“VACuum-Assisted closure for necrotizing soft tissue infecTIONs”

VACATION

RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS WITH MINIMAL RISKS AND BURDEN

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Coordinating Investigator: Pr Nicolas de PROST
Department of Medical Intensive Care Unit
Hospital Henri Mondor
Tel. 01 49 81 23 94
Email: nicolas.de-prost@aphp.fr

Scientific Director: Pr Olivier CHOSIDOW
Department of Dermatology
Hospital Henri Mondor
Tel. 01 45 17 81 72
Email: olivier.chosidow@aphp.fr

Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)
and by delegation: Délégation à la Recherche Clinique et à l’Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI-Head Office project advisor: Sabrina WILLIAMS
Tel. 01 44 84 17 26
Email: sabrina.williams@aphp.fr

Entity responsible for monitoring the study: URC (Clinical Research Unit) – HU Henri Mondor
51, av du Mal de Lattre de Tassigny
94000 Créteil
DRCI-URC project advisor: David SCHMITZ
Tel. +33 1 49 81 37 98 (secrétariat)
Tel. +33 1 49 81 41 64 (poste direct)
Email : david.schmitz@aphp.fr

SIGNATURE page for a research PROTOCOL

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Title: VACuum-Assisted closure for necrotizing soft tissue infecTIONs

Version no. 2.0 dated on September 5th /2022

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Coordinating Investigator:

Pr Nicolas de PROST
Department of Medical Intensive Care Unit
Hospital Henri Mondor
94000 Créteil

Date: ……/……/……..
Signature:

Sponsor

Assistance Publique – Hôpitaux de Paris
Délégation à la Recherche Clinique et à l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 Paris

Date: ……/……/……..
Signature:

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1 SUMMARY

Full title	VACuum-Assisted closure for necrotizing soft tissue infecTIONs
Acronym/reference	VACATION
Coordinating investigator	Pr Nicolas DE PROST Department of Medical Intensive Care Unit Hospital Henri Mondor Tel. 01 49 81 23 94 Email: nicolas.de-prost@aphp.fr
Scientific Director (if applicable)	Pr Olivier CHOSIDOW Department of Dermatology Hospital Henri Mondor Tel. 01 45 17 81 72 Email: olivier.chosidow@aphp.fr
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Necrotizing and soft tissue infections (NSTI) are life-threatening bacterial infections characterized by subcutaneous tissue, fascia or muscle necrosis. The hospital mortality of NSTI is high, comprised between 20 and 30%. NSTIs represent the 4th cause of septic shock (1). Early management of NSTIs requires a coordinated and multidisciplinary approach, including broad-spectrum antibiotic administration, management of organ failures and aggressive surgical debridement with excision of all necrotic and infected tissues. NSTIs involve the lower limbs in about 70% of cases and lead in 15% of cases to limb amputation (2). During the early post-operative phase, daily wound care is required using conventional dressings. As soon as the infectious process is controlled, typically within 7 to 10 days of the initial debridement, the main goal of wound dressing is to allow for a granulation tissue to develop so that to perform a skin grafting. Negative pressure wound therapy (NPWT), which consists in applying a negative pressure on the wound surface, may be used to this effect. A dedicated dressing is connected to a device that generates a negative pressure and collects exudates. NPWT may have a positive effect on wound healing by removing exudate, increasing regional perfusion and patient comfort and reducing infections. Beneficial effects of NPWT have been suggested by case series (3). However, a recently published Cochrane review concluded that no randomized controlled trial was available to adequately assess its efficiency (4) and the guidelines of the *Infectious Diseases Society of America* (IDSA) on NSTI (5) did not provide recommendations regarding NPWT use for managing NSTI wounds. We hypothesize that in patients managed for NSTIs, NPWT: 1) may accelerate skin grafting and complete wound healing; and 2) improve functional outcomes.
Main objective and primary endpoint	Main objective: To demonstrate in patients who underwent a surgical debridement of the lower limb for NSTI a superiority of a wound dressing strategy using NPWT (intervention) as compared with conventional wound dressing on local healing (complete) and the recovery of walking. Primary endpoint: The time elapsed between randomization and the onset of a combined outcome measure including both: **a complete healing of the diseased limb** clinically assessed

	according to the investigator's judgment (defined by more than 90% of functional skin covering the wound) **and the recovery of walking** (defined by the ability to walk at least 100 steps, corresponding to approximately 30 meters, without help).
Secondary objectives and endpoints	<u>Secondary objectives:</u> To demonstrate the impact of the intervention (wound dressing with NPWT) on: 1. The functional status at 3 and 6 months 2. Health-related quality of life at 3 and 6 months 3. Pain 4. The number of anesthesia procedures 5. Time to skin grafting 6. Local superinfections 7. Walking capacity at 3 and 6 months 8. The duration of hospital stay 9. The duration of nurse care needed for wound dressing 10. The feasibility of maintaining NPWT until skin grafting 11. The number of surgical procedures performed between randomization and skin grafting 12. The number of surgical procedures performed after skin grafting 13. Mortality at 3 and 6 months <u>Secondary endpoints:</u> 1. ADL score: measured by a research nurse at 3 and 6 months 2. SF-36 score: measured by a research nurse at 3 and 6 months 3. Pain assessment at each wound care by the patient (visual analogic scale), the nurse (behavioral pain scale) and quantification of morphine consumption (in morphine base equivalent): measured by the investigator at each wound care 4. Quantification of the number of anesthesia procedures (general anesthesia, sedation): measured by the investigator at each wound care 5. Time elapsed between randomization and skin grafting: measured by the investigator 6. Number of local superinfection episodes: measured by the investigator 7. Quantification of the walking capacity: measured over one week with a pedometer by the research nurse, at 3 and 6 months 8. Duration of hospital stay: measured by the investigator 9. Quantification of the time needed for each wound care before randomization and skin grafting: this measure will be recorded at each wound care 10. Need for stopping the NPWT 11. Number of surgeries performed between randomization and skin grafting: all surgeries will be recorded, including their date and indication 12. Number of surgeries performed after skin grafting: all surgeries will be recorded, including their date and indication 13. Mortality assessed at 3 and 6 months
Design of the study	Open-label randomized controlled trial with blinded assessment of the primary end point. Patients will be eligible

	for inclusion in the study after a minimum of 5 days following the first surgical debridement. Randomization in two arms: experimental group (NPWT) *versus* control group (conventional dressing) until skin grafting (decided by the attending surgeon). Weekly visits after skin grafting by a dedicated research nurse blinded to the study arm who will record the two variables composing the primary end point (i.e., complete healing of the diseased skin and the ability to walk at least 100 steps without help). The time between randomization and the onset of the combined primary end point will then be computed. Visits of the research nurse will be performed weekly until the primary end point is reached and then at 3 and 6 months for recording secondary end points.
Population of study participants	Patients needing skin/soft tissue debridement for an NSTI of the lower limb
Inclusion criteria	- Age ≥ 18 years - Written informed consent - NSTI of the lower limb clinically suspected and confirmed by surgery with a first debridement performed since 5 days or more - Infection considered controlled (i.e., no more surgical debridement is necessary) - Last debridement performed at least 72 hours before - Affiliation to a social security system
Exclusion criteria	- Limited life expectancy - NPWT already initiated for the current NSTI episode - 1st surgical debridement performed less than 5 days or more than 15 days before - High risk of bleeding (blood vessels exposed) - Local neoplasia - Risk of organ or peripheral nerve injury - Impossibility to set up a NPWT dressing hermetically - Limb amputation - Patient unable to walk without help - Women who are pregnant or are breast-feeding, or are of childbearing age and do not use or do not plan to use acceptable birth control measures - Patients under legal protection - Prisoners
Interventions or product under investigation	Negative pressure wound therapy (NPWT): an NPWT device will be applied hermetically from randomization to skin grafting. Centers participating in the study will use the device they use routinely, validated by HAS (French National Authority for Health) (6).
Comparator arm	Conventional dressing will be performed from randomization to skin grafting. The dressings will be performed following usual procedures of investigating centers.
Other interventions added by the study	Weekly assessment of: ability to walk, quantification of walking at 3 and 6 months. SF-36 score and ADL at 3 and 6 months.
Expected benefits for the participants and for society	Current knowledge on wound healing with NPWT suggests this intervention might have a positive impact by reducing not only

