and much larger sample sizes.

The international corporation Smith + Nephew (Donator) will support the BALPIC-Study with a grant/donation, with scientific information and the necessary PICO material for the trials. The Balgrist University Hospital will keep the academic freedom of publication, but may provide the Donator with encrypted study data and will submit the final graft, before publication, for critical review, to the Donator. The Balgrist will organize the insurance and monitoring for this trial and will perform all the correspondence with the regulatory authorizes in Switzerland.

3.2 Identification and description of the Investigational Medical Device

This study will be performed with an existing PICO 7 “device set” manufactured by Smith & Nephew. SMITH & NEPHEW MEDICAL LTD. PICO 7 15CM X 20CM; NEGATIVE PRESSURE WOUND THERAPY POWERED SUCTION PUMP Unique Device Identification (UDI) 04582111156419. Its Clinical Manual is summarized in Appendix 1. The device is freely available on the Swiss market and widely used in daily clinical life.

3.3 Preclinical Evidence

Not applicable. The PICO device and professional debridement for wounds are daily used and performed in Switzerland since many years.

3.4 Clinical Evidence to Date

See chapter 3.1

3.5 Justification for the design of the clinical investigation

We prospectively compare two established wound treatments in a randomized (1:1) superiority study design. We think that this randomized study design is the best to answer which concept would be clinically the best. The PICO is the newer concept and allocated to the Investigational (superior) Arm.

3.6 Explanation for choice of comparator

The comparator is professional debridement for wounds. This technique and concept are acknowledged surgical measures for (acute) wounds since antiquity, and correspond widely to daily practice and surgical recommendations for wound in Switzerland and worldwide.,

3.7 Risk evaluation (Risk-to-Benefits rationale)

All patients can witness adverse events related to surgical procedures and professional wound care, which however, are related to the therapy itself, and not to the specific study protocol. A theoretical risk could be a higher incidence of SSI, local hematoma and discomfort in the PICO arm, when the device should be defective or disconnected. Patients in the debridement arm could witness more skin irritation, intolerance and allergy to antiseptics and/or ingredients of the formulations. The potential benefits are a more rapid wound closure reduction in the PICO arm with less surgeries and overall health costs compared to the patients and episodes treated in the debridement arm. Conversely, the lack of a PICO use could theoretically lead to a lack of closure, or more probably, to a timely slower wound closure.

Pregnancy and breast-feeding

Orthopaedic wound care in general, and the BALPIC Study in particular, are not associated with a particular risk for pregnant and breastfeeding women and their (un)born infants. These women may participate in the BALPIC Study.

3.8 Justification of the choice of the investigation population

See chapter 3.1.

4. CLINICAL INVESTIGATION OBJECTIVES

4.1 Overall Objective

To determine if a PICO use during and/or after hospitalization and in the outpatient management of acute uninfected wounds will achieve significantly better, and a more rapid, closure results than standard wound care among adult orthopaedic patients.

4.2 Primary Objective

To determine if a PICO use during and/or after hospitalization and in the outpatient management of acute uninfected wounds will achieve significantly better, and a more rapid, closure results than standard wound care among adult orthopaedic patients.

4.3 Secondary Objectives

None.

4.4 Safety Objectives

None. The investigation will, however, assess long-term safety of the PICO and its tolerability in terms of any unexpected adverse events and mechanical non-functionality during treatment).

5. CLINICAL INVESTIGATION OUTCOMES

5.1 Primary Outcome

Wound closure without surgical revision at Day 42 (+/- 7 days).

5.2 Secondary Outcomes

- Rapidity of wound closure, adverse events of wound therapy, length of hospital stay, overall costs of hospitalization
- Wound closure without surgical revision at Day 7, 14, 21, 28 or 35 days
- Wound closure without surgical wound revision for foot ulcers only (stratified analysis)

5.3 Other Outcomes of Interest

Not applicable.

5.4 Safety Outcomes

Not applicable.

6. CLINICAL INVESTIGATION DESIGN

6.1 General clinical investigation design and justification of design

The BALPIC trial is a prospective-randomized, controlled, unblinded, superiority trial in favour of PICO use. The study population are surgical patients with acute uninfected wounds necessitating a medical intervention for their wounds, or with acute diabetic foot ulcers. We test two established wound therapy concepts with a direct head-to-head comparison during a reasonable time period for the treatment of most acute wounds, which is 1 to 2 weeks. The clinical follow-up period of 6 weeks corresponds to widespread experience. The BALPIC study is adapted, to the best possible, to our clinical experience, treatment modalities and resource use.

The PICO system is a Single Use Negative Pressure Wound Therapy (NPWT) System designed to provide NPWT to a closed environment over a wound, it allows exudate to evacuate from the wound site into an absorptive dressing, from which the fluid evaporates through a specialized layer with a high moisture vapor transpiration rate (MVTR). The closed environment is created by applying a sterile wound dressing to the wound site and connecting the sealed wound to the suction device.

