COMPARACHILLE Protocol

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"Comparison of the efficacy of two techniques for applying medical compression bandages by measuring interface pressures depending on whether or not the heel is included in patients with open venous ulcers: controlled, **randomised** non-inferiority trial**"**

Person directing and supervising the research:

Ms [redacted]
Nurse
Mobile "vascular wound" unit, Nantes
University Hospital – Hôtel-Dieu site
1 Place Alexis Ricordeau, 44093 Nantes cedex 01
Tel: 02. [redacted]
Email: [redacted] @chu-nantes.fr

Methodologist:

Mr [redacted]
Statistical Engineer
Methodology and Biostatistics Platform - Nantes University Hospital
INSERM U1246 SPHERE - University of Nantes
Health Research Institute 2 (IRS2) 22
Boulevard Benoni Goullin, 44000 Nantes
Tel: 02. [redacted]
Email: [redacted] @univ-nantes.fr

Sponsor:

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Nantes University Hospital
Medical Affairs and Research Department

5, allée de l'île Gloriette
44 093 Nantes cedex 01 (FRANCE)

Tel: 02 [redacted]
Fax: 02 [redacted]

SIGNATURE PAGE

SIGNATURE OF THE SPONSOR

The sponsor undertakes to conduct this study in accordance with all legislative and regulatory provisions applicable to the research and in accordance with the protocol.		
Name and position of the signing representative: **For the sponsor and by delegation from the Chief Executive Officer, the Director of Research and Innovation**	**Date:**	**Signature:**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol sponsored by Nantes University Hospital. I confirm that it contains all the information necessary to conduct the trial. I undertake to conduct the trial in accordance with the protocol and the terms and conditions set out therein. I undertake to conduct the trial in accordance with:

- the principles of the "Declaration of Helsinki",
- the rules and recommendations of international (ICH) and French (rules of good clinical practice for biomedical research relating to medicinal products for human use)
- European regulations and/or national legislation and regulations relating to clinical trials,

I also undertake to ensure that investigators and other qualified members of my team have access to this protocol and to the documents relating to the conduct of the trial so that they can work in accordance with the provisions contained in these documents.

	Name:	**Date:**	**Signature:**
Coordinating investigator	[redacted] Nantes University Hospital		
Principal Investigator	**Name and institution:** [redacted] Nantes University Hospital	**Date:**	**Signature:**

LIST OF ABBREVIATIONS

ANSM	French National Agency for Medicines and Health Products Safety Health
CRA	Clinical Research Associate (monitor)
BCM	Medical Compression Bandage
GCP	Good Clinical Practice
CEAP	Clinical – aetiology – anatomy – pathophysiology
CIS	Independent Monitoring Committee
EC	Ethics Committee
CNIL	French Data Protection Authority
CRF	Case Report Form (case report form)
eCRF	Electronic Case Report Form Medical device(s)
MD	
EHPAD	Accommodation for Elderly Dependent Persons for Elderly
EMA	European Medicines Agency
SAE	Serious Adverse Event
SAE	Serious Adverse Effect
EIGI	Unexpected Serious Adverse Effect
HAS	French National Authority for Health
ICH	International Conference on Harmonisation (International Conference on Harmonisation)
IPS	Systolic Blood Pressure Indices
mmHg	Millimetre of mercury
MR	CNIL Reference Methodology
RCP	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
study-co	Clinical Research Technician

TABLE OF CONTENTS

INTRODUCTION

Medical compression using multi-type bandages or short-stretch bandages is the recommended basic treatment for open venous ulcers according to the Clinical-Etiological-Anatomical-Pathophysiological (CEAP) classification. At the open ulcer stage, under medical compression, the pressure measured at the ankle (called interface pressure) recommended for healing should be between 30 and 40 mmHg at rest (1).
Because some patients find wearing bandages uncomfortable, particularly when putting on shoes, their compliance is limited, delaying healing.
In our "vascular wound" clinic at the Nantes University Hospital (CHU), we regularly observe that bandage application techniques vary at the heel, which is sometimes covered and sometimes not covered by the bandage. We have confirmed through a single-centre observational study involving 261 patients (100 hospitalised patients and 161 living at home), currently in press, that among patients wearing compression bandages, 54% of hospitalised patients and 48% of outpatients had their heels uncovered. The qualitative survey conducted among private nurses reports that the choice of application technique is mainly guided by the patient's wishes, who sometimes wants to leave the heel uncovered so as not to change their footwear and sometimes prefers to include the heel, thinking that the bandage is more effective if it covers it. However, the recommendations of the Haute Autorité de Santé (HAS) stipulate that the heel should be included under the bandage (1), but these recommendations are not based on evidence, and patient discomfort is known to be a source of poor compliance with the devices.

Nevertheless, the choice of application technique could affect: the achievement of therapeutic pressure, patient comfort, and the appearance of oedema.

We would therefore like to evaluate, through a controlled, randomised non-inferiority trial, whether the interface pressure measurements at the ankle at rest comply as well with the pressure threshold necessary for venous ulcer healing when the heel is left uncovered compared to when it is covered, in patients wearing multi-type bandages or short-stretch dry bandages.

1. JUSTIFICATION FOR THE STUDY

1.1. OPEN VENOUS ULCER

Open venous ulcers represent the final stage of venous disease. The *Clinical-Etiology-Anatomy-Pathophysiology* (CEAP) (2) classification system classifies the different stages of venous disease according to their symptoms: from stage C0 to C6 in order of increasing severity. Stage C6 corresponds to an open, non-healing venous ulcer.

The latest study on the cost of wounds in France dates back to 2011. The only figures available for France concern venous or mixed ulcers (with an arterial aetiological component). In its report "Improving the quality of the healthcare system and controlling expenditure: proposals from the Health Insurance Fund for 2014" (3), the Health Insurance Fund estimated that 115,000 patients had venous (or mixed) ulcers. These patients were 71 years old on average, and two-thirds of them were women.
The cost of treating venous (or mixed) ulcers covered by the health insurance system amounted to €272 million in 2011 for outpatient care alone (care provided by doctors, auxiliary staff, products on the List of Products and Services, medicines), not including hospitalisation and transport. Of these expenses, 42.4% were attributed to nursing care, or €115 million; 33% to compresses and dressings, or €90 million; and 2.3% to compression devices, or €6 million.

1.2. AETIOLOGY

A pure venous ulcer is defined (professional agreement) as a leg wound:
- not healing for more than a month (except in cases of recurrence, where the diagnosis can be made without waiting for this period to elapse),
- whose pathophysiology is ambulatory venous hypertension, which may be secondary to:
    - reflux in the superficial, perforating or deep veins,
    - and/or to obstruction in the deep veins,
    - and/or to a deficiency of the calf muscle pump;
- for which there is no arterial involvement. (4).

The treatment of venous ulcers combines local care, most often provided by a private nurse[1], primary dressings and medical compression (4).

[1] This professional category is predominantly female: 88% of the 520,000 professionals working in France. Source: Directorate for Research, Studies, Evaluation and Statistics (DREES) (2010). The nursing profession: Demographic situation and career paths. France: Ministry of Labour, Employment and Health, Ministry of the Budget, Public Accounts, Civil Service and State Reform, Ministry of Solidarity and Social Cohesion. This is why we use the feminine form.

