Smith+Nephew

INVESTIGATOR-INITIATED STUDY AGREEMENT

The Parties named below agree as follows:

This Investigator-Initiated Study Agreement (**Agreement**) includes the Schedules attached and any other documents expressly incorporated by reference. As used in this Agreement, the definitions set out below will apply:

Effective Date: means date of the last signature below.

Expiration Date: Provided in Section 10 of this Agreement

Study: the study entitled "*PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence - an unblinded, randomized-controlled, superiority trial (BALPIC Trial)*" (**Study**) as set out in the study proposal (**Study Proposal**) designed by Investigator, and a subsequently developed study protocol derived from the Study Proposal, (collectively, the **Protocol**), attached hereto as Schedule 1.

Site: Balgrist University Hospital, Zurich, Switzerland

	For **INSTITUTION (Institution) Sponsor ☒**	For **INVESTIGATOR (Investigator) Sponsor ☐**	For **SMITH & NEPHEW (S&N)**
Parties	Balgrist University Hospital, Zurich UCAR, Universitätsklinik Balgrist, Forchstrasse 340, 8008 Zürich, SWITZERLAND		T.J. Smith and Nephew, Limited, 101 Hessle Road, Hull HU3 2BN England
Signatures	Printed Name: Mazda Farshad Title: _Medical Director, Prof. Dr. med. **Signed:**_____ **Date:** 22.11.24 ***Legal authority to bind the company***	Read and understood Printed Name: Ilker Uçkay_____ Title: Prof. Dr. med. **Signed** _____ **Date:** 8 Nov. 2024 ***Legal authority to bind the company***	DocuSign Amir Kamali Sr. Director Global Clinical Strategy ***Legal authority to bind the company***

Addresses for Notices: Notices under this Agreement will be addressed as follows:

- for routine matters in the ordinary course of business:

By **Hand** or **Mail**	Balgrist University Hospital, Zurich UCAR, Universitätsklinik Balgrist, Forchstrasse 340, 8008 Zürich, SWITZERLAND		Smith & Nephew Inc 7135 Goodlett Farms Parkway Cordova, Tennessee 38016 USA Attention: Jenna Moss

By **Email**	Ilker u4kay Ilker.uckay@balgrist.ch		Jenna.Moss@smith-nephew.com

- for other matters, same as above, plus copy to:

By **Hand** or **Mail**	NAME AND ADDRESS Ilker.uckay@balgrist.ch		Smith & Nephew plc Building 5 Croxley Park Watford WD18 8YE United Kingdom Attention: Company Secretary
By **Email**			Company.Secretary@smith-nephew.com

The Parties agree as follows:

1. CONDUCT OF THE STUDY

1.1 Institution or Investigator, as provided on page 1 of this Agreement is the sponsor for this Study and shall not represent to any third party, including Study participants, that S&N is a sponsor. S&N has agreed to provide support for the Study as set out in the Study Budget attached as Schedule 2 (**Study Budget**) or as may otherwise be provided herein.

1.2 If Investigator is an employee of Institution and not a Party to this Agreement, by his/her signature acknowledges that he/she: (i) has read and agrees to abide by the terms and conditions that apply to Investigator; (ii) agrees to communicate the terms and conditions of this Agreement to and ensure compliance with its applicable obligations by all personnel who are providing services under or assisting with the Study under his/her supervision or direction.

1.3 The Study will be conducted in accordance with a protocol developed by the Institution and/or Investigator and will be conducted by and under the direction of the Investigator strictly in accordance with the approved Protocol. In the event the study protocol developed from a Study Proposal is finalised after execution of this Agreement, the Parties agree that such study protocol, once agreed in writing between the Parties, shall be deemed as incorporated into this Agreement. If for any reason Investigator is unwilling or unable to continue to serve as the Investigator, Institution will have 30 days to find a replacement investigator acceptable to S&N or S&N may immediately terminate the Study.

1.4 Sponsor will ensure that all Study personnel comply with the applicable Institutional Review Board [IRB], Research Ethics Board [REB] or other Independent Ethics Board [IEC]; (collectively the **Ethics Committee**) approved Protocol, (including any Ethics Committee approved amendments), the Informed Consent Form **(ICF),** the terms of this Agreement, and all applicable laws, or any other equivalent or successor worldwide laws (including local and regional laws), codes or guidelines (**Laws**).

1.5 Sponsor will and will cause sub-investigators and all of their employees and personnel involved with the Study to conduct the Study: (i) in accordance with the Protocol, this Agreement and any written instructions from S&N, and (ii) in compliance with generally accepted standards of good clinical practice and in accordance with all applicable Laws.