Smith & Nephew will provide between 150 and 900 PICO devices free of charge for use during the BALPIC Study. The sets will be used according to the instruction provided (Appendix 1). Before the study, there will be one online educational meeting (per ZOOM or Microsoft Teams) between the specialized wound nurses of the Balgrist and teaching nurses of Smith & Nephew. The intervention arms will only use the additional PICO. During hospitalization, the wound controls (without PICO removal) will be performed daily (or every second day on week-end) assessing any eventual adverse events of PICO or of the general therapy, and the success of treatment at 7, 14 and, for control, ultimately at 42 days. Only in case of dysfunction, the PICO will be changed prematurely. During hospitalization, PICOs' will be changed routinely every 7 days. During an eventual outpatient period, wound evaluation will be once or twice a week, and PICO change once a week. Appendix 1 represents the official device “brochure”. Appendix 1 is a summary in English language of the larger manual in German language, which is available online Smith Nephew PICO 7 Einweg-Unterdruck-Wundtherapiesystem – Benutzerhandbuch.

6.2 Methods for minimising bias

The methods of minimising bias applied in our study are the randomization to add validity of the statistical tests used to demonstrate significance. The differences between intervention and control groups should behave like differences between two random samples from the population so that they can be compared to what would be expected in the population by chance.

6.2.1 Randomisation

After written informed consent given participants will be randomized with a 1:1 ratio in either treatment group. Randomization is done by designated study staff drawing a sealed envelope containing a randomization card or electronically. Patients are informed about the assignment by the investigators.

6.2.2 Blinding procedures

There will be no blinding of patients, and no placebos.

6.2.3 Other methods for minimising bias

Not applicable

6.3 Unblinding Procedures (Code break)

Not applicable

7. CLINICAL INVESTIGATION POPULATION

7.1 Eligibility criteria

Inclusion criteria:

- Patient of orthopaedic surgery or of the (Diabetic) Foot Polyclinic at the Balgrist
- Presence of an acute, dehiscent, clinically uninfected wound requiring additional measures
- First episode of wound treatment for the actual wound (no recurrences) in the last 12 months
- Wound measuring >=0.5 cm in wide, length or depth
- Age ≥ 18 years
- Able to consent

Exclusion criteria:

- Patient's individual refusal to participate
- Patient already treated with any vacuum-assisted wound device for any wound in the last 12 months; independently of therapy success, the hospital or the localization of the prior wound
- Underlying liquor leak (spine surgery)
- Visually active bleeding from the wound
- Wound size >10 cm in any dimension
- Anticipated active clinical follow-up of less than 42 days
- Other wound treatments besides PICO and debridement (e.g. hyperbaric oxygen therapy, other negative-pressure devices, local antibiotics, local antibiotic dressings) (however, local antiseptics and dressing changes remain allowed)
- Immediate surgical wound revision in the operating theatre for closure
- Planned plastic or reconstructive surgery already at inclusion
- Actual Wound / Surgical Site Infection (superficial or deep space) at randomization

7.2 Recruitment and screening

The concerning patients will be screened every day by the clinicians, the nurses and the study investigators in all orthopedic wards of the Balgrist. In case of potential eligibility for the BALPIC Trial, the patient will be informed about the study by one of the investigators (see chapter 2.7) and orally instructed about the handling of the PICO device. He/she will have enough time for consenting if the signature needs to be collected the same day. If there is sufficient time from an organizational point of view, the signed consent can be obtained the following days. The in- and exclusion criteria will be re-controlled after the signature. Clinically, it is important that the study investigator instructs the patient (and his/her accompanying family members) directly.

7.3 Assignment to investigation groups

7.4 A randomization list will be generated electronically using sealedenvelope.com. The parameters selected are two groups, a block size of 10, and a total of 300 patient entries. This list will be downloaded and securely stored in the eTMF. Participants will then be assigned to study groups (control or intervention) according to the randomization list, with each new patient receiving the next available subject ID.Criteria for withdrawal / discontinuation of subjects

All patients are free to withdraw from participation in this study at any time, for any reason, and with-out prejudice. A patient who withdraws consent by refusing to continue with study procedures/observations will be terminated from the study. The reason for withdrawal of consent will be clearly documented wherever possible. However, it is not required for patients to provide their reason.

The investigator should make every effort to address non-compliance issues and ensure that relevant study data are obtained from patients whenever possible. If consent is withdrawn, data collected up to

that point will be included in the analysis and subsequently stored in encrypted form to ensure patient safety. Full anonymization is not possible in this context due to the need for traceability in case of medical concerns.

To enable collection of follow-up data, the investigator may stop study treatment at any time without withdrawing the patient from the study (e.g. the patient experiences intolerable or unacceptable AEs possibly related to study treatment and where such treatment cannot be modified within the confines of the protocol).

On rare occasions, the investigator may exclude a patient from the study to protect his/her best interest e.g. to protect them from excessive risk or risk with a demonstrated lack of benefits (serious side-effects) or to maintain the integrity of the data (when participates are not following study procedures or may be deliberately providing false information). The investigator must explain to the participant the reasons. If a patient is withdrawn before completing the study, the reason for withdrawal will be entered in the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that are required at the next scheduled visit will be performed at early termination.

8. CLINICAL INVESTIGATION / INTERVENTION

8.1 Identity of the medical device under investigation

8.1.1 Experimental Intervention (medical device)

The duration of the PICO use is planned to be during 7 days, and can be prolonged to 42 days; and in case of clinical necessity. The frequency of the professional debridement by specialized wound nurses is at the discretion of the responsible nurse and orthopedic surgeons and bases on internal professional documents, which are in line with nursing procedures of the Balgrist University Hospital and Switzerland.