1.3. MEDICAL COMPRESSION IN THE TREATMENT OF OPEN VENOUS ULCERS

1.3.1. Recommendations concerning the choice of type of medical compression

Medical compression is a Class 1 MD according to European regulations (5). Pressure is considered to be the active principle of medical compression. It is measured in millimetres of mercury (mmHg).

There are several types of bandages:
- inelastic bandages (elongation < 10%)
- short elongation strips (>10% and <100%)
- long elongation strips (≥ 100%)

In terms of surface area, they are classified as:
- dry tapes
- adhesive strips
- cohesive tapes
- coated bandages

A **multi-type** bandage is defined as one in which at least two different types of compression bandages are superimposed. The terminology used in the HAS recommendations changed between 2006 (4) and 2010 (1): from multi-layer bandage (4) to multi-type bandage (1): the term multi-layer bandage is no longer used because, by definition, all bandages have several layers (when the overlap is greater than or equal to 50%).

Regarding the treatment of stage C6 chronic venous disorders (open ulcer), the HAS, in its latest recommendations from 2010, recommends applying pressure between 30 and 40 mmHg (1). Clinical data supports the use of **multi-type bandages** (1,6). However, it should also be noted that when compliance is unsatisfactory, the choice of compression must be adapted individually and take into account the patient's tolerance in order to promote adherence to treatment. In this case, short-stretch dry bandages may be an alternative treatment (7). They are also often chosen when the wound is highly exudative and the dressing needs to be changed daily. This is because the short-stretch dry bandage is washable and reusable, whereas the multi-type bandage, although it can remain in place for up to seven days, is an expensive, single-use MD.

[2] **A medical device** is defined as any instrument, apparatus, equipment, software, material or other article, used alone or in combination, including software intended by the manufacturer to be used specifically for diagnostic and/or therapeutic purposes, and necessary for its proper functioning. A medical device is intended by the manufacturer to be used in humans for the purposes of:

-diagnosing, preventing, monitoring, treating or alleviating a disease,

-diagnosing, monitoring, treating, mitigating or compensating for an injury or disability,

-studying, replacing or modifying the anatomy or a physiological process,

-controlling conception,

and whose principal intended action in or on the human body is not achieved by pharmacological or immunological means or by metabolism, but whose function may be assisted by such means; (European Directive 93/42/EEC)

1.3.2. Recommendations for use

Commercially available multi-purpose bandage kits contain at least two **single-use** strips, the length of which can be adjusted to fit the patient's leg by cutting the strip to cover the leg to below the knee, in accordance with the manufacturer's instructions for use. The multi-purpose bandage is applied 24 hours a day and can remain in place for up to seven days. It is replaced at the same frequency as the dressings, as specified in the medical prescription.

Short-stretch dry bandages exert high pressure during physical activity and low pressure at rest. Bandages come in several lengths and widths. The length and width of the bandage is chosen according to the morphology of the limb segment and must be specified on the medical prescription. They are worn 24 hours a day, from one dressing to the next. This device is reusable, washable and must be replaced every six months.

Regardless of the type of medical compression bandage (MCB), recommendations based on professional agreements are available to guide the application of MCBs (1):
- The bandages must be applied by trained personnel.
- The use of compression devices requires patient education by each of the practitioners involved.
- Compression equipment must be maintained according to the manufacturer's instructions and replaced as necessary due to wear and tear.

1.3.3. Recommendations concerning application technique

In France, the latest recommendations concerning the application of BCM date from October 2015. Drafted by the French National Health Insurance and the French and Francophone Society for Wounds and Healing (8), they incorporate elements from the 2010 HAS report on medical compression (1). The steps for applying a BCM are described as follows:
- Protect the skin if necessary (skin fragility, wounds, dressing protection), for example with a tubular jersey.
- Insert filling material (foam, cotton) if necessary (thick dressing, retro-malleolar oedema).
- Begin applying the bandage at the base of the toes with a diagonal strip across the top of the foot, followed by a circular strip around the metatarsal, which will ensure that the bandage stays in place.
- Wrap the bandage around the foot, gradually working your way up to the ankle, covering 1/2 to 2/3 of the previous wrap (adjusting to obtain the desired pressure according to the instructions for the material used).
- Apply constant tension.
- **Position the heel at the middle third of the band width to ensure it stays in place. Continue with site initiation visits along the limb either in a circular, oblique or semi-oblique pattern (the choice of pattern depends on the practitioner's preference).**
- Finish the bandage 5 cm below the knee crease and never overlap the last turns of the bandage (if there is excess length, start the bandage again, increasing the overlap and reducing the stretch, or cut the bandage if using a multi-type bandage).
- Recommend choosing shoes with a suitable size (generally one size larger than the usual size).

1.3.4. Limitations of monitoring recommendations for the application of medical compression bandages

A 2009 literature review (9) found that only 59% of patients monitored wore their BCM as directed. The reasons reported by patients were discomfort with the bandage and footwear, as reported in eight articles cited.
Although there is little data on adherence to wearing MCBs, a few therapeutic education initiatives are reported in the scientific literature (10). This meta-analysis concludes that there is a lack of studies on interventions aimed at patient adherence to MCB treatment.

A French study evaluating professional practices in this area
(11) reports that patients' refusal to wear a BCM is often due to poor tolerance and the inability to put on shoes. It also highlights that only a small proportion of healthcare professionals are aware of the current recommendations. Finally, as the act of applying a BCM is not classified as a nursing procedure, private nurses may be reluctant to undertake training on this MD.

We also observe that patients attending consultations frequently wear BCMs that have been fitted in a manner that does not comply with best practice recommendations. In 2016, we therefore conducted a descriptive study funded by Nantes University Hospital as part of an internal call for tenders dedicated to paramedical research. The aim of this study was to assess the differences between the insertion technique observed and the recommended technique, and to explore the factors taken into account by home nurses when choosing the insertion technique. Data was collected by completing an observation grid that had been tested beforehand with ten professionals. Semi-structured interviews conducted using an interview guide with six home nurses made it possible to describe the reasons for non-compliance with the recommendations.

Over a four-month period, following "vascular wound" consultations, we included 161 non-hospitalised patients with BCM and 100 patients hospitalised in the internal medicine and geriatric care departments of Nantes University Hospital. The results, currently being published, show that 48% of outpatients and 54% of hospitalised patients with BCM had their heels uncovered. The nurses interviewed reported that dressing practices differed among colleagues, leading to contradictory information being given to patients and therefore a detrimental effect on compliance with the treatment.
These results are consistent with those described in a study evaluating professional practices conducted in France in 2014, in which 55.8% of the BCMs observed had the heel included under the bandage (11).

1.4. POSITIONING OF THE STUDY

One of the reasons frequently cited by patients who refuse to wear a BCM is the discomfort caused by the bandage, particularly when putting on shoes (11). It is necessary to modify the bandage, which incurs additional costs.

Recommendations for best practice were sought on the websites of health authorities abroad: Joanna Briggs Institute, NCH, NICE. All recommendations specified that the heel should be included under the bandage, but these are not based on evidence (12, 13, 14).