1.6 Sponsor will prepare and obtain the ICF and all authorization forms required by applicable privacy and data protection Laws, (collectively referred to as the **Authorization**) in accordance with the Ethics Committee guidelines and will obtain the ICF and all applicable Authorizations signed by Subjects (as defined below).

1.7 A Study subject (**Subject**) means a research participant who meets all Protocol criteria for inclusion in the Study, has signed an ICF and is enrolled in the Study.

2. S&N PRODUCTS

2.1 Subjects will be enrolled who (i) have previously had S&N products implanted or used as part of their clinical care and are the subject of the Protocol, or (ii) will have S&N products implanted or used in accordance with the Protocol (**S&N Products**).

2.2 Sponsor agrees and represents that:

2.2.1 S&N Products and any patient diagnostic tests, bodily fluids, tissue biopsies, data and/or other materials collected in the Study will be used by Institution and Investigator solely for purposes of such Study and only as specified in the Protocol and applicable Laws.

2.2.2 If and to the extent the Institution or Investigator handles S&N Products pursuant to the Protocol, Institution and Investigator will not modify the S&N Products and will ensure S&N Products are stored under proper conditions as specified in the Protocol and stored in an appropriately secure area accessible only to authorized Study personnel. Institution and Investigator will use and handle the S&N Products in accordance with the S&N Product label and written instructions for use furnished by S&N. Complete and current records shall be maintained for all received, used and returned S&N Products. Institution and Investigator shall not use any S&N Product after its labelled expiration date.

Institution and Investigator will comply with applicable Laws including, without limitation, those governing off-label use and disposal of hazardous substances.

2.2.3 Sponsor will promptly report all serious adverse events relating to the S&N Products as defined by the Protocol or, in the absence of a definition in the Protocol, as defined under applicable Laws (**SAE**) to S&N, and will reasonably assist S&N in investigating any SAE. In addition, Sponsor will promptly inform S&N of any test or Study results which suggest: (i) a significant risk for humans, (ii) mutagenicity, (iii) teratogenicity or (iv) carcinogenicity. Reportable complaints, adverse events and SAEs should be directed to S&N as follows:

If reporting by email (preferred communication):

complaints@smith-nephew.com

If reporting via telephone:

US: +1 800 238 7538
OUS: +41 62 832 0660

Non-English speakers are encouraged to report complaints through their local sales or customer service office.

3. **FUNDING.**

Funding set out in the Study Budget. The Parties acknowledge and agree that this Agreement and the funding provided by S&N does not impose on Institution or Investigator any obligation to purchase or promote or recommend the purchase of any of S&N's product(s), and this Agreement is not intended to encourage or induce Institution to purchase or promote or recommend the purchase of any of S&N's product(s). Upon presentation of a valid invoice to S&N by Institution, payment will be made by wire/bank transfer, at S&N's election, payable to Institution, and sent with reference to the name specifically identified in this Agreement, Institution's address, Study Protocol and number to the attention of:

Attn: _____

4. PUBLICATION.

4.1 S&N supports the exercise of academic freedom and encourages Investigator to publish the results of the Study. Accordingly, Institution and Investigator will have the right to publish the results of the Study in accordance with this Section.

4.2 Sponsor will provide S&N with a minimum of 90 days prior to submission or other public disclosure, any proposed publication, abstract or other type of disclosure that reports the results of the Study to ensure against inadvertent disclosure of S&N Confidential Information, if provided, or its intellectual property rights. In addition, S&N may provide comments on the proposed publication; however, notwithstanding anything in this Agreement to the contrary, scientific conclusions regarding the results of the Study in any publication will be determined solely by the Investigator in his/her professional judgment.

4.3 The support awarded to Institution by S&N for use in the Study will be disclosed in any publications that result from or are related to this Agreement.

4.4 If applicable, Institution will register the Study in accordance with the International Committee of Medical Journal Editors' guidelines or any similar and worldwide Laws or guidelines.

4.5 Sponsor will provide interim and final summary reports resulting from the Study and S&N will have the right to use such reports for its own internal purposes in accordance with applicable Laws (including applicable copyright laws). In addition, S&N reserves the right to request and receive from the Sponsor copies of the Study results or any de-identified data.

4.6 Sponsor hereby grants to S&N a perpetual, irrevocable, royalty free license, including the right to sublicense, to make and distribute copies of such publications to the extent Institution and/or the Investigator have such rights.