8.1.2 Control Intervention (standard/routine/comparator)

Professional wound care according to hospital-intern14 and Swiss nursing guidelines, and the surgeon's instruction. The intensity of the wound debridement, its extent, and the use of the dressing or eventual antiseptic solution, lies at the discretion of the individual wound nurse; and will be recorded. We do NOT define a strict "standard" for dressings and debridement. The specialized wound nurses might use an antiseptic product according to the intolerance of the patient, the clinical indication, or her personal preferences. For example, they might use iodine, octenidin, or just simple saline. The dressing products can also be different.

8.1.3 Labelling and Supply (re-supply)

This is a post-market device investigation. Individual device labelling is not mandatory, but we will monitor which devices has been for which patients in the study, and will keep the study-associated PICO's physically and administratively separated from the usual clinical devices, which are the same.

Smith & Nephew will donate, in tranches and upon request by the study team, up to 900 study PICO devices for the BALPIC trial; and will abstain from donating for patients not participating in the trial. During the study period, the Balgrist will continue to purchase PICO devices for clinical use as usual.

8.1.4 Storage Conditions

We will recuperate used PICO devices. They will be in the (locked) office of the wound care nurses and/or in the Prof. Uçkay's office.

8.2 Discontinuation or modifications of the intervention

In the BALPIC trial, we will use the PICOs as highlighted in the manufacturer's manual. No specific technique will be investigated, and we will not modify the manufacturer's clinical recommendations, frequency of PICO use, or of its precautions (Appendix 1). In case of unexpected adverse events of any nature or device malfunction, we will replace the study device by another study device, or exclude the patient from the interventional part of the trial (according to a medical judgement of the individual case).

8.3 Compliance with clinical investigation intervention

Both, the PICO use, and the professional debridement, will be performed by specialized wound nurses. As the patients have no active therapies to perform (besides seeing the nurse), we expect no major compliance problems from the patients' side.

8.4 Data Collection and Follow-up for withdrawn subjects

Withdrawn participants are instructed to continue surveillance according to the protocol and to contact the investigators if there are any questions or concerns that arise after completing the study.

If consent is withdrawn, data collected up to that point will be included in the analysis and subsequently stored in encrypted form to ensure patient safety. Full anonymization is not possible in this context due to the need for traceability in case of medical concerns.

The medical follow-up of withdrawn subjects, or of subjects that drop out from the investigation prematurely is described in chapter 9.2.5 and chapter 9.2.6.

8.5 Clinical investigation specific preventive measures

There are no trial-specific preventive measures which would be beyond the usual care according to the manufacturer's instructions. The wound treatment, in either study arm, will be performed, controlled and supervised by professionals with clinical and academic experience in orthopedic wounds. Moreover, we

offer regular educational information concerning the PICO use and the BALPIC study for colleagues, who concomitantly treat other aspects of our study patients.

8.6 Concomitant Interventions (treatments)

Standard wound control for all patients will include eventual wound debridement (during hospitalization or at clinic visits and only if clinically indicated), regular wound care with dressing changes and eventual negative-pressure use in selected cases upon surgical clinical indication. We will avoid topical antibiotics.

8.7 Medical Device Accountability

We recuperate the used study PICO devices from the individual patients. This process will be documented (e.g. accountability log). This log should also serve to record any damages of the set.

8.8 Return, Analysis or Destruction of the Medical Device

Returned used and unused PICO devices will be destroyed at the end of the investigation, as the PICO devices will be provided for the purpose of this clinical investigation only. The patient will also have been informed about the return of the investigational product. This notice will be captured in the participant information sheet or in the informed consent.

In case of major device deficiencies, including malfunction, usability issues, or inadequacy in the information supplied by the manufacturer, the devices will be returned to Smith & Nephew for analysis.

9. CLINICAL INVESTIGATION ASSESSMENTS

9.1 Table of clinical investigation procedures and assessments

Study Periods	**Screening / Baseline***	**Visit 1* Enrolment**	**Visits 2 to 6 potential End-of-Treatment**	**End-of-Treatment**	**Test-of-Cure**
Time	Day -30 to 0	Enrolment, Day 0 or 1	Day 7,14,21,28, 35 (+/- 2 days).	Day 14 (+/- 2 days).	Day 42 (+/- 7 days)
In-/ Exclusion criteria	X				
Patient information	X				
Informed consent	X				
Demographics	X	X			
Co-morbidities	X	X			
Concomitant medication		X	X	X	X
Wound closure			X	X	X
Randomization	X				
Handing out of the PICO's		X	X		
Compliance		X	X	X	X
Adverse Events		X	X	X	X
Device Deficiencies	X	X	X	X	X
Study End				X	X

Assessments of outcomes

9.1.1 Assessment of primary outcome

. Thw wounds will be assessed during the study visits. The wound healing will be assessed visually by orthopaedic surgeons and the professional wound nurses, who treat the patient and/or are part of the Study investigators. The wound nurses will photography the wound from very close and measure its size and volume in all three dimensions(in cm).. For any dimension (depth, width, length), the will take the largest diameter, and repeat theses assessments accordingly in the following visit. We will not consider photographies that has been taken from colleagues and personnel who are not part of the study investigators.