Meta-analyses on this topic were also found: in 2013, a Cochrane collaboration published an article on the treatment of venous ulcers (6). None of the studies included in this meta-analysis addressed the position of the heel.

Original studies published after the Cochrane meta-analysis were finally found by searching the Pubmed, Pedro and EMBASE databases. The search equation included the following keywords:
#1 varicose ulcer [MeSH]
#2 compression bandage [MeSH] #3=
#1 AND #2
After removing duplicates, 336 articles were found, including 68 trial articles and 36 published after January 2012.

None of these 36 articles dealt with interface pressures according to the BCM placement technique.

The Clinical.trial.gov website was also consulted in order to list studies currently being included on this topic: no protocols were found.

We therefore wish to study the interface pressure under the medical compression bandage when the heel is left uncovered or covered by the bandage and prove, through a controlled, randomised, non-inferiority study, that leaving the heel uncovered outside the BCM results in a level of interface pressure that is not significantly lower than that obtained when the heel is covered by the bandage.

One of the secondary objectives of this study will be to assess patient satisfaction based on the application technique.

1.5. ISSUES ADDRESSED BY THE STUDY

In its 2006 recommendations entitled "Treatment of predominantly venous leg ulcers without dressings", the HAS proposes to continue research "evaluating the compliance and acceptability of compression methods" and, in terms of regulatory action, "assess the relevance of including the nursing procedure of applying compression devices in the general nomenclature of professional procedures (NGAP)," since this procedure does not currently generate remuneration for nurses who apply them at home.

The report also points out that these studies would identify areas for improvement in terms of healing time and recurrence rates for chronic wounds. This improvement could also lead to significant savings. For example, a 30-day reduction in healing time for patients in the 6th decile (i.e. 23% of the duration) would represent a saving of €66 million (8).

Furthermore, new knowledge about health promotion suggests that patients should be involved in healthcare decisions. This requires providing them with information to help them make informed choices. Brown (15) proposes that care for venous insufficiency should be geared towards shared decisions regarding the choice of BCM application technique in order to improve patient adherence. However, knowledge about the impact of the placement technique on the pressure maintained around the lower limb is lacking and does not

enables nurses to provide accurate information about their choice regarding this professional practice.

At a time when nursing sciences are seeking to seize opportunities to conduct research aimed at improving care, several nursing practices deserve to be questioned from the perspective of evidence-based practice. While the recommended method of applying BCMs involves placing the heel under the bandage, which reduces patient comfort and therefore risks decreasing their adherence to treatment, this application technique should be evaluated in a randomised controlled trial.

This would enable a decision to be made on the merits of modifying the currently recommended application technique, while proposing a simple research design. If no effect on interface pressure were proven, this would enable the results to be communicated and professionals' knowledge of medical compression in the treatment of venous ulcers to be updated.

This study therefore falls under axis 1-1 "Promoting healthy behaviours" and axis 3-2.b to facilitate "the dissemination of recommendations, support professionals and encourage them to adopt best practices in medical relevance" of the National Health Strategy for the period 2018-2022. It also aims to involve private nurses, who are often new to research, in a study on empirical practices. The objective is to enable these professionals to embrace evidence-based practice by participating in a simple research design.

1.6. BENEFITS AND RISKS FOR PEOPLE PARTICIPATING IN THE RESEARCH

1.6.1. Benefits

1.6.1.1. *Individual benefits*

Individuals who agree to participate in the study will have their blood pressure measured (something that is not usually done during treatment) to assess whether the medical device has been placed within the therapeutic zone.

1.6.1.2. *Collective benefit*

This study will provide scientific data to support recommendations for best practice in the technique used to fit BCMs. The expected outcomes will be, on the one hand, the harmonisation of the techniques taught in initial and continuing training. On the other hand, if the two techniques show similar results, the freedom to include or exclude the heel will be left to the patient as part of a shared decision-making process and with the aim of maintaining compliance.

Finally, this is a research project involving private nurses. The aim is therefore to introduce them to clinical research and evidence-based practices. We hope that this initial initiative will strengthen ties between the city and the hospital and enable

continue nursing research projects on care topics of interest to both modes of practice.

1.6.2. Risks

1.6.2.1. Individual risk

- Physical risks and constraints

For patients who agree to participate in the study, randomisation may require them to follow a different application technique than the one they are used to during the study. However, participating in the study will not change the frequency of dressing changes to which they are accustomed.
The risk of allergy to any of the components of these two types of medical compression must also be taken into consideration.

Pressure measurement and the wearing of flexible sensors are painless.

- Risks related to the disease

The risk of ineffective compression is delayed healing or even extension of the wound, resulting in continued treatment and reduced comfort. That said, the data collected in our exploratory study and in the assessment of professional practices
(9) show an equivalent distribution of application techniques across the population.

1.6.3. Benefit/risk balance

The benefit/risk balance is positive. This nursing research is low-risk and low-constraint (MRCR) because it does not alter patient care. Study visits correspond to visits that are usually planned as part of the patient's medical care, thus ensuring good adherence to the study protocol.

1.7. FEASIBILITY

In order to verify the initial hypothesis of this study, 102 patients will need to be included, i.e. between 4 and 5 patients per month of consultation.

For the first exploratory study conducted at Nantes University Hospital in 2016, we included 161 patients with BCM attending outpatient consultations over a 4-month period. Based on this study, the objective of recruiting 102 patients over 24 months seems achievable.

In addition, several home nurses participated in the exploratory study (a qualitative component aimed at identifying barriers and drivers of compliance), demonstrating their motivation. Contact has already been made with the Pays de Loire Regional Union of Health Professionals (URPS) to present the protocol to them, as well as with the

GRINN network[3] (Nantes North Nursing Network Group): they all support this study and seem motivated to participate if training time is offered to them. We have therefore planned an information meeting on the research project during the site initiation visit and a 20-minute e-learning training course to provide the necessary information to nurses from the home nursing practice working with an included patient (Appendix V).
In addition, the protocol provides for a study nurse to visit the home nursing practice after the patient has been included in order to answer any questions, thus ensuring a point of communication that allows the protocol to be properly followed. The project is based on the investigation unit composed of three study nurses, which will cover inclusions throughout the study period.

Regarding the availability of the interface pressure measuring device (Picopress®), which is an expensive MD (€2,000), two companies (Urgo® and Lohmann&Rauscher®) that market medical compression devices have agreed to finance the loan of the device and sensors.
The nurse, who is the principal investigator, participates as a trainer in the University Diploma "skin, wounds, burns and healing" at the University of Nantes, which has enabled her to maintain a network of trained independent professionals.

This research project is supported by Mr Vallée, general care coordinator, and Ms Loiseau, senior health executive responsible for cross-disciplinary initiatives in the field of "healing" as well as Dr Durant, who provides this consultation, and Prof Pistorius, medical advisor for the vascular medicine outpatient clinic at Nantes University Hospital.

[3] https://grinnnantes.wordpress.com/author/grinnnantes/

2. OBJECTIVES AND EVALUATION CRITERIA

2.1. OBJECTIVE AND MAIN EVALUATION CRITERION

2.1.1. Main objective

Compare the interface pressure measurements generated by a medical compression bandage between two groups of patients with open venous ulcers at stage C6 of the CEAP classification:
- experimental group: heel uncovered
- control group: heel covered by the bandage.