	the time to skin healing, but also by improving the quality of healing. Such effects could allow for a better functional recovery of patients who underwent skin/soft tissue debridement for an NSTI of the lower limb, associated with a shorter time to recovery of walking. We also hypothesize that other aspects pertaining to the dimensions explored by health-related quality of life questionnaires (e.g., Activity of Daily Living and Instrumental Activity of Daily Living) might be improved by the NPWT strategy. We also expect that the NPWT strategy will allow for reducing the number of dressing procedures needed (NPWT dressings are usually changed every three days while conventional dressings are changed daily), overall pain, the risk of local superinfection, the duration of hospital stay.
Minimal risks and burden added by the study	NPWT is a safe procedure. The main risks associated with its use are regional wound bleeding and wound superinfection. ➔ *Risk level of the study:* A minimum level.
Scope of the study	Patients will be eligible for inclusion after a minimum of 5 days after the first surgical debridement. - 1:1 randomization in 2 arms: **intervention** (negative pressure treatment) *versus* **control** (conventional dressings) until the skin graft is carried out, to be decided by the attending surgeon. - Weekly visits after the skin graft or D21 from a clinical research nurse who is blinded to the therapeutic intervention and will record the occurrence of the primary endpoint, i.e. a **clinical cure** (defined by **complete healing**, which means that at least 90% of the wound's surface is covered, **AND the recovery of walking,** defined by the ability to walk at least 100 consecutive steps unaided). The time of occurrence of the primary endpoint in relation to randomization will be calculated. - Follow-up visits will be planned by the clinical research nurse at 3 and 6 months to record secondary endpoints.
Number of participants included	130
Number of centres	19 sites in France Investigator's specialty: intensive care medicine
Schedule for the study	Specify: - inclusion period: 3 years - maximal participation period (treatment + follow-up): 6 months - total duration: 3 years and 6 months
Number of enrolments expected per site and per month	0.19
Statistical analysis	No interim analysis is planned
Funding sources	PHRC-N 2019

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 CURRENT STATE OF KNOWLEDGE IN VIEW OF THE RESEARCH

Necrotising soft tissue infections and necrotising fasciitis (NSTIs/NF) are severe infections affecting the skin and soft tissue. They can be mono- or polymicrobial and generally affect the lower limbs in around 70% of cases. NSTIs/NF are the number four cause of septic shock and are linked to a high hospital mortality rate of 25-30%, as well as to a high morbidity level (1). Known risk factors are being aged over 60, male, having obesity, diabetes, alcohol consumption, renal failure, hepatopathy, immunosuppression, including neoplasia and corticoid therapy (7). Other local factors must be added, such as chronic wounds, pre-existing lesions, injections or needle holes. However, an NSTI/NF may occur even if there are no risk factors, with descriptions of an NSTI/NF following a blunt trauma (8). Taking non-steroidal anti-inflammatory drugs (NSAIDs) probably causes a delay in treatment by reducing the initial intensity of the symptoms.

The cutaneous indications, apart from erythema and oedema, which are also common to non-necrotising soft tissue infections, are the presence of areas which are cyanotic, showing skin discolouration, blistering, necrosis and sometimes haemorrhaging, hypoesthesia, crepitus and intense pain. The rapid progression of the lesions supports a diagnosis in favour of NSTI/NF, as opposed to a diagnosis for erysipelas, especially as the most obvious clinical signs (i.e. areas of the skin which are cyanotic, showing discolouration, necrosis, the presence of blisters and subcutaneous crepitus) are inconsistent during the early stage (9). This diagnosis must not be discounted at all if these signs are not present. Around half of patients present signs of systemic impact (e.g. sepsis or septic shock). According to international recommendations, any cutaneous infection associated with the failure of one or more organs or showing a dramatic deterioration must include the diagnosis of a necrotising infection for consideration, even if there is no local sign of the condition being severe (5). The diagnosis is confirmed by identifying intra-operatively deficient tissue, sometimes necrotic, which comes away easily in the fingers and by the presence of the typical, foul-smelling "dishwasher" exudate. The surgeon will notice necrosis of the dermis and hypodermis, which may be isolated or associated with necrosis of the fascia or even the muscle.

Emergency treatment of NSTIs/NF is carried out on a multidisciplinary basis, combining treatment with broad spectrum antibiotics, according to French (10) or American (5) recommendations, emergency surgery with debridement of the necrotised tissue, local post-operative care and treatment for any associated organ failure. The role of adjuvant measures is debatable (11). There is contradictory data available as to the benefit of intravenous immunoglobulins (13-15) and of hyperbaric oxygen therapy (15,16). Generally speaking, the level of proof presented by these treatment interventions could be described, at best, as weak, based on the recommendations of the *Infectious Diseases Society of America* (IDSA) (5). In fact, only three randomized controlled trials have been published on NSTIs/NF, as reported in a Cochrane review recently published by our group (17). Therefore, conducting clinical trials presenting a high level of proof is regarded by the IDSA as one of the priorities in terms of research into NSTIs/NF in the years ahead (5). Several variable factors likely to end up changing the prognosis for patients with NSTI/NF have been identified by observational studies: shortening the time between admission and surgical treatment (18), treatment in a centre with a high level of activity in this field (i.e. treating more than 3 NSTI/NF cases per year) (19) or the implementation of certain strategies for post-operative dressings (3, 20).

This last field of investigation seems particularly relevant as surgical excision of the infected tissue generally requires several operations (2 to 4 depending on the series (18, 21)), often causing extensive deterioration and resulting in amputation in around 15% of cases (2) and causing in every case a loss of tissue across the whole debrided area. During the initial treatment phase, dressings are applied daily with the aim of encouraging debridement of the wound and controlling infection locally. Local care is then continued beyond infection control until the point where granulation tissue is formed, enabling a skin graft to be performed to cover the wound, which generally takes place after 3 to 4 weeks of treatment. The regular

treatment of these post-operative wounds involves mechanical and chemical debridement while applying daily dressings. *Negative pressure wound therapy* (NPWT) is an alternative to daily dressing, which involves placing the surface of a wound under a pressure lower than atmospheric pressure. A dedicated dressing is connected to a negative pressure source and an exudate collection system. The benefits of NPWT seem to be linked to better drainage of secretions, an improvement in local perfusion conditions and making patients more comfortable. This is not to mention the fact that NPWT usually only requires dressings to be changed every 72 hours, thereby reducing the number of procedures required compared to the conventional treatment. The potential benefit of NPWT for the treatment of NSTIs/NF has been suggested by case series (3, 22, 23), but a recent Cochrane review concluded that no randomized controlled trial was available to assess its efficacy (4), and the recent IDSA recommendations (5) do not express any view about the role of NPWT.

2.2 Summary of relevant pre clinical experiments and clinical trials

NPWT operates on the principle of applying a dressing to a wound via which a negative pressure is exerted (24). The fluids draining from the wound and surrounding tissue are collected in a container. This device was developed in the 1990s (25) and has undergone major development since the early 2000s, with a 600% increase in healthcare expenditure linked to its use in the United States between 2001 and 2007 (USD 164 million refunded by Medicare (26)). NPWT is used to treat post-operative wounds when they have failed to heal by first intention (e.g. secondary dehiscence of a scar whose edges were initially joined together) or to treat wounds using second intention healing (e.g. when there is a major loss of tissue, preventing the wound from closing). The main action mechanisms involved in NPWT are as follows (27):

- Macrostrain on the wound, depending on the deformability of the surrounding tissue, getting both edges to meet and reducing the space to be filled by secondary granulation;
- Microstrain on the wound's surface due to overstretching the tissue by 5–20% to encourage healing at cellular and vascular level (28);
- Draining extra-cellular oedema and exudates;
- Maintaining a moist, warm environment which prevents the wound drying and encourages tissue granulation (29);
- Improving local perfusion with a beneficial effect on the healing process.

Even though NPWT is very widely used to treat secondary-intention wounds. The authors of a Cochrane review to evaluate the use of NPWT in surgical wounds were unable in 2015 to reach any conclusion about its benefit, based on the data produced by randomized controlled trials using a good-quality methodology (4). Out of 26 studies completed, only two were finally included in the review as their methodology was considered to be satisfactory: the Monson *et al*. study (30), which included 20 patients and compared NPWT to alginate dressings for treating infected wounds of the groin after vascular surgery, reported a healing period which was significantly shorter than the NPWT group (57 vs 104 days), but the low number of subjects and absence of any pre-defined follow-up period created a high risk of bias in this study according to the authors of the Cochrane review (4). The other study included compared NPWT for 14 days with a conventional treatment used after surgical treatment for a pilonidal sinus disease (31): 49 patients were included; the primary endpoint (duration of healing) was negative, even though a reduction in the wound's surface was observed after two weeks of treatment in the NPWT group. The authors of the Cochrane review reached an uncertain conclusion about the efficacy of NPWT in the secondary-intention treatment of surgical wounds, expressing the need to conduct randomized controlled trials to evaluate its benefit (4). A pilot randomized controlled trial, aimed at evaluating the feasibility of conducting a wider trial for testing NPWT against a conventional dressing in healing surgical wounds by secondary intention, was recently published, concluding that it was feasible to conduct such a trial: 40 patients were included across 3 centres for a total duration of 20 months and the healing time was measured (32).