Persistent postsurgical pain, serum laboratory markers, or the patient's subjective wound feelings will not serve as objective criteria for wound healing (or in the contrary, wound discharge and dehiscence). A wound problem solely due to stitches and localized suture problems will not count as a wound problem. A keloid or altered pigment features will not be counted as a problem in this trial. The primary outcome

will be assessed on both, the intention-to-treat and the per-protocol populations.

9.1.2 Assessment of secondary outcomes

Other outcomes are the individual length of hospital stay and the overall costs of hospitalization, which we will have from the hospital's administration in our single-center study.

9.1.3 Assessment of other outcomes of interest

Not applicable

9.1.4 Assessment of safety outcomes

We will also note potential device deficiencies, even if these deficiencies are not an objective of the BALPIC Trials. They will be noted separately and technically count as SAE in the frame of the BALPIC Study.

9.1.4.1 Adverse events

See chapter 10

9.1.4.2 Laboratory parameters

n/a. No study specific laboratory parameters will be assessed.

9.1.4.3 Vital signs

No study specific vital sign measurements will be performed. These vital signs are collected and noted several times per day according to the clinical protocols of the operated patients for various reasons.

9.1.5 Assessments in subjects who prematurely stop the clinical investigation

Participants who prematurely stop the investigation are defined as patients who withdraw consent or who, in the opinion of the investigator, are no longer eligible to participate in the study. Where possible, such patients will complete an early-termination visit to undergo all assessments applicable to the corresponding (or next) scheduled study visit. For these patients, we will record eventual adverse events, physical examination, laboratory parameters, vital signs during a follow-up period determined by clinical control, which is usually up to one-year post intervention.

9.1.6 Follow-up of the subjects after the regular termination of the clinical investigation

All our study patients are regular patients of the Universitätsklinik Balgrist, who we treat regularly. These patients are independently seen and collected at the regular surgical visits at 6 weeks, 6 months or 12 months after hospitalization, and more frequently if necessary (e.g. by professional wound nurses and or by physiotherapists). These surgical controls routinely occur independently of the patient's participation in the BALPIC trial.

9.2 Procedures at each visit

At enrollment (Visit 1 / Day 0 or 1), patients will be randomized at ratio 1:1 into the investigational group (PICO) and the control group (no PICO). The study investigators will instruct the correct wound care. One or at maximum two PICO devices will used over the wound for 7 to 42 days.

Daily visits during hospitalization or outpatient professional wound care.

Overall, there might up to six visits before the Test-of-Cure Visit, if the PICO or a wound treatment are needed for up to 42 days. In the PICO arm, one PICO device should remain for 7 days. PICO use might be repeated every week until wound closure or latest to the TOC visit at Day 42. The minimum duration of PICO use is 7 days. In the non-PICO, arm, a wound control is equally needed one a week, and minimally for one week. Each of the following weekly Visits 2 to 6 can formally represent the EOT-Visit (End of Treatment), whereas the Test-of-Cure Visit is always at Day 42 (+/- 7 days) for both randomization arms. If the wound is (prematurely closed), these additional Visits have no longer a

therapeutic intervention and can be skipped until Day 42. Hence, in prematurely closed wounds, the Visits 3 to 5 are allowed not to take place (only for control purposes), if not they are not theoretically indicated. Formally, lacking of all control visits (in case of premature success) will not represent a protocol failure in the BALPIC Study.

The treatment period includes the following daily study visits:
Visit 1 – Enrollment (Day 1)
Assessment of the basic study variables (clinical and laboratory), randomization, wound care

Visit 2 - or - End-of-treatment visit (EOT) – Day 7 (+/- 2 days)
Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events. Decision to continue the PICO, or the no-PICO debridement, for another week; or not.

Visit 3 - or - End-of-treatment visit (EOT) – Day 14 (+/- 2 days)
Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, device deficiencies. Decision to continue the PICO, or the no-PICO debridement, for another week; or not.

Visit 4 - or - End-of-treatment visit (EOT) – Day 21 (+/- 2 days)
Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, device deficiencies. Decision to continue the PICO, or the no-PICO debridement, for another week; or not.

Visit 5 - or - End-of-treatment visit (EOT) – Day 28 (+/- 2 days)
Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, device deficiencies. Decision to continue the PICO, or the no-PICO debridement, for another week; or not.

Visit 6 - or - End-of-treatment visit (EOT) – Day 35 (+/- 2 days)
Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, device deficiencies. Decision to continue the PICO, or the no-PICO debridement, for another week; or not.

Test-of-cure visit (TOC) – Day 42 (+/- 7 days).
Wound assessment, adverse events, device deficiencies (if not done at EOT).

9.2.1 Enrolment (Visit 1)

Information collected during routine pre-surgical consultation and during orthopaedic surgery is not study specific. This data will be used as general demographic information and medical history within the study in case of an orthopaedic infection and study participation.

If a patient appears to be eligible the following study-related procedures are performed:

1. Patient information and obtaining written informed consent.
2. Assign a study identification number.
3. Record/complete medical history and demographics.
4. Review inclusion/exclusion criteria.
5. Randomize the patient and handing out of the PICO device.