5. PUBLICITY AND PROMOTIONAL ACTIVITIES.

No Party will use any other Party's or its affiliate's names or trademarks for publicity or advertising purposes, except with the written consent of such other Party or Parties.

6. INVENTIONS.

Investigator will notify Institution, and Institution will, in turn, promptly notify S&N in writing of any new invention, improvement or discovery, whether or not patentable, derived, conceived or reduced to practice as a result of the use of the funds, S&N provided materials or information, any S&N Product, and any intellectual property rights associated therewith, will be owned as follows:

6.1 Inventions which involve the use of, composition of, or improvement to any S&N Product, or S&N provided materials or information, or a derivative or analogue thereof (**Invention**), will belong to Institution and/or Investigator, as applicable under the Law, and Institution and/or Investigator grants S&N a perpetual, world-wide, royalty-free, non-exclusive license, with the right to sublicense, to use any such Invention. S&N shall provide reasonable assistance to Institution and/or Investigator in filing and prosecuting any patent applications relating to the Invention, at Institution's and/or Investigator's expense.

6.2 Inventions which cover a scientific process, technique, procedure, medium, device or other process which is not an Invention, will be owned by Institution and/or Investigator, as applicable under the Law, and S&N shall be given an option to negotiate a license thereto.

7. CONFIDENTIALITY.

7.1 Confidential Information means all non-public information, including hard copy or electronic form, written or oral which is treated by S&N as confidential or proprietary (**Confidential Information**). These obligations of confidentiality shall not apply to any information that: (i) at the time of disclosure or thereafter becomes publicly known without breach of this Agreement; (ii) was known to Institution and Investigator prior to the disclosure thereof as evidenced by its written records; (iii) is disclosed to Institution and Investigator by a third party rightfully in possession of such information who owes no obligations of confidentiality with respect to such information; or (iv) has been independently acquired or developed by Institution or Investigator without violating any of its obligations under this Agreement.

7.2 Institution and Investigator will only use Confidential Information for purposes of its performance in accordance with this Agreement. Institution and Investigator will disclose Confidential Information only to those employees, affiliated entities and contractors and only on a need-to-know basis for purposes of its performance in accordance with this Agreement and provided that Institution and Investigator obligate such employees, investigators and affiliated entities and contractors to restrictions of confidentiality and use substantially similar to such obligations under this Agreement.

7.3 In the event Confidential Information is required to be disclosed pursuant to regulatory or legal requirements, Institution will promptly notify S&N in writing and reasonably assist S&N in seeking a protective order or taking other reasonable and lawful actions to protect S&N's rights prior to disclosure of the Confidential Information. Institution and Investigator acknowledge that a violation of their obligations with respect to Confidential Information could cause irreparable harm to S&N for which a remedy at law would be inadequate. Therefore, in addition to any and all remedies available at law, S&N will be entitled to seek an injunction or other equitable remedies in the event of any threatened or actual violation of any or all of the provisions hereof, without any requirement to post a bond.

8. DEBARMENT CERTIFICATION.

Institution and Investigator each represent and certify that it/he/she has not been debarred, suspended or excluded under the Laws of any jurisdiction or by any governmental authority or agency. If S&N becomes aware that a debarment action or threat of action has been brought against Institution or Investigator, S&N shall have the right to terminate this Agreement immediately.

9. LIABILITY AND INSURANCE.

9.1 Institution will be responsible for Institution's own intentional or negligent acts or omissions and the

negligent acts or omissions of Investigator and Institution's employees and duly authorized agents under this Agreement. Institution will carry liability insurance to meet Institution's obligations under this Agreement. Institution's insurance will cover the Study and Investigator, and will not be materially encumbered by existing claims. Institution will maintain insurance coverage for the duration of this Agreement and, if the policy is claims-made, for 2 years thereafter. Institution will provide evidence of insurance to S&N upon request. Institution will notify S&N within 20 days of any notice of cancellation or non-renewal of, or material reduction in, or claim against, Institution's insurance coverage affecting its obligations hereunder.

9.2 The Sponsor, and not S&N, shall be responsible for all claims or proceedings arising in respect of personal injury (including death) brought by or on behalf of a Subject as a result of or in connection with the Study, and the Sponsor shall indemnify S&N and its employees from and against any claim or proceeding arising in respect of personal injury (including death) brought against S&N or any of its employees by or on behalf of a Subject as a result of or in connection with the Study except only insofar as such claim relates to a defect in a product manufactured or distributed by S&N. Nothing in this section shall restrict or exclude the liability of any Party in relation to death or personal injury caused by the negligence of that Party or its employees or to restrict or exclude any liability of either Party which cannot be restricted or excluded in law.