NPWT has also been evaluated during orthopaedic surgery in patients being treated for an open fracture and, therefore, at a high risk of secondary infection. An initial randomized controlled trial, which included 59 patients and compared NPWT *versus* a conventional treatment, reported one fifth of the risk of infection

in the NPWT group (33). Unfortunately, these encouraging results were not confirmed by the recent trial by Costa et al. (34), which randomized 460 patients with an open fracture of the lower limbs into two strategies: NPWT versus conventional treatment. No significant difference was observed with regard to the primary endpoint (a functional disability score evaluated at 12 months) nor to the occurrence of infections on the operation site. However, the negative results of this trial, which tested NPWT in open fractures of the limbs, cannot be generalized to the population of patients with an NSTI/NF. In fact, differences regarding the extent of the loss of cutaneous tissue, the mechanism causing the tissue loss (trauma versus infection) and the previous medical history of the patients (more co-morbidities among patients being treated for NSTI/NF) suggest that it is not possible to extrapolate these results to the population of patients with an NSTI/NF.

Data reporting the use of NPWT among patients who have had cutaneous debridement for an NSTI/NF is very limited. Huang *et al*. (3) have reported an observational series of 12 patients treated with NPWT, compared to 12 patients who received conventional treatment. The authors noted a minor reduction in the size of the wound in the NPWT group without any clear indication of the duration after which this measurement was taken, as well as a reduction by a factor of 4 in the time required to deliver the care. Bronchard *et al*. (35) have also reported their experience of six patients receiving NPWT for treating an NSTI/NF affecting the perineum. NPWT was initiated after a median period of 7 days following initial surgery for a total duration of 15 days. The authors emphasised the excellent tolerance of this method and its benefit in terms of reducing the number of anaesthetic procedures involved (with the NPWT dressing being changed every 72 hours), compared with conventional dressings, which required, in some series, to be changed several times a day (36). Therefore, these studies highlight that, while NPWT may be widely used, its benefit has not been clearly demonstrated, neither for treating surgical wounds by secondary intention in general, nor for treating secondary wounds resulting from skin and soft tissue debridement in patients with NSTI/NF in particular.

2.3 Hypothesis for the study

Our hypothesis for this study is that NPWT could: 1) accelerate the skin graft procedure and the healing of the wound; and 2) improve functional outcomes for patients treated for an NSTI/NF.

2.4 Description of the population to be studied and justification for the choice of participants

Participants will be adults admitted to one of the intensive care units taking part in the study to receive treatment for a confirmed NSTI/NF of the lower limbs (intra-operative aspect or through microbiology or histology). NSTIs/NF of the lower limbs account for roughly 70% of all occurrences of these conditions. The aim of excluding other NSTIs/NF (e.g. abdomino-perineal, cervico-thoracic, etc.) is to include a group of patients presenting a *clinically homogeneous* picture, making it possible to evaluate them on the basis of an identical, functional endpoint (recovery of walking). Patients will be eligible to be included in the study as soon as the initial infection is considered to be cured by the responsible clinician (see inclusion criteria “infectious episode cured locally” and “last debridement performed at least 72 hours before”).

2.5 Interventions and products which will be performed or used as standard

Conventional dressings will be performed from randomization to skin grafting and applied every day based on the methods normally used in the participating centres, and also until the recovery of the skin has been achieved by the skin graft.

This generally involves local care provided on a daily basis, ensuring gentle mechanical and chemical debridement by covering the wound with alginate type or other dressings, according to the condition of the wound. The methods used to apply these *conventional* dressings will be recorded.

In both arms, the forms of analgesia used during and between dressings will be left to the discretion of the care team.

2.6 Interventions added for the research

The therapeutic intervention being tested is the use of a *negative pressure wound therapy* (NPWT) device. Several medical devices are currently being used and are based on the same principle. They involve applying negative pressure, generally between -100 and -150 mmHg, to a wound using a dressing (mostly a polyurethane foam dressing with hydrophobic pores), which hermetically covers the wound's surface and is connected to a container for collecting the fluids drained off. As described in detail earlier, these devices are widely available and used to treat post-operative wounds.
All the centers participating in the study will use the same device than that they routinely use, available in their centers and validated by HAS (French National Authority for Health) (6).

The treatment of wounds using NPWT will be proposed to patients randomized in the intervention arm within 24 hours of randomization.

Terms of use: The dressing will be changed every 72 hours, unless it is necessary to change it sooner (dressing's degradation of leak tightness, occurrence of a haemorrhagic, infectious or local mechanical complication, need to reassess the wound). The dressing will be used according to the manufacturer's recommendations, following the steps below, carried out in a sterile manner:

- Cutting and applying the polyurethane foam on the wound (no silver-impregnated foam will be used)
- Covering the foam with plastic film
- Inserting a suction tube connected to the collector
- Initiating the negative pressure gradually (starting at -50 mmHg and increasing the pressure in increments of 50 up to 150 mmHg, except if any pain occurs)

All the nursing teams at all the participating centres will be given specific training prior to the trial to ensure that they can technically provide this treatment in the proper manner and that it is provided consistently across the centres. This training will be delivered by the study's designated nurses (see the section on intervention in the study). A tutorial describing how to apply the NPWT will be shown to all the participating centres.

Duration of treatment: the use of NPWT will be maintained until the recovery of the skin has been achieved by the skin graft. An average duration of 3 weeks' treatment is expected in the intervention group.

Tableau 1 : List of NPWT devices validated by HAS (6)

Dispositif	Fabricant (ou distributeur France)
041 Wound	Atmos Médical France SARL
Renasys	Smith and Nephew
V.A.C Therapy	FCI Medical
Venturi	Annie Bauer Confort (fabricant : Talley Medical)
Wound Assist	HNE

2.6.1.1 Standardization of the intervention

The methods for using the NPWT device will be standardised in order to ensure that consistent practices are followed among the centres. The centres participating in the study have been selected for their experience in treating NSTIs/NF and in using the NPWT devices.

However, in order to ensure the consistent use of NPWT during the study, training will be given when setting up the study and every year in each of the participating centres by the study's clinical research nurses.

Furthermore, the study's designated clinical research nurses will provide an on-call telephone service to provide assistance to carers in the participating centres, should a technical problem arise linked to the NPWT. In each centre two nurses belonging to the care team will be appointed to assist the investigator in coordinating and applying the treatment correctly according to the randomization arm.

2.6.1.2 Procedure applied if the intervention can not be applied

If it is impossible to continue the NPWT, it will be discontinued and the local treatment will be continued at the discretion of the doctor treating the patient. The reason for discontinuing the NPWT will be recorded and the patient will not be removed from the study.

2.6.1.3 Common aspects of management of patients of the intervention and control groups

The patients included in the study will be treated in an identical manner for the NSTI/NF, apart from differences linked to the randomization arm. The common treatment will combine the following measures: surgical evaluation several times a week, along with additional debridements if necessary, antibiotic therapy adapted to the micro-organisms identified until a clinical cure is achieved and for a duration of 7 to 15 days, treatment of associated organ failures, support measures (analgesia, nutrition). The wound will be covered with a skin graft with the date when it will be carried out being decided upon by the attending surgeon. The follow-up process after the skin graft will be identical between the two groups. Rehabilitation in an outpatient facility or admission to a rehabilitation centre, depending on the patient's clinical state and needs.

2.6.1.4 Treatments allowed and forbidden including rescue treatments

All treatments are authorised. No treatment will be forbidden while the patient is being cared for, regardless of what stage it is at: initial treatment phase, interventional phase or follow-up phase (Figure 1). The therapeutic intervention evaluated in this trial relates, in fact, to a local treatment and there is no reason for contraindicating therapeutic intervention.

2.7 Summary of the known and foreseeable benefits and risks for the research participants

The benefit/risk ratio of this protocol is clearly in favour of using this treatment.

2.7.1 **Foreseeable benefits**

Based on the numerous beneficial effects locally provided by NPWT and some data arising from the literature (see section 2.3), it is possible to make the assumption that, compared with the patients in the control group (receiving conventional treatment), the patients in the intervention group (receiving NPWT) will benefit by healing more quickly and in a better quality way, potentially resulting in a faster functional recovery of the affected limb, reflected in being able to resume walking sooner. It would seem unrealistic to look for any direct benefit on the mortality rate, given that the intervention being tested is carried out after the infection control phase. On the other hand, a benefit in terms of healing and becoming active again is realistic. The relevance of an endpoint including a functional dimension is corroborated by recent clinical trials testing NPWT after an open fracture of a lower limb (33) or another treatment intervention (intravenous immunoglobulins) in patients affected by an NSTI/NF (37).
We also hypothesize that other aspects pertaining to the dimensions explored by health-related quality of life questionnaires (e.g., Activity of Daily Living and Instrumental Activity of Daily Living) might be improved by the NPWT strategy. We also expect that the NPWT strategy will allow for reducing the number of dressing procedures needed (NPWT dressings are usually changed every three days while conventional dressings are changed daily), overall pain, the risk of local superinfection, the duration of hospital stay.
In case the study is negative, this would provide a strong argument against the use of NPWT in patients with NSTI. Such result would question further using NPWT in this setting.