9.2.2 Visit 2 (potential End-of-Treatment)

1. Record any concomitant medications as well as any additional interventions required
2. Assess all adverse events of therapy and potential device deficiencies.
3. Assess all study objectives. The primary objective wound closure and/or size and volume.
4. The secondary objectives are the rapidity of wound closure, adverse events of wound therapy, length of hospital stay, overall costs of hospitalization, a Wound closure without surgical revision

at Day 7, 14, 21, 28 or 35 days, and Wound closure without surgical wound revision for foot ulcers only (stratified analysis). The secondary objectives are basically analyses of the primary outcomes which we be noted separately. The assessment of the secondary outcomes, as a procedure, will be the same as for the primary outcomes. The investigator team will assess them at the corresponding visit (study) timepoints. The professional wound nurses will photography them.

5.

9.2.3 End-of-Treatment

Every effort will be made to ensure that final efficacy assessments (i.e., primary outcome data) are available for all subjects. As all our study visits are part of the routine surgical and postsurgical assessments, we do not expect major drop-out rates; or drop out in very exceptional situations (e.g. transfer to another service because of stroke, non-infectious postsurgical fatalities, etc.) Outpatients should return to the clinic (assessments can be performed in the hospital for inpatients), where the following assessments will be performed:

1. Assess anamnestically all (past) adverse events and potential device deficiencies.
2. Record clinical and microbiological infection and its treatment (if any)

9.2.4 Test-of-Cure

Wound assessment. Anamnestic assessment of all past adverse events of surgery, the hospitalization and wound care.

9.2.5 Early Termination of Study Patients

Patients who withdraw consent or who, in the opinion of the investigator, are no longer able or eligible to participate in the study (including patients who require antibiotic therapy beyond EOT) will be early terminated. Where possible, such patients will complete an early-termination visit to undergo all assessments applicable to the corresponding (or next) scheduled study visit. For example, patients developing wound infections cannot further participate in the interventional part of the BALPIC trials (and hence will not have any negative-pressure device therapy any more). Their data remain in the database and are censored at the day of infection diagnosis.

10. SAFETY

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 Abs 57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.

Serious Adverse Event (SAE) (Art. 2 Abs 58 MDR)

Any adverse event that led to any of the following:

(a) death,
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalisation or prolongation of patient hospitalisation,
  (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

EXCEPTIONS: Of note, in the BALPIC study, we define wound failures NOT as SAE. In this study, the same outcome will not be counted twice or differently, e.g. once as a Wound Failure, and a second time as an SAE. Likewise, a planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE.

Wound infection

A present wound infection is an exclusion criterion for the BALPIC Trial. An occurrence of infection during wound management (after randomization) is a formal SAE leading to the discontinuation of the PICO (in the PICO-Arm) and to clinical treatment of the infected wound. The patient's data are kept in the database but are censored at the Day of infection diagnosis.

Hence, a "bacterial wound infection" is no variable of interest for the BALPIC Trial, but an important complication (SAE) that we pre-define hereby:

In the soft tissues of infected wounds, the presence of an infection relies on clinical criteria and not on the presence of bacteria in superficial microbiological swabs. These local criteria are new signs of inflammation (rubor, calor, *functio laesa*, tumor, or dolor (in non-neuopatic patients), with or without (systemic) complications such as fever, shivering, lymphangitis, and/or a rapid spread of visual local and asymmetric inflammation that cannot be explained better than with a bacterial cause.

Device deficiency (Art. 2 Abs 59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Event (SAE) potential (Art. 80 Abs 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

This includes any adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the MD under investigation. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible. Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the PI and the Sponsor using the following algorithm:

Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related AE
    - Yes: ADE
- Yes, it is serious: SAE
  - Is the relationship to the device or the procedure possible, probable or causal?
    - No: non-related SAE
    - Yes: SADE
- Is it anticipated (within expected type, severity and frequency of the complications)?
    - No: unanticipated SADE (USADE)
    - Yes: anticipated SADE (ASADE)

10.3 Documentation and reporting in Medical Device Category A clinical investigations

Device deficiencies (DD) and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from patient's informed consent until the last CIP-specific procedure, including a safety follow-up period.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop

dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).

- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).

The AE are collected and noted by the research assistants /study nurse, in collaboration with the Sponsor-Investigator and other members of the Study Team.

10.3.1 Foreseeable adverse events and anticipated adverse device effects

There are no unplanned adverse events foreseen or expected. In case of an adverse event, this can be very various and heterogenous in the postsurgical period such as wound bleeding, pain, secondary dehiscence, ischemia, lung embolisms, inappetence etc,, which would be beyond the scope of any table. Of note, we do not test a device, but a concept.

10.3.2 Reporting of Safety related events

Reporting to the Sponsor:

All SAEs, DDs with SAE potential and health hazards that require measures are reported to the Sponsor by the PI (or authorized designee) without delay after becoming aware of the event. DD are assessed regarding their potential to lead to an SAE.

Pregnancies

Reporting of pregnancies is not necessary

10.3.3. Reporting to the Competent Ethics Committee:

The Sponsor reports to the CEC without delay any SAE for which a causal relationship between the event and the test procedure used in the clinical trial has been ascertained (Art. 33 ClinO-MD).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

Once a year, the sponsor submits to the CEC a list of the SAEs and DDs and provides it with a report on their severity, causal relationship with the device and the intervention, as well as on the safety of the participants. The sponsor informs the CEC about the general progress of the clinical investigation, annually.

Materiovigilance reporting to Swissmedic:

The treating surgeon and the Sponsor-Investigator are responsible for ensuring that *Swissmedic* is informed of serious incidents in accordance with Art. 66 MedDO.