2.1.2. Primary endpoint

Measurement of interface pressure 48 hours after application of the MCB (i.e. during the V3 follow-up visit).

2.2. SECONDARY OBJECTIVES AND EVALUATION CRITERIA

2.2.1. Secondary objectives

- Compare the development or appearance of oedema in the ankle (a risk considered in cases of uncovered heels) between the two groups.
- Compare, between the two groups, the interface pressures measured during BCM application at home by the home nurse (follow-up visit V2), compared to the recommended pressures (30-40 mmHg) (1)
- Compare, between the two groups, the evolution of interface pressures after 48 hours of wearing BCM (during V3)
- Compare patient satisfaction between the two groups
- Assess the number of bandage changes required to reach the therapeutic area (at V1).

2.2.2. Secondary evaluation criteria

- Measurement of the figure of 8 (16) at inclusion (follow-up visit V1) and at the last follow-up visit (follow-up visit V3)
- Measurement of interface pressure at follow-up visit V2 (at home)
- Measurement of interface pressure at V2 and V3
- Responses to the hetero-questionnaire on patient satisfaction (Appendix VI).
- Number of bandage changes required to reach the therapeutic zone at V1

3. *- MEASUREMENT OF PRESSURE AT V1 AND NUMBER OF BANDAGE REPLACEMENTS TO ACHIEVE A PRESSURE BETWEEN 30 AND 40 mmHg.* STUDY POPULATION STUDIED

3.1. DESCRIPTION OF THE POPULATION

This study is aimed at patients wearing medical compression bandages as part of treatment for one or more venous ulcers (CEAP stage C6) who are attending the "vascular wound" clinic at Nantes University Hospital. The patients included will be non-hospitalised, i.e. living at home: in private accommodation or in a residential care home for elderly dependents (EHPAD) or other collective accommodation. Home care will be provided by their usual nurse.

In order to verify the initial hypothesis (exposing the heel results in the same pressure under the bandage as when the heel is covered), 102 patients divided into two groups will be included in this study:
- the experimental group: uncovered heel
- the control group: heel covered by the bandage.

The results of this study will be applicable to the technique for applying all types of compression bandages: at the patient's home or in hospital.

3.2. INCLUSION CRITERIA

- Adult patient
- Patients with at least one venous ulcer that has been developing for at least 4 weeks (CEAP stage C6)
- Patients attending a specialist outpatient clinic for vascular wounds at Nantes University Hospital
- Patients affiliated with a social security scheme
- Patients who agree to participate in the study (written consent)

3.3. EXCLUSION CRITERIA

- Patients under guardianship or curatorship
- Patients with major cognitive disorders incompatible with following the protocol[4] .
- Pregnant women

[4] This criterion will be left to the discretion of the medical and paramedical team without using an assessment scale, as administering these scales (MMSE or NPI) takes time and is quite removed from the nature of the research (which could cause concern for the patient, and for the NPI, the presence of an accompanying person is necessary, which is not always the case for consultants.

- Patients with an open leg ulcer and a systolic pressure index < 0.8 (reflecting underlying arterial damage)

4. STUDY DESIGN AND PROCEDURE

4.1. STUDY AND ANALYSIS TECHNIQUES

4.1.1. Detailed description of the evaluation parameters

The primary endpoint is based on pressure measurement under BCM.
Pressure is considered to be the active principle of compression. To enable comparison with the authorities' best practice recommendations and to avoid having to convert the measurement read directly on the device, it is expressed in millimetres of mercury (mmHg) even though the international unit of pressure is the Pascal.

The compression pressures actually exerted by bandages can be measured directly *in vivo*. This is referred to as interface pressure. It depends on the underlying radius of curvature, which must not be altered by the volume of the pressure sensor (1).

4.1.2. Detailed description of techniques and analyses

Interface pressure measurement:

Interface pressure is measured using the Picopress® device (see photo 1). It consists of a base for measuring pressure and a sensor placed between the patient's leg and the BCM.

Photo 1: Measuring device Picopress®

The Picopress® model was chosen because of its proven reliability (17). This system allows the sensor to be left in place for several days under the compression device in order to measure the pressure at a distance from the application site. However, this measuring device is expensive and cannot be purchased for every nurse participating in the study, as it costs around €2,000 per unit, which would represent an investment expense for the university hospital that is incompatible with research expenditure funded by the PHRIP.

The pressure measured will be that exerted by the BCM at the ankle, at point B1 (see Figure 1) on the inner side of the lower limb in the supramalleolar region (the area where the Achilles tendon transforms into muscle between 10 and 15 cm above the medial malleolus) (18).

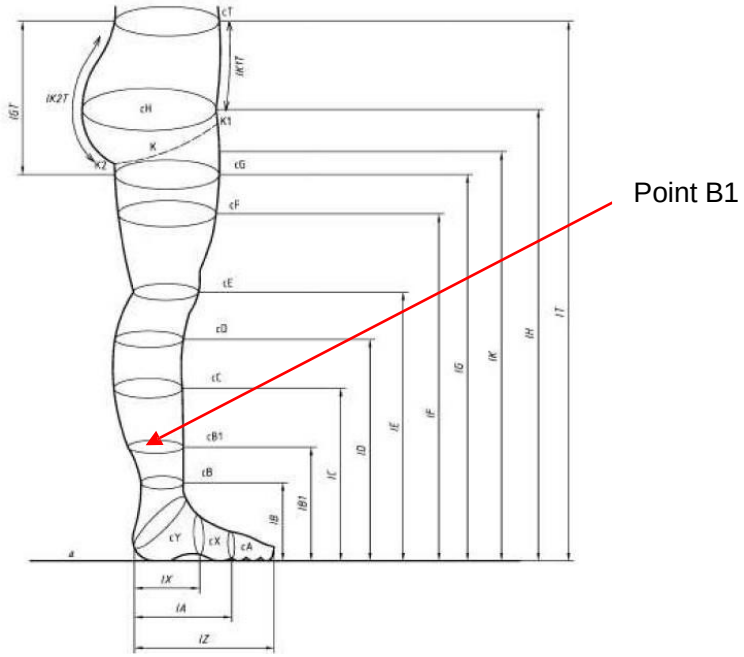


Figure 1: Measurement points, lengths and circumferences on the leg (Excerpt from draft standard XP ENV 12718 of December 2001)(1)

Pressure measurements at V1, V2 and V3 will be taken on the extended leg after a 2-minute rest period (18).

<u>Assessment of oedema by measuring the figure of 8</u>

The figure-of-eight measurement shall be taken with a tape measure, according to the method described by Perry S. ESTERSON (16).