10. TERM AND TERMINATION

10.1 Unless earlier terminated in accordance with this Section, this Agreement will continue in force until the Study has been completed in accordance with this Agreement (**Expiration**).

10.2 Any Party may terminate this Agreement at any time on 60 days written notice to the other Party(ies). If Institution or Investigator (if a Party to this Agreement) should decide, for any reason, to terminate this Agreement prior to its completion, payments received by Institution hereunder with respect to the Study will be refunded to S&N within 30 days after termination of this Agreement, except for direct pass-through costs and costs for visits and procedures performed before notice is given.

10.3 Either Party may terminate this Agreement if the other breaches a material provision of this Agreement and such breach continues uncured for more than 30 days after receipt of written notice of the breach from the non-breaching Party.

10.4 Termination of the Agreement will not affect any rights or remedies of any Party at law or in equity.

11. JURY WAIVER.

The parties, after consultation with respective counsel, hereby waive trial by jury in any proceeding or counterclaim brought by either party against the other on any matters arising out of or in any way connected to this Agreement, the relationship between the parties, or any injury or damage claim.

12. NOTICES.

All notices relating to this Agreement will be in writing and delivered by any reasonable, commercially available means providing proof of delivery, and will be effective upon delivery, indicated by the commercially provided proof of delivery. Notices will be sent to the addresses set forth on page one of this Agreement.

13. CHOICE OF LAW AND JURISDICTION

This Agreement is governed by and interpreted in accordance with the laws of Switzerland. Any dispute, controversy or claim arising out of this Agreement or other agreements and arrangements connected to or being the result of this Agreement shall be resolved between the Parties by negotiations in good faith within 90 days of a dispute being notified by one Party to the other Party in writing. Failing such resolution within the 90 day period, the dispute shall be finally resolved by the competent tribunals within the jurisdiction of the court of appeal of Switzerland (Canton Zurich).. The application of the UN Convention on Contracts for the International Sale of Goods is expressly excluded. In any litigation, arbitration or other proceeding arising out of or related to this Agreement, the prevailing Party will be entitled to receive its reasonable attorneys' fees, and reasonable costs and expenses.

SCHEDULE 1

STUDY PROTOCOL (PROPOSAL)

(Study Proposal and subsequently developed Study Protocol)

The purpose of this form is to facilitate a process to review, approve, and support clinical study proposals initiated by an external clinical investigator. studyrequest@smith-nephew.com (Please complete this form in English)		
Date Completed: 30.11.2023	Completed by: Ilker UCKAY	
Investigator Name: Ilker UCKAY	Institution: Balgrist University Hospital, Zurich	
Investigator Specialty(ies)/Area of Practice: Osteoarticular infections; diabetic foot infections; clinical trials		
Mailing Address: UCAR, Universitätsklinik Balgrist, Forchstrasse 340, 8008 Zürich, SWITZERLAND		
Email Address: iilker.uckay@balgrist.ch	Office Phone: ++4144 3863705	Mobile/Cell Phone: ++4144 3863705
Other contact (if any): Felix WAIBEL	Title: PD Dr. med.	
Mailing Address (if different from above):		
Email Address: felix.waibel@balgrist.ch	Office Phone: ++41443865759	Fax: -
Would you like this person copied on all print/electronic communications? ☐ Yes ☒ No		
Contact person name from Smith & Nephew: Dr Sally Moores, Dr Hilary Watkins		
STUDY INFORMATION		
Study Title: PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence - an unblinded, randomized-controlled, superiority trial (BALPIC Trial)		
What is the publication/presentation plan of the study results? ☒ Journal Publication ☒ Abstract Publication ☒ Podium ☒ Other: We will largely present at every Swiss congress possible, and in targeted European congresses. Target journal(s) for publication: (Orthopedic) Surgical Journal Target conference for presentation(s): National and International Orthopedic Congresses		
Market product(s) or procedure to be investigated (*please use full market name[s] and manufacturer if non-S&N*): PICO by Smith + Nephew		
What is the main objective of the study? To show that PICO use by Smith + Nephew fastens wound and foot ulcer healing, reduces length of hospital stay and reduces overall costs.		
What is the primary endpoint for this study? How is it going to be measured? - Wound closure without surgical wound revision at Day 42. Clinical assessment		

What are the secondary endpoints? How are they going to be measured?