10.4 Assessment, notification and reporting on the use of radiation sources

Not applicable for the BALPIC study. However, the study patients may be exposed clinically to radiation as any other orthopedic patient during and after hospitalization. In case of an unplanned and unusual exposition, the Universitätsklinik Balgrist has a commission for this specific problem. Major radiology-related SAE and AE will be noted in the study files.

11. STATISTICAL METHODS

11.1 Hypothesis

We presume that PICO use will lead to wound closure more often (or more rapidly) than iterative professional debridement alone. We have the recruitment potential in our single center. We perform at least 7000 orthopedic procedures per year at the Balgrist, and see 200-300 acute dehiscent wounds per year. We manage approximatively 80 (diabetic) foot ulcers per year.

11.2 Determination of Sample Size

We expect 10% more conservative resolution of wound problems in favor of the PICO use (85% success with PICO treatment vs. 70% with standard care), leaving only 15% for ultimate surgical revision. We target an overall superiority analysis including all kind of orthopedic surgery with an established moderate or severe wound problem (5% of all orthopedic patients and 30% of patients with diabetic foot ulcerations). Randomization 1:1, power 80%.

The calculated sample size is 2 x 134 treatment episodes of moderate to severe wound problems, i.e. 2 x 150 (300 episodes in 300 different patients targeted). This includes the stratum of (diabetic) foot ulcers. This stratified sample size would be 2 x 58 ulcers, i.e. 116 (diabetic) foot ulcers in total. These are a total of 268 patients. With an additional reserve of 32 episodes (=12% of the official sample size), we stand at 2 x 150 episodes to compensate for the losses during the trial. We think that 80% of all eligible patients will sign for the trials, because this is our experience with a similar population in other trails running.

This targeted sample size is sufficient, because with at least 7000 orthopedic procedures per year in the hospital, and assuming that 20% of the patients may eventually renounce on a randomized trial, we would need two years to complete this RCT (7000 episodes, 200-300 acute wounds per year).

11.3 Statistical criteria of termination of the investigation

We will perform one interim analysis one year (+/- 3 months) after the inclusion of the first patient. If group comparison between the PICO and non-PICO arms are striking and statistically significant in terms of any study objectives, the independent Data Monitoring committee will decide upon the interruption and early termination of the trial. If the PICO is significantly more efficacious than the standard treatment in any of these futility analyses, we will stop the trials. The final decision will be made by an independent supervision committee at the Balgrist. Otherwise, the study continues. Of note, the Data Monitoring committee has the right to call on a premature, additional interim analysis.

11.4 Planned Analyses

All analyses will be performed for the entire study population. In a second step, all analyses will be separately performed for foot ulcer patients, Group comparisons with the Pearson-Chi2-test or the Wilcoxon-ranksum-test, as appropriate. Multivariate adjustments on the primary outcomes using a cluster-controlled Cox regression analyses (with clustering on the individual patient's level. Variables with a p value ≤0.2 in univariate analysis will be included in a stepwise forward selection process for multivariate analysis. Key variables will be checked for co-linearity and interaction. The number of variables in the final model is limited to the ratio of 1 variable to 5 to 8 outcome events. The significance level is p≤0.05 (two-tailed).

11.4.1 Datasets to be analysed, analysis populations

The Sponsor-Investigator will analyse the entire dataset in both study populations, ITT (Intention-to-treat and Per Protocol; PP), after database cleaning-

11.4.2 Primary Analysis

The Sponsor-Investigator Prof. Ilker Uçkay will perform the first analyses during the interim and final study analyses, which can be controlled and re-run by additional experts in biostatistics. The nature of analyse will be descriptive, comparative between both intervention arms (using the Pearson-χ^2, the Fisher exact, or the Wilcoxon-ranksum test, as appropriate). In a second step Prof. Uçkay and/or a

statistician with experience in orthopedic wound problems will adjust for the large case-mix with cluster-controlled, multivariate Cox-regression analyses. For this latter, the study outcomes will be corresponding to the statistical outcomes.

11.4.3 Secondary Analyses

In the BALPIC study, we emphasize on separate analyses for the ITT and PP populations.

The intent-to-treat (ITT) population will consist of all randomized patients. Patients will be analyzed according to treatment group assignment. Patient disposition and baseline characteristics will be based on the ITT population.

The per-protocol (PP) population will consist of all randomized patients who complete the study (or who are otherwise defined as a treatment failure) according to the clinical investigation plan and who have not deviated significantly from the protocol. All efficacy analyses will be repeated using the PP population.

11.4.4 Interim analyses

We will perform one interim analysis one year (+/- 3 months) after the inclusion of the first patient. If group comparison between the PICO and non-PICO arms are striking and statistically significant in terms of any study objectives, the independent Data Monitoring committee will decide upon the inter-ruption and early termination of the trial. If the PICO is significantly more efficacious than the standard treatment in any of these futility analyses, we will stop the trials. The final decision will be made by an independent supervision committee at the Balgrist. Otherwise, the study continues. Of note, the Data Monitoring committee has the right to call on a premature, additional interim analysis. The Monitoring will base on the recommendations of the SCTO regarding a risk-based monitoring (sctoplatforms risk-based-monitorlng-guidelines feb22 v3.pdf).