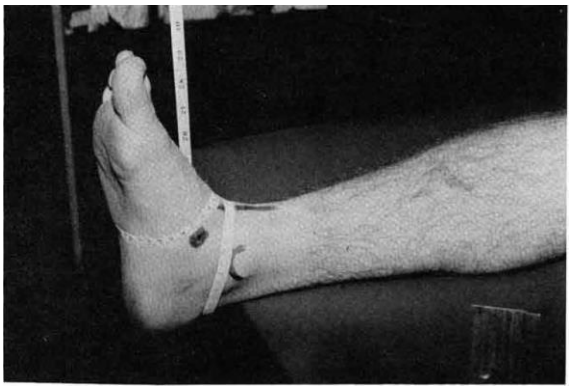


Photo 2: position of the tape measure known as the "figure of 8" (16)

Heterogeneous satisfaction questionnaire

A satisfaction questionnaire was developed to gather patients' opinions on their preference for wearing the BCM (covered heel, uncovered heel). (Appendix VI).

4.2. STUDY SCHEDULE

The contacts established during the protocol drafting phase with the Pays de Loire Regional Union of Health Professionals (URPS), the Nantes Nord Nursing Network (GRINN) and the nursing homes in Nantes will be reactivated in order to organise an information meeting for home nurses to inform them about the protocol during the site initiation visit.

V0 - informing the patient and their home nurse prior to inclusion

During a "vascular wound" consultation, the study will be presented to patients who meet the inclusion/exclusion criteria. If the patient agrees, a study nurse will collect the contact details of their home nurse. After a study nurse contacts them by telephone to present the study, the home nurse will receive an email containing a link to a short e-learning training course covering the following points: a presentation of the study, a video demonstration of how to apply the BCM with the heel covered and the heel left outside the bandage, how to apply the Picopress® pressure measurement sensor and how to take the measurement.

V1 - Inclusion and randomisation visit to the investigation site

On the day of the "vascular wound" consultation visit, the information about the study will be repeated by the research nurse. The patient's written consent will be obtained and randomisation will be carried out.

If the patient has venous ulcers on both legs, the randomised application technique will be applied identically to both legs, but measurements will be taken on the left leg (arbitrary choice).

After the dressing has been replaced, the figure-of-eight measurement (photo 2) will be taken with a tape measure and markings will be made with a skin pencil to standardise the measurements. The Picopress® sensor will then be placed and secured at point B1 (Figure 1 and Photo 3), the position of which will also be marked with a skin pencil.

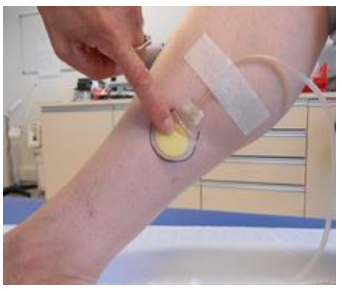


Photo 3: position of the pressure sensor

Then, depending on the randomisation arm, the nurse will apply the BCM:

In the experimental arm:

The BCM will be applied, leaving the heel exposed.

Photo 4: application of bandage with heel uncovered

In the control arm:

The BCM will be applied covering the heel as indicated in the HAS recommendations (1).

Photo 5: application of a bandage covering the heel

The patient will rest in a sitting position with their legs extended for 2 minutes to stabilise the pressure, then the interface pressure will be measured using the Picopress®. If the pressure exerted is outside the 30-40 mmHg range, the bandage will be reapplied until the therapeutic pressure is reached. The number of times the bandage is reapplied to reach the therapeutic zone will be recorded. The sensor will be left in place and removed by the home care nurse when the dressing is reapplied so that she can see its location for the measurement she will have to take at V2.

The follow-up consultation appointment at V3, corresponding to the usual follow-up carried out between four and eight weeks after V1, will be scheduled. A protocol follow-up logbook will be given to the patient. This will include a reminder of the important dates in the protocol (V1, V2, V3) and a follow-up table in which the home nurse will record any deviations from the protocol (interruption in wearing the band, failure to follow the technique for placing the inclusion arm) and, finally, a space dedicated to recording the interface pressure measured at V2 (Appendix VII).

Home monitoring between V1 and V2

Each time the dressing is changed, the home care nurse will:

- ensure that the figure-8 marking made at V1 is visible and that the Picopress® sensor, which will have been removed by the home nurse during the first dressing change, is correctly positioned
- apply the BCM as indicated by the randomisation arm application technique (as described in the monitoring log)
- will fill in the monitoring log.

The week before V2, a study nurse will contact the home nurse to deliver the Picopress® to the nursing practice. This measuring device is expensive and cannot be purchased for every nurse participating in the study follow-up.

V2 (48 hours before V3) - Home follow-up visit

During the last dressing change before the V3 consultation, the home nurse will apply the pressure measurement sensor to the marked area after changing the dressing, then apply the BCM. After a 2-minute rest with the leg extended, she will take a measurement using the Picopress® provided. The measurement obtained will be recorded in the monitoring log.

V3 (4 to 8 weeks after V1) - End-of-study visit to the investigation site

During the end-of-study visit, the patient will be welcomed and a study nurse will measure the interface pressure at B1 after 2 minutes of rest. She will then remove the BCM and measure the figure 8. The patient will be seen by the doctor. Finally, a study nurse will administer the satisfaction questionnaire (Appendix VI).

STUDY TIMELINE

Actions	**V0**	**V1** (Inclusion visit)	**V2** At home Last dressing change dressing before V3	**V3** End of study
Presentation of the study to patients meeting the inclusion/exclusion criteria	X			
Information and e-learning training for home nurses*	X			
Updating patient information		X		
Obtaining written consent		X		
Inclusion and randomisation		X		
Placement of the interface pressure sensor		X	X	
Interface pressure measurement		X	X	X
Measurement of the number of bandage changes required to reach the therapeutic zone		X		
Measurement of the figure 8		X		X
Satisfaction questionnaire				X

** Between V0 and V1*

4.3. GENERAL RESEARCH METHODOLOGY

The research has the following characteristics:

- **Nursing practice evaluation study**

The application of compression bandages (term used in the Public Health Code) falls within the prescribed role of nurses (19). However, "checking for signs of complications that may arise in a patient wearing an immobilisation or compression device" falls within the specific role of nurses (14).