2.7.2 **Foreseeable risks**

The data arising from the literature has emphasized the excellent tolerance of NPWT devices. The recent randomized controlled feasibility study conducted by Arundel et al. did not report any unexpected serious adverse reaction on 19 patients treated using NPWT for a post-operative wound with healing by secondary intention, compared with 21 patients treated using a conventional dressing (31). The non-serious adverse reactions reported in this trial were as follows: skin irritation (3 patients), dressing coming loose (3 patients), problem with the device's pump (8 patients). In the study conducted by Costa et al. (33), 226 patients with an open fracture of the leg receiving NPWT were compared to 234 patients receiving a standard dressing. In spite of the negative result across all the endpoints, this study made it possible to highlight, across a large cohort of patients, the excellent tolerance of NPWT in terms of local development, risk of infection, haemorrhaging or repeat surgery.

Even if, based on the experience of using the NPWT devices and on the literature data, this treatment would seem to have an excellent safety profile, we will systematically look out for the occurrence of severe haemorrhaging and local superinfections. Any report will be made as part of the vigilance procedure applicable to the product or intervention under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device, etc.) (see section 10 for further information).

3 OBJECTIVES OF THE RESEARCH

3.1 Main objective of the research

To demonstrate in patients who underwent a surgical debridement of the lower limb for NSTI a superiority of a wound dressing strategy using NPWT (intervention) as compared with conventional wound dressing on local healing (complete) and the recovery of walking.
To do this, the time will be recorded when the primary endpoint occurs associating both aspects (see primary endpoint definition below) in relation to the randomization date.

Justification
The ultimate objective of the therapeutic intervention being tested is to facilitate the ideal preparation of the operation wound to be covered by skin following a skin graft, which is clinically relevant in the field of

the mid-term management of NSTI/NF and therefore the full recovery of the patients. If this skin graft is performed under ideal conditions, it should enable the graft to take more quickly and in a better quality way, which means that it will heal sooner, enabling the patient to resume functional activities more quickly. The current trial will only include patients with an NSTI/NF of the lower limbs. Therefore, the endpoint which is most relevant in terms of reflecting functional recovery – while still being patient-centred – is the recovery of walking. Using this type of endpoint is consistent with the primary endpoints used in recent trials testing NPWT in other situations (33) or other interventions during NSTIs/NF (37).

3.2 Secondary objectives

To demonstrate the impact of the intervention (wound dressing with NPWT) on:

1. The functional status at 3 and 6 months
2. Health-related quality of life at 3 and 6 months
3. Pain
4. The number of anesthesia procedures
5. Time to skin grafting
6. Local superinfections
7. Walking capacity at 3 and 6 months
8. The duration of hospital stay
9. The duration of nurse care needed for wound dressing
10. The feasibility of maintaining NPWT until skin grafting
11. The number of surgical procedures performed between randomization and skin grafting
12. The number of surgical procedures performed after skin grafting
13. Mortality at 3 and 6 months

4 DESCRIPTION OF THE RESEARCH

4.1 Primary endpoint

The time elapsed between randomization and the onset of a combined outcome measure including both: **a complete healing of the diseased limb** clinically assessed according to the investigator's judgment (defined by more than 90% of functional skin covering the wound) **and the recovery of walking** (defined by the ability to walk at least 100 steps, corresponding to approximately 30 meters, without help).
The occurrence of this endpoint will be recorded on a weekly basis by a clinical research nurse*, who will be blinded to the therapeutic intervention*, from the time the skin graft is performed and up to a maximum period of 6 months after randomization. A clinical research nurse will go and see patients in the participating centres or in other institutions, if patients have been transferred (e.g. a rehabilitation centre), to record the occurrence of this combined endpoint (examination of the wound and carrying out a walking test). The clinical research nurses will be trained to carry out this assessment. Alternatively, weekly follow-up visits will be set up by the research nurse or the investigator at the investigating center.

4.2 Secondary endpoints

1. ADL score: measured by a research nurse at 3 and 6 months
2. SF-36 score: measured by a research nurse at 3 and 6 months

3. Pain assessment at each wound care by the patient (visual analogic scale), the nurse (behavioral pain scale) and quantification of morphine consumption (in morphine base equivalent): measured by the investigator at each wound care
4. Quantification of the number of anesthesia procedures (general anesthesia, sedation): measured by the investigator at each wound care
5. Time elapsed between randomization and skin grafting: measured by the investigator
6. Number of local superinfection episodes: measured by the investigator
7. Quantification of the walking capacity: measured over one week with a pedometer by the research nurse, at 3 and 6 months
8. Duration of hospital stay: measured by the investigator
9. Quantification of the time needed for each wound care before randomization and skin grafting: this measure will be recorded at each wound care
10. Need for stopping the NPWT
11. Number of surgeries performed between randomization and skin grafting: all surgeries will be recorded, including their date and indication
12. Number of surgeries performed after skin grafting: all surgeries will be recorded, including their date and indication
13. Mortality at 3 and 6 months

5 DESCRIPTION OF RESEARCH METHODOLOGY

5.1 Design of the study

This will be an **open two parallel group randomized controlled** study with **blinded** assessment.
Patients will be eligible for inclusion after a minimum of 5 days after the first surgical debridement.

- 1:1 randomization in 2 arms: **intervention** (negative pressure treatment) versus **control** (conventional dressings) until the skin graft is carried out, to be decided by the attending surgeon.
- It is assumed that the intervention arm will have superiority over the control arm.
- Weekly visits after the skin graft or D21 from a clinical research nurse who is blinded to the therapeutic intervention and will record the occurrence of the primary endpoint, i.e. a **clinical cure** (defined by **complete healing**, which means that at least 90% of the wound's surface is covered, **AND the recovery of walking,** defined by the ability to walk at least 100 consecutive steps unaided). The time of occurrence of the primary endpoint in relation to randomization will be calculated.
- Follow-up visits will be planned by the clinical research nurse at 3 and 6 months to record secondary endpoints.

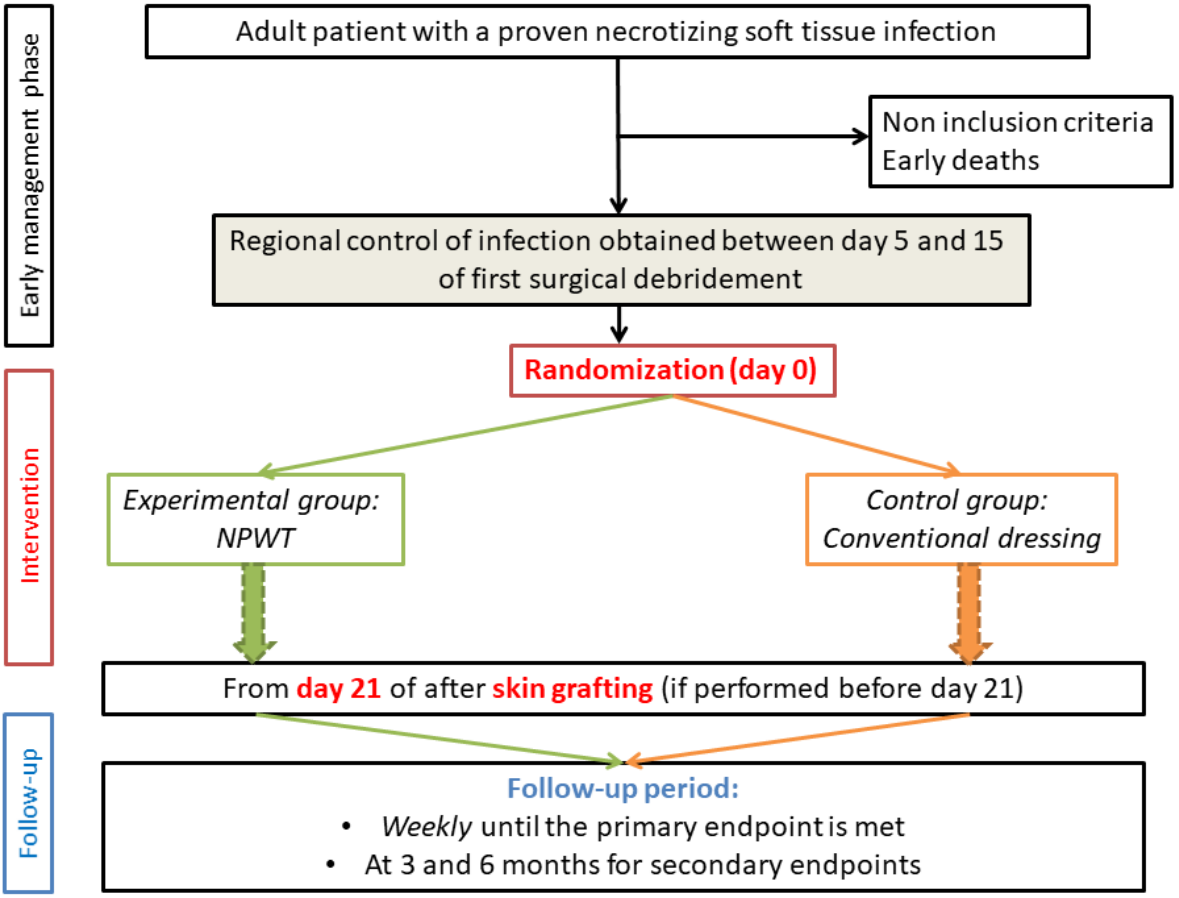


Figure 1 : Study schema

5.2 Number of participating sites

This is a national multi-centre study. Patient inclusion will be facilitated by the participation of a center (Henri Mondor Hospital, Créteil, France), which has created a multidisciplinary team dedicated to the management of NSTI 24 hours a day / 7 days a week. This dedicated team relies on a dermatologist available 24 hours/7 days on site (see more information in the SURFAST network in Addendum 2).
Recruitment will be carried out within the hospital intensive care units of the participating centers (see addendum 1).