- Rapidity of wound closure, adverse events of PICO therapy / wound management, length of hospital stay, overall costs
- Wound closures without surgical closure at Days 7 and 14.
- Stratum of wound closure without surgical wound revision for foot ulcers only.

What Health Care Economic Assessments will be included?

We will compare the total costs of hospitalization for episodes with and without PICO use

Potential proposed countries: Single-center study at Balgrist University Hospital, Zurich, Switzerland

Study design (e.g. prospective, randomized, matched, single-blind): an unblinded, randomized-controlled, superiority trial with randomization scheme of 1:1

Comparison group(s) if any: Standard wound care

Population description and inclusion/exclusion selection criteria:

Inclusion criteria:

- Patient of orthopedic surgery or of (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
- Clinical indication for clinically anticipated PICO use during 7 and 14 days

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, local antibiotics) (use of local antiseptics and dressing changes allowed)
- Immediate surgical wound revision in the operating theatre for closure
- Planned plastic or reconstructive surgery already at inclusion
- Wound / Surgical Site Infection (superficial or deep space)

Brief description of study procedures to be used (e.g. measurement methods, questionnaires, standard scales):

At enrollment, the patients will be randomized in the ratio 1:1 (PICO vs. no PICO) 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 we will take 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 eventual antiseptic solution, lies at the discretion of the individual professional wound nurse; and will be recorded. 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 42 days. Only in case of dysfunction, the PICO will be changed prematurely. During hospitalization, PICOs' will be changed routinely every 3 to 7 days. During an eventual outpatient period, wound evaluation will be once or twice a week, and PICO change once a week. One or at maximum two PICO devices will used over the wound for 7 to 14 days The treatment period includes the following daily study visits: Visit 1 – Enrollment (Day 1) End-of-treatment visit (EOT) – Day 7 (+/- 2 days) Wound assessment, decision to continue the PICO for another week; or not. 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. Daily visits during hospitalization or outpatient professional wound care. End-of-treatment visit (EOT) – Day 14 (+/- 2 days) Wound assessment (size and depth, study outcomes or exclusion criteria), adverse events, questionnaire Test-of-cure visit (TOC) – Day 42 (+/- 7 days). Wound assessment, questionnaire, adverse events, (if not done at EOT) The therapy and the Trials will be supervised by UCAR and Mrs. Judith Soto, Specialist Wound Nurse
Define all visit time points (e.g. pre-op, op, discharge): 7, 14, and 42 days
STATISTICS
How is the study powered? 80% power. 2 x 150 episodes.
Sample size: 300 different wounds in 300 different patients Sample size per arm/cohort (if applicable): 150
Statistical Methodology ☒ Superiority ☐ Non-inferiority ☐ Other:
BUDGET AND MILESTONES
Please confirm the total study cost. (Please attach the budget form to your IIS submission.):

Total study budget: 160,000 Swiss Francs (or its equivalent in foreign currency) PLUS the donated PICOs for 150-160 patients for the randomized study, donated upon invoice in 1-3 tranches	**Please confirm currency** Swiss Francs *(currency optional)*
Please note that no work can be reimbursed prior to contract execution	
Please complete the anticipated dates for following milestones for the study:	
Milestones	**Anticipated dates (Please refer to Milestones at Schedule 2)**
1. IRB/IEC Target date	Oct 2024
2. First subject first visit	February 2025
3. Last subject last visit	June 2026
4. Final data analysis	Sept 2026
5. Publication submitted	January 2027

SCHEDULE 2

STUDY BUDGET

Funding and Materials Support Schedule

Study Description	**Total Study Budget (CHF)**
PICO Negative Pressure for the Treatment of Uninfected Foot Ulcers and Wound Dehiscence	**159,250 + maximum of 900 PICO 7 sNPWT devices**

TOTAL BUDGET: to be paid in six (6 instalments, + PICOs as needed)

Study Milestone	**Study Budget (CHF)**	**Submission Date**
Contract executed, IRB approval and provide copy of protocol	22,950	Oct 2024
First Patient First Visit (FPFV) – defined as first patient randomised	15,250	Feb 2025
25% of patients randomised	31,850	August 2025
50% of randomised patients completed the follow-up visits and interim clinical study report	31,850	December 2025 to April 2026
100% follow-up visits Complete and copy of final Clinical Study Report3	25,500	June 2026
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	January 2027

All Costs Are In Swiss Francs including the Swiss VAT taxes.