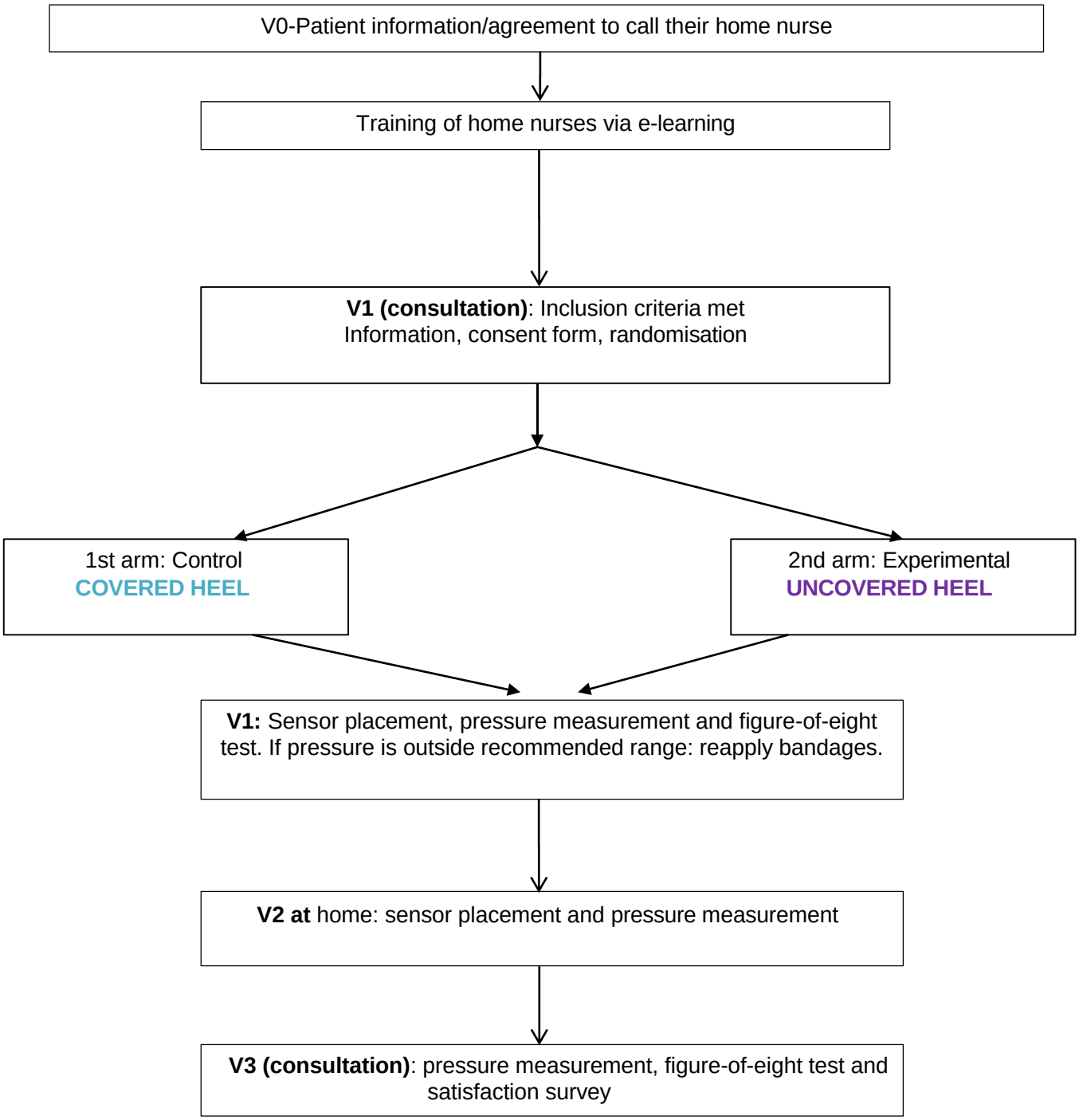
- **Single-centre study**

This study will be conducted at Nantes University Hospital with non-hospitalised patients who will be cared for by their usual nurse at home. Although this study is being conducted at a single site, the participation of several home care nurses will ensure that it is representative of the diversity of professional practices.

- **Controlled parallel group study**
- **Open study**
- **Randomised study**
- **Prospective study**

4.4. STUDY DESIGN

Recruitment period: 24 months
Follow-up period for each patient: four to eight weeks (patients are usually seen every four weeks at Nantes University Hospital). To prevent appointment delays due to weeks of absence by practitioners or patients, the maximum follow-up period for patients may be eight weeks. The period between V1 and V3 will be recorded in the case report form.
Total duration of the study: 25 months



4.5. IDENTIFICATION OF ALL SOURCE DATA NOT INCLUDED IN THE MEDICAL RECORD

- Technique usually used for heel placement
- Contact details for the home nursing practice
- Interface pressure measurement
- Measurement of the figure 8
- Compliance or non-compliance with the randomisation arm technique allocated
- Satisfaction questionnaire data
- Number of times the V1 bandage was reapplied to reach the therapeutic area

4.6. RULES FOR DISCONTINUING A PERSON'S PARTICIPATION

4.6.1. Criteria for premature discontinuation of a person's participation in the research

Withdrawal from participation in the study is defined as:

- A patient who expresses a desire to withdraw their consent to participate in the study at any stage, without having to justify their decision
- Death of the patient

Withdrawals from studies can only take effect after confirmation by the investigator and the sponsor. These withdrawals from the study are always final.

4.6.2. Procedures for premature termination of participation of a person in the study

Patients who withdraw from the study prematurely will continue their standard follow-up at Nantes University Hospital in the "vascular wound" clinic.
For information on how data from individuals who have withdrawn prematurely from the study will be used, please refer to the statistics section.

4.6.3. Criteria for discontinuing part or all of the research (excluding biostatistical considerations)

Part or all of the study may be permanently or temporarily halted by decision of the ANSM, the EC or the study sponsor.

In all cases:
- Written confirmation will be sent to the study's coordinating investigator (specifying the reasons for premature termination).
- All persons participating in the research will be informed and will be required to attend their early exit visit.

4.7. COMPENSATION

No compensation is provided for patients as their care is not affected in any way (no additional visits).
However, participating home nurses will receive a gift voucher worth €150 per patient included, to compensate them for the time spent viewing the e-learning training and their involvement in the research.

5. DATA MANAGEMENT AND STATISTICS

5.1. COLLECTION AND PROCESSING OF STUDY DATA

5.1.1. Data collection, processing and circulation

Data collection for each person participating in the research is carried out using an electronic case report form (eCRF). Each person responsible for this collection (investigator, CRA, study-co, etc.):

- is identified in the responsibility delegation table (kept in the investigator's file)
- will have a "user" account with IT rights specific to their role (right to enter or modify data, right to lock, monitor or sign an eCRF page)

Data may only be entered, viewed or modified via the eCRF pages (input masks) at https://nantes-lrsy.hugo-online.fr/CSonline.

This data is first recorded on paper and then entered into the eCRF corresponding to a database hosted on a dedicated server, with controlled access (username/password) depending on the user's role. Any additions, modifications or deletions of data will be tracked in a non-modifiable electronic file (the audit trail).

5.1.2. Participant identification

The principal investigator and co-investigators undertake to keep the identities of the persons participating in the research confidential by assigning them a code.

This code is used for all eCRFs and all attached documents. It is the only information that can be used to identify the participant retrospectively.

The coding rule is as follows: Patient's initials (^{first}letter of surname and ^{first}letter of first name) and inclusion number ranging from 1 to 102.

5.2. STATISTICS

For this study, 102 patients are expected to be included.

Statistical analyses will be performed by [redacted] , Statistical Engineer at Nantes University Hospital.

The statistical analyses will be performed using Stata 15.1 software.

A data review will be carried out at the end of the study, before the statistical analyses begin. The following individuals will be present during this review: the principal investigator, the project manager, the monitoring CRA, the data manager, the statistician, and any other individuals involved in the protocol. The objective will be to review the progress of the study, identify any problems encountered, and classify any deviations as minor or major.

5.2.1. Description of planned statistical methods, including the schedule for planned interim analyses

The variables measured at inclusion will be described for all patients and in each of the two groups by the numbers and percentages of each modality for qualitative variables and by the minimum, maximum, mean, standard deviation and quartiles for quantitative variables.