5.3 Description of measures taken to reduce and prevent biases

5.3.1 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

5.3.2 Randomization

The process of including and randomizing the patients presenting the selection criteria will be carried out directly by the investigator online (via a secure Internet protocol), using the CleanWeb software, as part of the Public Contract entered into between the AP-HP and TELEMEDICINE TECHNOLOGIES S.A, announced 17 November 2003, with reference no. 033845. The data will be stored centrally on a server hosted in the Department of Operational Services (DSO) in the AP-HP, 67 boulevard Bessières, 75017 PARIS. Randomization will be carried out at least 72 hours after patient admission to the ICU.

The randomization list is drawn up by the Clinical Research Unit (URC des Hôpitaux Universitaires Henri Mondor) before the trial begins. Randomization will be stratified by centre.

The pre-prepared randomization list will be integrated in CSV format into the CleanWeb software, under the control of the unit responsible for the Quality management of risks in the DRCI.

6 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Whose consent must be obtained	**Who informs the individual and collects his/her consent**	**At what point the individual is informed**	**At what point the consent of the individual is obtained**
• The individual participating in the study	• The principal investigator or collaborating physician declared and trained in the study (ICU)	• If possible, before inclusion in the study • If not, as soon as the state of patient awareness allows it	• If possible, before inclusion in the study • If not, as soon as the state of patient awareness allows it
• The trustworthly person	• The principal investigator or collaborating physician declared and trained in the study (ICU)	• If possible, before patient inclusion in the study • Otherwise as soon as possible	• If possible, before patient inclusion in the study • Otherwise as soon as possible

6.1 Schedule for the study

Duration of enrolment period The length participation for participants, of which: • Maximum period before screening and enrolment • Duration of interventions performed: • Maximal duration of follow-up:	36 months 10 days variable 6 months
Total study duration:	**maximum of 42 months + 6 days**

6.1.1 Screening visit

The inclusion and exclusion criteria will be examined every morning from the 3rd day following the 1st debridement in all the patients admitted to the participating centers for an NSTI/NF of the lower limb. This visit will provide an opportunity, if necessary, to plan when to obtain consent for participation from the person taking part in the study or from a relative.

6.1.2 Information and consent

Prior to any examination or activity linked to the study, the investigator will obtain the free, informed and written consent of the person taking part in the study or a member of their family.

A detailed description of the methods used to provide information and obtain consent is given in Chapter 15 (ethical and legal aspects).

In practical terms, consent will be sought as follows:

1. If the patient is capable of giving consent, the investigator will obtain the patient's written consent after providing information explaining the study.
2. If the patient is unable to give consent, the investigator will obtain the written consent of the family or of the trusted person (Article L1122-1-3 of the French Public Health Code).
3. If the patient is unable to give consent and there is no family or trusted person available at the time of validating the selection criteria, the patient will be included in an emergency procedure (Article L1122-1-3 of the French Public Health Code).

Proceeding with the inclusion of the patient in emergency is justified by the following arguments: i) NSTIs/NF are clinical conditions posing a high risk of mortality and secondary disability; ii) the data available on NPWT suggests that its use is particularly beneficial if initiated at an early stage.
In the cases in 2. and 3., consent to continue the study will be obtained from the patient as soon as he or she has recovered the ability to give consent.

6.1.3 Baseline visit or randomization visit

The inclusion visit takes place on the day when the patient is included (between D5 and D15 of the 1st surgical debridement). The date when the patient was admitted to the hospital and ICU will be recorded, along with the date and time of randomization. The following variables will be recorded:

- **Medical history and clinical examination:**
    - Demographic variables, main active co-morbidities;
    - Severity scores: SAPS II on admission (worst values in the first 24 hours after admission to ICU for each of the score items), SOFA on admission and on the day of inclusion (see Addendum 3);
    - Characteristics of the NSTI/NF: topography, number and date of debridements performed;
    - Antibiotics administered: on admission (molecules, duration);
    - Evaluation of quality of life before admission, when possible to carry it out: measurement of SF-36 score;
    - Evaluation of independence before admission (Clinical frailty scale; see Addendum 3);
    - Evaluation of pain: by the patient (visual analogue scale) and by the carers (Behavioral Pain Scale; see Addendum 3).
- **Biological examinations:**

- Microbiological data: blood cultures on admission, intra-operative samples
- Standard blood biochemistry: full blood count (haemoglobin, white blood cells, platelets); urea, creatinine, CPK, arterial or venous lactates, procalcitonin, albumin, pre-albumin.

6.1.4 Follow-up visits

The follow-up visits will be planned according to two separate stages in the study:

- **During the intervention period** (between randomization and cutaneous recovery via skin graft, see Figure 1 and Table in section 5.7 for details and visits time points): visits made by the investigators from the participating centres, recording:
  - Evaluation of pain: by the patient (visual analogue scale) and by the carers (Behavioral Pain Scale)
  - Dressing:
    - change (yes/no); procedure duration (in min.); impossible to maintain NPWT and the reason, if relevant (pain, bleeding, superinfection, leaks, other)
    - for the control arm: type of dressing used (see table of dressings; Addendum 4)
    - for the intervention arm: pressure applied (in mmHg), volume collected by the collector
  - Anesthetic procedure: yes/no and molecule(s) (morphine and other opioids, ketamine) and dose administered
  - Administration of analgesia, dose
  - Local superinfection
  - Timeframe to carry out skin graft in relation to randomization
  - Recording the occurrence of adverse events: local superinfection, haemorrhaging, pain preventing maintenance of NPWT

- **During the follow-up period** (from the skin graft (or day 21 if skin graft not performed at this time) up to 6 months post-randomization): weekly visits during 12 weeks made by the clinical research nurses (at home or at the investigating center) or until the primary endpoint has been achieved and at three and six months post-randomization.
  The following items will be recorded:
  - Evaluation of *ability to walk* (ability to walk at least 100 consecutive steps unaided)
  - Evaluation of *how the wound is healing* (covering at least 90% of the wound's surface); weekly photographs will be taken to allow the research nurse to make between-weeks comparisons (if needed).
  - Length of stay in hospital (the patient will be discharged after the skin graft, but sometimes before the primary endpoint is reached).
  - At 3 and 6 months ± 2 days : measurement of SF-36 scores (38) (Addendum 3), ADL (39) (Addendum 3), quantifying the walking activity using a pedometer (fitted by the clinical research nurse to record activity over a 7-day period)

NB : The visit at 3 months and the weekly visit can be combined

6.1.5 Last study visit

The last study visit will take place 6 months ± 2 days after inclusion. The clinical research nurse will go to see the patient (at home or in a rehabilitation centre) to record the data from the pedometer fitted a week earlier and to collect the data from the quality of life questionnaires and from evaluating the patient's functional independence (SF-36, ADL, Clinical Frailty Scale).

6.2 Table summarising the chronology of the study

Actions	D-2 to D0 (Screening visit)	D0 (Baseline visit)	D0 to DX	D3, D7, D10, D14, D21	Skin grafting (DX)	Each week during 12 weeks after DX or D21[a]	M3 ± 2d and M6 ± 2d post-randomization
Verification of inclusion and exclusion criteria	X						
Informed consent	X						
Randomization		X					
Comorbidities		X					
Clinical frailty scale		X					X (M6 only)
SAPS II		X					
Clinical examination		X					
SOFA		X					
Microbiology[b]		X					
Blood tests[c]		X					
Wound care, anesthesia procedures			X				
Photographs		X				X	
pain assessment (visual analogue scale, Behavioral Pain Scale)		X	X			X	
Activity of Daily Living		X					X
Instrumental Activity of Daily Living		X					X
Walking distance[d]							X
SF-36 score		X					X
Ability to walk[e]						X	
Skin healing[f]						X	
Side effects			X			X	X

[a] If skin grafting has not been performed before day 21; [b] Blood cultures upon admission, per-operative samples ; [c] Complete blood count, urea, creatinine, lactates, CPK, procalcitonine, albumine, pre-albumine ; [d] A pedometer will be used for 7 days; [e] At least 100 steps without any help; [f] Wound covered for more than 90%; D, day; M, month

6.3 Distinction between standard care and study

The entire course of treatment received by the patient will be in line with current recommendations, especially the aspects relating to early surgery and probabilistic treatment with antibiotics (5, 9) and are, therefore, part of the care provided. The dressing strategy (NPWT or conventional dressing) is also part of the care and will be applied according to the centres' usual procedures. No additional examination will be carried out exclusively for the needs of the study. The variables recorded include some recorded during the study (see the table below).