11.4.5 Deviation(s) from the original statistical plan

The Sponsor-Investigator might add stratified groups according to clinical strata yet to be defined among the final study population. These strata would be clinically distinct from the rest of the study population, which cannot be controlled for in the multivariate assessment. Consequently, they might be analysed separately from the entire study population. However, no such particular patients' strata are expected.

11.5 Handling of missing data and drop-outs

Missing data regarding the outcome parameters and the PICO use/professional debridement will lead to patient dropout of the study. Drop-outs will be reported in the patients & methods section of the publication, drop-out data will be archived for a minimum of 10 years after study termination or in case of premature termination of the clinical trial. Major deviations from the protocol will be regarded as drop-outs and excluded from both, the ITT and the PP populations. The independent Data Monitoring Committee may help in case of difficult interpretations of the case among the trial investigators. The Monitoring will base on the recommendations of the SCTO regarding a risk-based monitoring (sctoplatforms risk-based-monitorlng-guidelines feb22 v3.pdf).

12. QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator will implement and maintain quality assurance and quality control systems with written SOPs and Working Instructions to ensure that the clinical investigation is conducted, and data are generated, documented (record), and reported in compliance with the clinical investigation plan, GCP, and applicable regulatory requirement(s). Monitoring and audits will be conducted during the study for quality assurance purposes.

12.1 Data handling and record keeping / archiving

Data is exclusively stored using the secured REDCap® electronic data capture tool. The PI is responsible for collection of data and possesses the screening log, where confidentiality is ensured by using participants' ID. Study IDs are distributed by REDCap® automatically in ascending order. Access authorization via Log-in (User) and password will be given by the PI to people on the staff list (people involved in the study), as necessary. For this reason, data cannot be changed by non-authorized people. REDCap® documents every relevant processing step to ensure traceability with registration software and is secured daily via backups. All transaction logs between performing of two backups will be secured for one week while every study data in REDCap® will be secured for an unconfined time, at least for 10 years. Its data base server is allocated in highly modern rooms in Rümlang ZH and Altstetten ZH with protection of access. Collected data of this study is visible for inspection of independent ethic committee and authorities.

When the study is terminated, data will be stored in the same system. Data can only be accessed by defined persons that have contributed to the project. Source Data are going to be stored in the institutions PACS and KISIM system according to the institutional standard at the Balgrist.

12.1.1 Case Report Forms

Electronic case report forms (eCRF) will be used, one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either completed the screening successfully or were considered not-eligible or were eligible but not enrolled into the study have to be documented on a screening log. The participation of each study participant will be documented on the Enrolment Log, which can be an EXCEL™ sheet. For data and query management, monitoring, reporting and coding an internet-based secure data base REDCap® developed in agreement to the Good Clinical Practice (GCP) guidelines will be used. It is the responsibility of the PI to assure that all data in the course of the study will be entered completely and correctly in the respective data base. Corrections in the eCRF may only be done by the investigator or by other authorized persons. In case of corrections the original data entries will be archived in the system and can be made visible. For all data entries and corrections date, time of day and person who is per-forming the entries will be generated automatically. Documented medical histories and narrative statements relative to the participant's progress during the study will be maintained. These records will also include the following: originals or copies of laboratory and other medical test results (e.g. ECGs, etc.) which must be kept on file with the individual participant's eCRF. The investigators per-form a complete and accurate documentation of the participant data in the eCRF.

12.1.2 Specification of source data and source documents

Source data will be available at the site to document the existence of the study participants and the integrity of study data collected. Source data will include the documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) will be included in the source documents:

- Demographic data (age, sex).
- Inclusion and Exclusion Criteria details.
- Participation in study and signed and dated Informed Consent Forms.
- Visit dates.
- Medical history and physical examination details.
- Key efficacy and safety data (as specified in the protocol).
- SAEs, AEs and concomitant medication.

- Results of relevant examinations.
- Laboratory printouts.
- Reason for premature discontinuation.
- Randomization number.

Source data will always be kept with the regular patient file.

The following documents are also considered source data, including but not limited to:

- SAE worksheets.
- Nurse records, records of clinical coordinators.
- Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if participant visited any during the study period and the post study period.

12.1.3 Archiving of essential clinical investigation documents

All the documents of the investigation must be archived for a minimum of 10 years after regular or premature termination of the investigation.

Data are stored using the proprietary hospital information system and REDCap electronic data capture tool hosted at the Balgrist.

12.1.4. Photos of the study wounds

We take the same photos not only for the study but also routinely for our clinical wound management. They are a medical documentation and thus routinely uploaded to the electronic medical files of the patient. We will not take any photos only for study purposes (that we would not take for clinical reasons alone). Formally, we will, however, treat them confidentially and keep their copies additionally for 10 years in the trial files. For study purposes, we will not accept, or keep photos, that have been taken by other professionals than the study investigators, or by the patient (and his/her family) themselves.

12.2 Data management

12.2.1 Data Management System

Subject-related data will be stored in the research electronic data capture software REDCap.

12.2.2 Data security, access and back-up

Back up will be kept on a hard drive belonging to the PI and later on stored in the archives of the UKB, as mentioned above. The PI and the co-investigators are responsible for data recording. The PI will grant the relevant personnel user rights to view and/or edit data entries by password as applicable. All edits will be automatically documented in the change history log.