Analysis of the primary endpoint
In each group, the mean pressure will be estimated. The 95% confidence interval for the difference between the mean pressures in each arm will be estimated using a linear model that takes into account the stratification criterion. The lower limit of this interval will be compared to the defined non-inferiority threshold. If this limit is greater than -5, the non-inferiority of the bare heel group compared to the covered heel group will be demonstrated.

Secondary criteria:
- The evolution of oedema between V1 and V3 will be compared between the two groups using a mixed linear regression model that takes into account the randomisation stratification factor.
- The proportion of patients with interface pressure outside the recommendations (<30 mmHg or >40 mmHg) will be compared between the two groups at each visit where pressure measurement was performed using a chi-square test.
- The change in pressure between the V2 and V3 measurements will be compared between the two groups using a mixed linear regression model that takes into account the randomisation stratification factor.
- Patient satisfaction will be compared between the two groups using logistic regression models.
- The number of dressing changes will be compared between the two groups using a linear regression model that takes into account the randomisation stratification factor.
Qualitative data will be analysed by theme.

5.2.2. Statistical justification for the number of inclusions

For this study, 102 patients are expected to be included.

The primary endpoint is the interface pressure measured in V3, 48 hours after application of the medical compression bandage. The objective is to demonstrate the non-inferiority of applying the MCB with the heel uncovered compared to applying it with the heel covered.

A study conducted by Protz in 2014 (20) on 35 volunteers showed that the UrgoK2® (multi-type bandage) had an average interface pressure at rest of 35.5 mmHg (+/-3.3) and 31.1 mmHg (+/-5.6) at 1 and 3 days after application, respectively. As this was a study on volunteers and not on patients with chronic venous ulcers, we favoured the largest standard deviation presented, i.e. the standard deviation after seven days of wearing the bandage, which was 6.9 mmHg.

With the following assumptions:

- Average pressure identical with heel covered and uncovered
- Common standard deviation of 6.9
- Power of 90%
- Alpha risk of 2.5%
- Non-inferiority threshold of 5 (defined based on the interface pressures recommended by the HAS)

A sample size of 84 patients is required. To ensure a sufficient number of patients in the per-protocol analysis, we are increasing this by 20%. Indeed, as this is a fragile population, we expect a certain number of deaths, hospitalisations during follow-up, patients not attending V3, patients for whom the bandage was not applied using the technique allocated by randomisation at V2 and/or more than four times during the eight weeks of follow-up.
A total of **102 patients** will be randomised, i.e. 51 patients per group.

The "vascular wound" clinic sees approximately 60 patients per month for venous or mixed vascular wounds. The recruitment potential is therefore achievable over a few months. However, given the availability of Picopress® and the possibility of training home nurses, we estimate that a recruitment period of 24 months will be necessary to include all 102 patients.

5.2.3. Expected degree of statistical significance

For the non-inferiority analysis on the primary endpoint: the lower limit of the 95% two-sided confidence interval of the difference between the two arms will be compared to the non-inferiority threshold set at -5.
For the analysis of secondary criteria: the degree of statistical significance is set at 0.05.

5.2.4. Method of into consideration of missing, unused or invalid data

As patient follow-up for this study is relatively short (four to eight weeks) and involves routine follow-up consultations, very few patients are expected to be lost to follow-up.

However, in the event of death, withdrawal of consent or any other reason preventing the collection of the V3 interface pressure value, this will be imputed using a multiple imputation method.

A sensitivity analysis will be performed in a second step to verify the robustness of the results obtained by imputing the missing data with the worst-case scenario, i.e. the minimum pressure observed in both groups, and then with the "average scenario", i.e. the average value observed in both groups.

Secondary criteria: no imputation will be performed on missing data for secondary criteria.

5.2.5. Management of changes to the initial strategy analysis plan

A statistical analysis plan will be drafted before the database lock is applied and will detail any changes made to the statistical section of the protocol.

5.2.6. Selection of individuals to be included in the analyses

As planned for non-inferiority trials, the analysis will focus on the per-protocol population and will be supplemented by an intention-to-treat analysis.

The "per protocol" population corresponds to patients who most closely adhere to the protocol: compliance with inclusion and exclusion criteria, no major deviations from the protocol (patient death, patient hospitalisation during follow-up, patient not attending V3, patient for whom the bandage was not applied using the technique allocated by randomisation at V2 and/or more than four times during the eight weeks of follow-up) and availability of the primary endpoint.

The "intention to treat" population corresponds to all patients randomised in the study.

5.2.7. Randomisation

Randomisation will be open-label and stratified according to the type of band (multitype or short-stretch band). It will be performed on a 1:1 ratio and will be balanced by blocks.

Randomisation will be performed using Clinsight software via the website: **https://nantes-lrsy.hugo-online.fr/CSOnline/.** Access will be granted using a login, password and study number (NTLRXXX) provided by a data manager from the Research Promotion Department of Nantes University Hospital.

The following information must be provided:

- First initial of surname
- First initial of first name
- Date of birth (month and year)
- Compliance with inclusion and exclusion criteria (yes/no)
- Informed consent (yes/no).

The randomisation number and arm will be assigned automatically during randomisation. A confirmation email will be sent to the person who performed the randomisation and to all persons concerned.

Randomisation lists will be drawn up by a statistician from the Research Promotion Department of Nantes University Hospital. An explanatory guide to randomisation will be available online at Clinsight.

6. SAFETY

Given the low risks and constraints of this protocol, and the distribution observed in observational studies (11) (approximately half of the patients had their heels covered and the other half had their heels uncovered), no adverse events related to the research are expected.

Consequently, the occurrence of any adverse event or adverse reaction associated with the normal care of persons included in this protocol must be reported in the appropriate safety system (pharmacovigilance, biovigilance, haemovigilance, medical device safety, etc.).

7. ADMINISTRATIVE AND REGULATORY ASPECTS

7.1. RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

Each person's medical data will only be transmitted to the sponsor or any person duly authorised by the sponsor, and, where applicable, to the authorised health authorities, under conditions that guarantee their confidentiality.
The sponsor and the supervisory authorities may request direct access to the medical file to verify the procedures and/or data of the trial, within the limits authorised by laws and regulations.
The data collected during the trial will be processed electronically in accordance with the requirements of the CNIL (compliance with reference methodology MR001).

7.2. TRIAL MONITORING

Monitoring will be carried out by the Promotion Department of the Research Directorate. A Clinical Research Associate (CRA) will visit the department regularly to carry out quality control of the data reported on case report forms.

The protocol has been classified according to the estimated level of risk for the person participating in the research. It will be monitored as follows:

Risk A: low or negligible foreseeable risk

On-site monitoring visits will be organised after appointment with the investigator. CRAs must be able to consult the following at each site:
- the data collection notebooks for the individuals included,
- the patients' medical and nursing records,
- the investigator's file.

7.3. INSPECTION/AUDIT

An inspection or audit may be conducted as part of this study. The sponsor and/or participating sites must be able to provide inspectors or auditors with access to the data.

7.4. ETHICAL CONSIDERATIONS

7.4.1. Written informed consent

The investigator undertakes to obtain free and informed consent, collected in writing, after providing the subject with information on the protocol (information note in Appendix IV). The investigator will provide the subject with a

copy of the information sheet. The person may only be included in the study after having read the information sheet and given their written consent.