Tableau 2: "Standard care" vs. "additional interventions" required specifically for the study

Interventions carried out for the research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures added for <u>research purposes</u>**
Treatments	conventional dressings, NPWT devices	
Imaging	All	
Visits	All visits until Skin healing	Weekly visits during 12 weeks after skin grafting or day 21 and visits at 3 and 6 months post-randomization
Inclusion and randomization		X
SAPS II	x	
Clinical examination	X	
SOFA	X	
Microbiology	X	
Blood tests	X	
Wound care, anesthesia procedures	X	
photographs		X
pain assessment	X	
Walking distance		At 3 and 6 months
SF-36 score, ADL		At 3 and 6 months
Ability to walk	X	
Surveillance	Superinfection, bleeding, pain assessment	

6.4 Photographs – photographs collection

Anonymized photographs will be recorded by the centers and will be uploaded on Cleanweb.

7 <u>ELIGIBILITY CRITERIA</u>

7.1 Inclusion criteria

- Age ≥ 18 years
- Written informed consent
- NSTI/NF of the lower limb clinically suspected and confirmed by surgery with a first debridement performed since 5 days or more
- Infection considered controlled (i.e., no more surgical debridement is necessary)
- Last debridement performed at least 72 hours before

- Affiliation to a social security system

7.2 Exclusion criteria

- Limited life expectancy
- NPWT already initiated for the current NSTI/NF episode
- 1st surgical debridement performed less than 5 days or more than 15 days before
- High risk of bleeding (blood vessels exposed)
- Local neoplasia
- Risk of organ or peripheral nerve injury
- Impossibility to set up a NPWT dressing hermetically
- Limb amputation
- Patient unable to walk without help
- Women who are pregnant or are breast-feeding, or are of childbearing age and do not use or do not plan to use acceptable birth control measures
- Patients under legal protection
- Prisoners

7.3 Recruitment procedure

The study is conducted on a multicentre basis. Subjects will be recruited according to the activity of the centres of expertise. Recruitment will be facilitated by the SURFAST care network, which is devoted to the treatment of NSTIs/NF, set up at the Henri Mondor Hospital and in the process of being accredited by AP-HP and the Regional Health Agency (Addendum 2). The participating centres have been selected on the basis of their broad experience of clinical trials in ICUs, in treating patients with an NSTI/NF and their technical support centre, enabling them to treat these patients 24 hours a day and 7 days a week. Patients will be recruited during their stay in ICU.

	Number of participants
Total number of participants selected	130
Number of centres	19
Enrolment period (months)	36
Number of participants/centre	7
Number of participants/centre/month	**0.2**

The average capability for recruiting centres participating in the study is shown in the table below. The following provisions have been adopted to ensure the best possible recruitment of patients:

- Participating centres have been selected based on their expertise and their case volume of NSTIs/NF patients (19);
- The surgeons involved in treating the NSTIs/NF in each of the participating centres have been contacted and agreed to participate in the study;
- As mentioned above, the coordinating centre (Henri Mondor, AP-HP) has developed the SURFAST network, devoted to dealing with NSTIs/NF. The annual recruitment is on the rise since 2012 (date when network set up; see figure shown in Addendum 2). In addition, the coordinating centre is the only centre in the Île-de-France which provides consultations for dermatological emergencies, with a

dermatologist being available 24 hours / 7 days, allowing patients coming from other hospitals to be recruited.

- The average anticipated capability for recruiting investigation centres is indicated in the file "PHRC_19-0209-DE PROST-Centres_20190910", submitted with the protocol and in the table below:

	Theoretical recruitment capability	
Centre	**Per Month**	**For the whole Study (36 months)**
AP-HP (H Mondor, medical ICU)	0.3	10
AP-HP (H Mondor, surgical ICU)	0.2	6
AP-HP (H Mondor, Dermatology)	0.2	8
AP-HP (Saint-Antoine, medical ICU)	0.2	8
AP-HP (Bichat, medical ICU)	0.2	8
AP-HP (Bichat, surgical ICU)	0.2	8
AP-HP (Cochin, medical ICU)	0.2	6
AP-HP (Louis Mourier, ICU)	0.2	6
AP-HP (Avicenne, ICU)	0.2	6
AP-HP (Saint-Louis, Burns ICU)	0.2	8
AP-HP (Kremlin-Bicêtre, medical ICU)	0.2	6
AP-HP (Ambroise Paré, medico-surgical ICU)	0.2	6
CH Victor Dupouy, Argenteuil (ICU)	0.3	10
Bégin Military Training Hospital, Saint-Mandé (ICU)	0.2	6
CH Sud Francilien, Corbeil (ICU)	0.2	6
CH Versailles, Le Chesnay (medical ICU)	0.2	6
Hôpital R. Salengro, Lille (ICU)	0.2	6
Hôpital Edouard Herriot (Lyon, ICU)	0.2	6
Hospices Civils de Lyon (ICU)	0.2	4
Total	**4.0**	**130**

8 TERMINATION RULES

Several situations are possible:

- Temporary discontinuation : the investigator must document the reason for the arrest and its recovery in the source file of the subject and the CRF
- Premature discontinuation, but the participant remains enrolled in the study until the end of his/her participation: the investigator must document the reason

8.1 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, the primary and secondary endpoints, as well as safety assessment will be collected by the managing clinician (NB: this must be stated in the information and consent form).
- Premature exit during the interventional phase will result in the clinicians pursuing standard treatments (i.e., either NPWT or conventional treatment), as clinically assessed; Premature exit after the interventional phase will not affect the participant's standard ongoing care. The patient will be followed-up as needed by the managing clinician.
- In case of serious adverse events, see the corresponding section on vigilance.

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

8.1.1 Full or partial discontinuation of the study

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

9 EFFICACY ASSESSMENT

9.1 Description of efficacy assessment parameters

Primary endpoint: following skin grafting (day X on table summarizing the chronology of the study available at paragraph 6.2), weekly visits will be performed by a dedicated research nurse and will allow for measuring the two components of the primary endpoint: the ability to walk more than 100 steps without help and a complete skin healing (defined by more than 90% of the wound covered by functional skin).

Secondary endpoints:
For secondary endpoints occurring before skin grafting: these will be recorded by the investigator during wound care visits.
For secondary endpoints occurring after skin grafting: these will be recorded by weekly visits performed by a dedicated research nurse.

9.2 Scheduled methods and timetable for measuring, collecting and analysing the efficacy assessment parameters

See the study schema (Figure 1) and the table summarizing the chronology of the study available (paragraph 6.2).

10 VIGILANCE

During this research, adverse events (serious and otherwise) do not need to be reported to the sponsor. The report must instead be made as part of the vigilance procedure applicable to the product or intervention under investigation (pharmacovigilance for a drug product; medical device vigilance for a medical device, etc.).

11 SPECIFIC STUDY COMMITTEES

The characteristics of the trial entail the setting up of a steering committee and a committee for validating critical events. The characteristics of the device being tested, widely used in current practice, the study methodology and its implementation methods do not require an independent supervisory committee to be set up.

11.1 Steering Committee

This committee comprises the following members: Prof N de PROST (coordinating investigator, Intensive Care Unit, Hôpital Henri Mondor); Prof. B GIRAUDEAU (methodologist, CHU de Tours), D. SCHMITZ (project manager, URC des Hôpitaux Universitaires Henri Mondor) and the DRCI project manager. It will define the general organization and operation of the study and will coordinate the information. This committee will initially determine the methodology to be used and will supervise the operation of the study, especially in terms of tolerance and adverse events. The committee will decide on any relevant modification to the protocol required to run the trial, in particular:

- Measures to help facilitate recruitment in the trial;
- Amendments to the protocol before they are presented to the ERC;
- The discussion of the results and strategy for publishing these results.

The committee will meet before the trial commences and then every time when required. At the end of the meeting, the sponsor must be informed of any decision requiring rapid intervention by the latter. Decisions relating to a major amendment or modification to the budget will have to be approved by the sponsor.

11.2 Scientific Committee

Not applicable.

11.3 Endpoint Adjudication Committee

Not applicable.