12.2.3 Analysis and archiving

For data analysis, subject-related data from REDCap will be exported and analyzed in statistics software (IBM – SPSS and/or STATA, Version 14, College Station, USA). Before data export, all patient identifiers will be removed. All eCRF data will be stored for a minimum of 10 years.

12.2.4 Electronic and central data validation

The Sponsor-Investigator and the study nurse / research assistant will validate the entered data during and after the BALPIC trial.

12.3 Monitoring

One monitoring visit at the investigator's site prior to the start and twice during the course of the study will be organised by the Sponsor-Investigator. Furthermore, there will be a close-out visit at the study end. During the monitoring, all documents including source data/documents will be accessible for the monitor and all questions will be answered. The Monitoring Plan is attached as **Appendix 2**.

All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

Study period	**Time**	**Monitoring**
Study begin	January 2026	Monitoring will be informed about study conduct concerning data sampling and safety reporting. Monitor controls if • Documents are approved and are at site • Investigators are familiar with study protocol and safety reporting • Investigators know their duties and responsibilities
Study end	August – December 2027	Control for completeness of source data

12.4 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the competent authority or CEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/ documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source data may be granted in the case of monitoring, audit or inspections. All personnel must treat patient data as confidential. As far as possible, encoded data will be used. Only persons listed on the staff list have access to the source data.

12.6 Storage of biological material and related health data

All health-related patient data will be stored and archived in the data capture software Redcap. Patient-source data will be registered using subject identifiers. After full data analysis, all subject identifiers will be erased. Patient-source data may still be saved in the patient’s medical record. Collection, disclosure, storage of patient-related data is carried out in accordance with Swiss data protection regulations and the Human Research Act. A requirement is the informed consent of every subject prior to inclusion in the clinical trial.

13. PUBLICATION AND DISSEMINATION POLICY

Ms. Daniela Richner, Ms. Cristina Damiano, Ms. Regina Sauer, Dr. Felix Waibel, Dr. Anita Hasler, and Prof. Ilker Uçkay be part of the author lists in every publication. Additional co-authors are welcome in line with their contribution. Eventually additional colleagues participating in the future, will be co-authors of this study according to their individual contributions. The main study nurse, all Sponsors and Principal Investigators will participate in all publications. In selected publications, members of the corresponding orthopaedic teams will participate as co-authors and depending on their investment into the study.

The Sponsor will enter and publish a summary of the results of the clinical investigation in a public recognized register (as specified in Art. 64 Abs. 1 lit a or b ClinO) immediately after submitting the final report.

The Sponsor also ensures that a lay summary of the results is entered in BASEC within the period specified in the paragraph above. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

14. FUNDING AND SUPPORT

14.1 Funding

The global (undetailed) Budget is planned as follows (all currencies in Swiss Francs CHF):

Provided that the PICOs for both RCT's are borrowed or donated, the study costs consist of very few anticipated administrative costs (Ethical Committee, publications) and practically most of the salaries for the study nurse(s) engaged to 50%. We anticipate the following dispenses: Provided that the PICOs are provided, we think that each episode in the trial would additionally costs (in addition to the regular therapy covered by the insurances) roughly 520 Swiss Francs, which are the additional work-load of the supervising wound specialists (10,000 CHF). the outpatient (19,000 CHF) and other costs.

Costs without PICO	Total	Start, 1st Year	2nd Year
a. Ethical Committee	3,000	3,000	0
b. Monitoring	10,000	5,000	5,000
c. Study Nurse 50%	95,000	47,500	47,500
- Securities study nurse	14,250	7,125	7,125
d. Outpatient PICO use	19.000	9,500	9,500
e. Transportations	8,000	4,000	4,000
f. Supervision time*	10,000	5,000	5,000
g. Miscellaneous	0	0	0
Swiss Frans (CHF)	**159,250**	**81,125**	**78,125**

***** By professional wound nurses

The BALPIC Study is investigator initiated and led. It is supported by Smith and Nephew Smith & Nephew provides an academically-unconditional grant (donation) to perform the BALPIC study with a cumulative sum of 159,250 CHF (VAT included), to be paid in six instalments. PICO 7 devices and dressings will be/are provided free of charge by Smith and Nephew".

Study Milestone	**Study Budget (CHF)**
Contract executed, IRB approval and provide copy of protocol	22,950
First Patient First Visit (FPFV) – defined as first patient randomised	15,250
25% of patients randomised	31,850
50% of randomised patients completed the follow-up visits and interim clinical study report	31,850
100% follow-up visits Complete and copy of final Clinical Study Report3	25,500
Copy of final draft manuscript/s for review prior to submission to appropriate journal and evidence of submission, and copy of any conference abstract/s (if available) prior to submission.	31,850

14.2 Other Support

See Chapter 14.1.

15. INSURANCE

The standard Balgrist research insurance is applicable.

Insurance police Nr. 14.050.565 Winterthur Versicherung.

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment. The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential. A copy of the insurance certificate will be placed in the Investigator's Site File and the trial master file.

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17. APPENDICES

Appendix 1 PICO 7 – Manufacturer's brochure. Healthcare Professional User Manual.

Appendix 2 Monitoring plan.

Appendix 3 List of CE Certificates, including for the PICO system of the BALPIC Study.

Appendix 4. EUROPEAN DECLARATION OF CONFORMITY