The information provided to the person and their agreement to participate in the research must be noted in their medical file.

7.4.2. Ethics Committee

The sponsor undertakes to submit the study proposal to an Ethics Committee for prior authorisation.

7.5. INFORMATION TO THE COMPETENT AUTHORITIES

This protocol will be communicated to the ANSM.

7.6. AMENDMENTS TO THE PROTOCOL

Requests for substantial amendments shall be submitted by the sponsor to the ANSM for information and to the relevant Ethics Committee for authorisation/information in accordance with the law in force and its implementing regulations.

The amended protocol must be updated and dated.
The information forms shall be amended if necessary.

7.7. FUNDING AND INSURANCE

The sponsor shall finance the study and take out an insurance policy covering the financial consequences of its civil liability, in accordance with the regulations.

7.8. RULES RELATING TO PUBLICATION

A copy of the publication shall be sent to Nantes University Hospital, the sponsor of the study, which must be cited. The coordinating investigator shall draw up the list of authors.

Publications resulting from projects funded under the Ministry of Health's calls for projects must bear the following statement: "This study was supported by a grant from the French Ministry of Health (programme acronym, programme year, registration number: e.g. PHRIP 2018 XXXXX, etc.)."

7.9. ARCHIVING OF SOURCE DATA

The investigator must retain all information relating to the study for at least 15 years after the end of the study.
At the end of the study, the investigator will receive a copy of the data for each person at their site sent by the sponsor.

LIST OF APPENDICES

- Appendix I: List of investigators
- Appendix II: Summary of the protocol
- Appendix III: Bibliographical references
- Appendix IV: Information sheet and consent form
- Appendix V: Training sheet
- Appendix VI: Satisfaction questionnaire
- Appendix VII: Protocol monitoring logs

APPENDIX I: LIST OF INVESTIGATORS

SURNAME AND FIRST NAME	Speciality	Position	Name of institution	Name and address of the relevant department	Telephone, fax and e-mail	ADELI number
[redacted]	Vascular wound consultation	Nurse	Nantes University Hospital	Unit Mobile "vascular wounds"	02 [redacted] [redacted]@chu-nantes.fr	[redacted]
[redacted]	Research clinical	Nurse	Nantes University Hospital	Research Clinical Paramedical	02 [redacted] [redacted]@chu-nantes.fr	[redacted]

APPENDIX II: SUMMARY OF THE PROTOCOL

Title of the study	**"**Comparison of the effectiveness of two techniques for applying medical compression bandages by measuring interface pressures depending on whether or not the heel is included in patients with open venous ulcers: controlled, randomised non-inferiority trial controlled, randomised trial**"**
Keywords	Venous ulcer ulcer, bandages compression therapeutic therapeutic compliance, heel, methods *From MeSH:* *varicose ulcer, compression bandages, patient compliance, heel, methods*
Study sponsor	**NANTES UNIVERSITY HOSPITAL**
Principal investigator Principal (if single-centre study)	Ms [redacted] (nurse)
Study schedule	➢ Total duration: 38 months ➢ Recruitment period: 36 months ➢ Follow-up duration per participant: 4 to 8 weeks
Study type and design	➢ Controlled study in parallel groups ➢ Open-label study ➢ Randomised study ➢ Prospective study ➢ Single-centre study
Number of cases	102
Study objectives	**Main objective:** Compare the interface pressure measurements generated by a medical compression bandage between two groups of patients with open venous ulcers at stage C6 of the CEAP classification: - the experimental group: heel uncovered - control group: heel covered by the bandage. **Secondary objective(s):** - Compare the development or appearance of ankle oedema (a risk considered in the case of uncovered heels) between the two groups. - Compare, between the two groups, the interface pressures measured when applying BCM at home, compared to the recommended pressures (30-40 mmHg) (1) - Compare the evolution of interface pressures after 48 hours of wearing BCM between the two groups. - Compare patient satisfaction between the two groups - Assess the number of bandage changes required to achieve therapeutic pressure during V1
Endpoints	**Primary endpoint:** Measurement of interface pressure at V3, 48 hours after application of the BCM. **Secondary endpoints:**

	- Measurement of the figure of 8 at inclusion and at the last follow-up visit (V3) - Measurement of interface pressure at V2 - Measurement of interface pressure at V2 and V3 - Responses to the hetero-questionnaire on satisfaction - Number of bandage changes at V1
Treatment, interventional procedure **Interventional procedure under consideration**	Application of medical compression bandages with or without heel coverage by the bandage.
Reference treatment	Heel covered by the medical compression bandage (1)
Main selection, inclusion, non-inclusion and exclusion criteria	**Inclusion criteria**: - Adult patient - Patient with at least one venous ulcer that has been developing for at least 4 weeks (CEAP stage C6) - Patient attending a specialised outpatient clinic for vascular wounds at Nantes University Hospital - Patient affiliated with a social security scheme - Patients who agree to participate in the study (written consent) **Exclusion criteria:** - Patient under guardianship or curatorship - Patients with major cognitive disorders incompatible with following the protocol - Pregnant women - Patients with open leg ulcers and a systolic pressure index < 0.8 (indicating underlying arterial disease)
Schedule of visits and examinations	-V0 presentation of the study and information + training of home nurses via e-learning before inclusion. -V1 at the "vascular wound" consultation at Nantes University Hospital: inclusion, randomisation, measurement of interface pressure, number of dressing changes required to achieve therapeutic pressure, and figure of 8. -V2 at the patient's home during the last dressing change before V3: placement of the pressure sensor and measurement of interface pressure -V3: measurement of interface pressure, figure-of-eight pattern and collection of patient satisfaction data.
Statistical analysis	**Analysis of the primary endpoint** In each group, the average pressure will be estimated. The 95% confidence interval for the difference between the average pressures of each arm will be estimated using a linear model that takes into account the stratification criterion. The lower limit of this interval will be compared to the defined non-inferiority threshold. If this limit is greater than -5, the non-inferiority of the uncovered heel group compared to the covered heel group will be demonstrated. **Secondary criteria:** - The evolution of oedema between V1 and V3 will be compared between the two groups using a mixed linear regression model that takes into account the randomisation stratification factor. - The rate of patients with interface pressure outside the recommendations (<30 mmHg or >40 mmHg) will be compared between the two groups at each visit where pressure measurement was performed using a chi-square test.

	- The change in pressure between the measurement at V2 and the measurement at V3 will be compared between the two groups using a mixed linear regression model taking into account the randomisation stratification factors. - Patient satisfaction will be compared between the two groups using logistic regression models. - The number of dressing changes will be compared between the two groups using a linear regression model that takes into account the randomisation stratification factor.
Observational study conducted in 2016, funded by the internal "paramedical research" call for tenders from Nantes University Hospital Over a four-month period, following "vascular wound" consultations, we included 161 non-hospitalised patients with BCM and 100 patients hospitalised in the internal medicine and geriatric care departments of Nantes University Hospital. The results, currently being publication, show that 48% of outpatients and 54% of hospitalised patients with BCM had exposed heels.	

APPENDIX III: BIBLIOGRAPHICAL REFERENCES

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