12 DATA MANAGEMENT

12.1 Data collection procedures

An investigator will inform the patient about the study and obtain his or her written consent before carrying out any activity specifically related to the study.
The investigating team will be responsible for gathering all the study data. It will also have to input the data on the e-CFR system and ensure that source documents are available to enable it to be validated.

12.2 Identification of data recorded directly in the CRFs which will be considered as source data

Not applicable

12.3 Right to access data and source documents

12.3.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring, quality control and auditing the research have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

12.3.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator, or by the hospital in the case of a hospital medical file, for 15 years.

In the context of the study, the list of source document: medical file, original biological examination results, rating scales.

12.3.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the Code de la Santé Publique (French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.

These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the Code Pénal [French Criminal Code]).

During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.

Under no circumstances shall the names and addresses of the participants involved be shown.

Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.

The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.4 Data processing and storage of research documents and data

12.4.1 Identification of the data processing manager and location(s)

The data-management work will be conducted by URC Henri Mondor (Créteil). The data-manager will design the eCRF on CleanWEB Software.

Data will be input by the investigating team electronically (using CleanWeb) via a web browser. Analysis will be carried out after the database is locked by Prof. Bruno Giraudeau.

12.4.2 Data entry

Non-identifying data will be entered electronically via a web browser by the investigative team.

12.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses

The statistical analysis will be carried out at CIC INSERM 1415 under the responsibility of Pr Bruno Giraudeau. The software applications SAS 9.4 and R 3.3 (or later versions) will be used. A statistical analysis plan will be defined beforehand. Any amendment to this plan must be made before the study is unblinded. The statistical analysis will be conducted according to the Intention To Treat (ITT) principle. The results will be reported in compliance with the recommendations in the CONSORT Statement and its extension for non-pharmacological interventions (http://www.consort-statement.org/).

13.2 Calculation hypotheses for the number of participants required and the result

The main endpoint is a survival type endpoint. It is assumed that the clinical cure endpoint will be observed for 70% of patients in the intervention group versus 50% of patients in the control group 6 weeks post-randomization, which is equivalent to an hazard-ratio of 1.94. To reach an 80% power, we would need to observe a total of 103 events. Therefore, it is planned to include 130 patients.

13.3 Baseline characteristics

The inclusion characteristics will be reported using descriptive statistics. No statistical test will be carried out.

13.4 Group comparisons

The ITT principle will apply.

If patients withdrew their consent, only data collected until the consent withdrawal will be used.

However, if patients withdrew their consent and be opposed to the use of their data, these patient's data would be withdrawn from the analysis, thus satisfying the French law..

Otherwise, it is unlikely that there will be anyone dropping out. However, should this happen, they would be censured from the last follow-up date.

13.5 Statistical analysis of the primary endpoint

The time before the clinical response occurs will be estimated in each of the groups using the Kaplan-Meier estimator. An inter-group comparison will be carried out using a log-rank test.

13.6 Statistical analysis of secondary outcome measures

- ADL score: measured by the clinical research nurse who goes to see the patients at 3 and 6 months

  The change in the score will be analyzed using a mixed linear model. If there is no convergence of the model (due to there only being a maximum of two points per patient), the M3 and M6 data will be analyzed independently using Student t-tests or Wilcoxon non-parametric tests,

- SF-36 score: measured by the clinical research nurse who goes to see the patients at 3 and 6 months

  The change in the score will be analyzed using a mixed linear model. If there is no convergence of the model (due to there only being a maximum of two points per patient), the M3 and M6 data will be analyzed independently using Student t-tests or Wilcoxon non-parametric tests,

- Pain assessment for each dressing by the patient (visual analogue scale), the carer (Behavioural Pain Scale, BPS) and by quantifying the amount of morphine analgesia taken by the patient (cumulative dose of morphine base): measured by the investigator for each dressing.

  An estimate will be made of the average pain score for each patient, based on all the dressings applied. In the intervention group pain will be quantified (VAS and BPS) for each dressing (applied every 72 hours on average); in the non-intervention group, pain will be recorded while each dressing is being applied (carried out every day on average), then averaged over three days. Change in pain score will be analyzed using a mixed linear model.

  With regard to the consumption of morphine analgesics, the inter-group comparison of the cumulative dose will be carried out using a Student t-test or Wilcoxon test, if necessary.

- Quantifying the number of anaesthetic procedures (general anaesthesia, sedation): measured by the investigator for each dressing.

  The number of anaesthetic procedures will be compared using a negative binomial model.

- Time elapsed between randomization and carrying out the skin graft: measured by the investigator.

  Time will be compared using a log-rank test.

- Number of local superinfection episodes: measured by the investigator

  The number of local superinfection episodes will be compared using a negative binomial model.

- Quantifying walking activity: measured over a week using a pedometer by the clinical research nurse who goes to see the patients at 3 and 6 months

  Walking activity will be analyzed using a mixed linear model. If there is no convergence of the model (due to there only being a maximum of two points per patient), the M3 and M6 data will be analyzed independently using Student t-tests or Wilcoxon non-parametric tests,

- Length of stay in hospital: measured by the investigator

  Length of stay in hospital will be compared using a log-rank test.

- Quantifying the time required to change the dressings between randomization and the skin graft: this measurement will be taken for each dressing.

  The amount of time calculated as being needed to change the dressings will be averaged across all the dressings applied to the same patient. The inter-group comparison will then be carried out using a Student t-test or Wilcoxon non-parametric test.

- Need to discontinue NPWT

  An estimate will be made of the number of instances where treatment is discontinued and the proportion of patients affected by this discontinuation.

- Number of repeat interventions between randomization and carrying out the skin graft: any repeat intervention will be recorded, as well as its date and reason for it.

  The number of repeat interventions will be compared using a negative binomial model.

- Number of repeat interventions after carrying out the skin graft (follow-up phase): any repeat intervention will be recorded, as well as its date and reason for it.

  The number of repeat interventions will be compared using a negative binomial model.

- Mortality at 3 and 6 months

  Mortality rates will be compared using chi-square tests or Fisher exact tests if necessary.

14 QUALITY CONTROL AND ASSURANCE

14.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.
For this purpose, the sponsor will define a strategy for opening the centers and may, if necessary, set up a quality control of the data.

14.1.1 Strategy for opening the centres

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan. The coordinator centre will be opened first. The opening of other participating sites will follow according to their enrolment potential and availability.

14.1.2 Data quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate.

14.2 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.

When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The original of this document will be archived by the sponsor. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

14.3 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor. These non-compliances will be managed in accordance with the sponsor's procedures.

14.4 Audit

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audit is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's audit requirements.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

14.5 Principal Investigator’s commitment to assume responsibility

Before starting the study, each investigator will give the sponsor’s representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with regulations, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor’s representative.
The investigators and their staff will sign a delegation of duties form specifying each person’s role and will provide their CVs.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

In accordance with Article L.1122-1-1 of the *Code de la Santé Publique* (French Public Health Code), no research involving human participants with minimal risks and burden can be carried out on a person without his/her freely given and informed consent, obtained expressly after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given written informed consent will be obtained by the principal investigator, a physician representing the investigator or a qualified person, before the person is enrolled on the study**.**

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator, the physician representing the investigator or a qualified person, will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent or consent from any other person in the cases set forth by Articles L. 1122-1-1 to L. 1122-2 of the Code de la Santé Publique (French Public Health Code) as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

Special circumstances: If the person is physically unable to give his or her written consent, consent may be witnessed, in descending order of priority, from a trustworthy person, a family member or a close relative. These persons must have be fully independent of the investigator and of the sponsor**.**

15.2 Prohibition from participating in another clinical study or exclusion period after the study, if applicable

No exclusion period of participation after the participant has finished this study is defined in the context of this research.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without first speaking to the doctor. A participation in a non-interventional, observational study can be allowed during the trial.

15.3 Compensation for participants

No remuneration is provided to patients for participating in the study to compensate for constraints linked to the study.

15.4 Registration on the national register of study participants to studies involving human participants

Not applicable.

15.5 Legal obligations

Assistance Publique-Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique-Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

15.6 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain approval from the CPP (Research Ethics Committee) for its Minimal Risks and Burden research study, within the scope of the committee's authority and in accordance with in force legislation and regulatory requirements.

15.7 Informing the ANSM

AP-HP will send the approval from the CPP (Research Ethics Committee) and the summary of the protocol to the ANSM for information.

15.8 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is not governed by the CNIL "Reference Method" (MR-001) since inclusions could be realized in an emergency situation without collection of consent at the time of inclusion.

The sponsor must obtain the authorisation of the CNIL (French Data Protection Agency) before implementing any data processing involving the data required to conduct the research.

Collaborations could be established according to the evolution of scientific knowledge and would require the sending of data outside French territory in a European Union country or an "adequate" country and outside the European Union.

15.9 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain approval from the CPP (Research Ethics Committee) before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

15.10 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study

15.11 Archiving

Specific documents for a research involving human participants with Minimal Risks and Burden are to be archived by the investigator and the sponsor for 15 years following the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- Study binders for the investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - decisions of the CPP (Research Ethics Committee)
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- Data collection documents

16 FUNDING AND INSURANCE

16.1 Funding sources

This research is funded by the PHRC-N 2019 (Hospital Clinical Research Program - French Ministry of Health).

16.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

17 PUBLICATION RULES

17.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "**AP-HP**" first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

17.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

"The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)"

17.3 Mention of the financial backer in the acknowledgements of the text

The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2019 (French Ministry of Health)

This study has been registered on the website http://clinicaltrials.gov/ under number NCT05071443.

18 BIBLIOGRAPHY

1. Stevens DL, Bryant AE. Necrotizing Soft-Tissue Infections. N Engl J Med. 2017 Dec 7;377(23):2253–65.
2. Pham TN, Moore ML, Costa BA, Cuschieri J, Klein MB. Assessment of functional limitation after necrotizing soft tissue infection. J Burn Care Res. 2009 Apr;30(2):301–6.
3. Huang W-S, Hsieh S-C, Hsieh C-S, Schoung J-Y, Huang T. Use of vacuum-assisted wound closure to manage limb wounds in patients suffering from acute necrotizing fasciitis. Asian J Surg. 2006 Jul;29(3):135–9.
4. Dumville JC, Owens GL, Crosbie EJ, Peinemann F, Liu Z. Negative pressure wound therapy for treating surgical wounds healing by secondary intention. Cochrane Database Syst Rev. 2015 Jun 4;(6):CD011278.
5. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52.
6. Haute Autorité de Santé - Traitement des plaies par pression négative (TPN) : des utilisations spécifiques et limitées - Fiche BUTS [Internet]. [cited 2018 Jul 17]. Available from: https://www.has-sante.fr/portail/jcms/r_1438055/fr/traitement-des-plaies-par-pression-negative-tpn-des-utilisations-specifiques-et-limitees-fiche-buts
7. van Stigt SFL, de Vries J, Bijker JB, Mollen RMHG, Hekma EJ, Lemson SM, et al. Review of 58 patients with necrotizing fasciitis in the Netherlands. World J Emerg Surg. 2016;11:21.
8. Nuwayhid ZB, Aronoff DM, Mulla ZD. Blunt trauma as a risk factor for group A streptococcal necrotizing fasciitis. Ann Epidemiol. 2007 Nov;17(11):878–81.
9. Kiat HJ, En Natalie YH, Fatimah L. Necrotizing Fasciitis: How Reliable are the Cutaneous Signs? J Emerg Trauma Shock. 2017 Dec;10(4):205–10.
10. [Management of erysipelas and necrotizing fasciitis (long text)]. Ann Dermatol Venereol. 2000 Dec;127(12):1118–37.
11. de Prost N, Lipman J, Mimoz O. Therapeutic targets in necrotizing soft tissue infections. Intensive Care Med. 2017;43(11):1717–9.
12. Darenberg J, Ihendyane N, Sjölin J, Aufwerber E, Haidl S, Follin P, et al. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003 Aug 1;37(3):333–40.
13. Kadri SS, Swihart BJ, Bonne SL, Hohmann SF, Hennessy LV, Louras P, et al. Impact of Intravenous Immunoglobulin on Survival in Necrotizing Fasciitis With Vasopressor-Dependent Shock: A Propensity Score-Matched Analysis From 130 US Hospitals. Clin Infect Dis. 2017 Apr 1;64(7):877–85.
14. Madsen MB, Skrede S, Bruun T, Arnell P, Rosén A, Nekludov M, et al. Necrotizing soft tissue infections - a multicentre, prospective observational study (INFECT): protocol and statistical analysis plan. Acta Anaesthesiol Scand. 2018 Feb;62(2):272–9.
15. Shaw JJ, Psoinos C, Emhoff TA, Shah SA, Santry HP. Not just full of hot air: hyperbaric oxygen therapy increases survival in cases of necrotizing soft tissue infections. Surg Infect (Larchmt). 2014 Jun;15(3):328–35.
16. Massey PR, Sakran JV, Mills AM, Sarani B, Aufhauser DD, Sims CA, et al. Hyperbaric oxygen therapy in necrotizing soft tissue infections. J Surg Res. 2012 Sep;177(1):146–51.
17. Hua C, Bosc R, Sbidian E, De Prost N, Hughes C, Jabre P, et al. Interventions for necrotizing soft tissue infections in adults. Cochrane Database Syst Rev. 2018 31;5:CD011680.
18. Elliott DC, Kufera JA, Myers RA. Necrotizing soft tissue infections. Risk factors for mortality and strategies for management. Ann Surg. 1996 Nov;224(5):672–83.
19. Audureau E, Hua C, de Prost N, Hemery F, Decousser JW, Bosc R, et al. Mortality of necrotizing fasciitis: relative influence of individual and hospital-level factors, a nationwide multilevel study, France, 2007-12. Br J Dermatol. 2017 Apr 27;
20. Yang D, Davies A, Burge B, Watkins P, Dissanaike S. Open-to-Air Is a Viable Option for Initial Wound Care in Necrotizing Soft Tissue Infection that Allows Early Detection of Recurrence without Need for Painful Dressing Changes or Return to Operating Room. Surg Infect (Larchmt). 2018 Jan;19(1):65–70.

21. El-Menyar A, Asim M, Mudali IN, Mekkodathil A, Latifi R, Al-Thani H. The laboratory risk indicator for necrotizing fasciitis (LRINEC) scoring: the diagnostic and potential prognostic role. Scand J Trauma Resusc Emerg Med. 2017 Mar 7;25(1):28.
22. Baharestani MM. Negative pressure wound therapy in the adjunctive management of necrotizing fascitis: examining clinical outcomes. Ostomy Wound Manage. 2008 Apr;54(4):44–50.
23. Yanaral F, Balci C, Ozgor F, Simsek A, Onuk O, Aydin M, et al. Comparison of conventional dressings and vacuum-assisted closure in the wound therapy of Fournier's gangrene. Arch Ital Urol Androl. 2017 Oct 3;89(3):208–11.
24. Guy H, Grothier L. Using negative pressure therapy in wound healing. Nurs Times. 2012 Sep 4;108(36):16, 18, 20.
25. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997 Jun;38(6):553–62.
26. General USD of H and HSO of I. Comparison of Prices for Negative Pressure Wound Therapy Pumps. Department of Health and Human Services, Office of Inspector General; 2009. 23 p.
27. Putnis S, Khan WS, Wong JM-L. Negative Pressure Wound Therapy – A Review of its Uses in Orthopaedic Trauma. Open Orthop J. 2014 Jun 27;8:142–7.
28. Saxena V, Hwang C-W, Huang S, Eichbaum Q, Ingber D, Orgill DP. Vacuum-assisted closure: microdeformations of wounds and cell proliferation. Plast Reconstr Surg. 2004 Oct;114(5):1086–96; discussion 1097-1098.
29. Winter GD, Scales JT. Effect of air drying and dressings on the surface of a wound. Nature. 1963 Jan 5;197:91–2.
30. Monsen C, Wann-Hansson C, Wictorsson C, Acosta S. Vacuum-assisted wound closure versus alginate for the treatment of deep perivascular wound infections in the groin after vascular surgery. J Vasc Surg. 2014 Jan;59(1):145–51.
31. Biter LU, Beck GMN, Mannaerts GHH, Stok MM, van der Ham AC, Grotenhuis BA. The use of negative-pressure wound therapy in pilonidal sinus disease: a randomized controlled trial comparing negative-pressure wound therapy versus standard open wound care after surgical excision. Dis Colon Rectum. 2014 Dec;57(12):1406–11.
32. Arundel C, Fairhurst C, Corbacho-Martin B, Buckley H, Clarke E, Cullum N, et al. Pilot feasibility randomized clinical trial of negative-pressure wound therapy versus usual care in patients with surgical wounds healing by secondary intention. BJS Open. 2018 Jun;2(3):99–111.
33. Stannard JP, Volgas DA, Stewart R, McGwin G, Alonso JE. Negative pressure wound therapy after severe open fractures: a prospective randomized study. J Orthop Trauma. 2009 Sep;23(8):552–7.
34. Costa ML, Achten J, Bruce J, Tutton E, Petrou S, Lamb SE, et al. Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb: The WOLLF Randomized Clinical Trial. JAMA. 2018 12;319(22):2280–8.
35. Bronchard R, de Vaumas C, Lasocki S, Jabbour K, Geffroy A, Kermarrec N, et al. Vacuum-assisted closure in the treatment of perineal necrotizing skin and soft tissue infections. Intensive Care Med. 2008 Jul;34(7):1345–7.
36. Ferreira PC, Reis JC, Amarante JM, Silva AC, Pinho CJ, Oliveira IC, et al. Fournier's gangrene: a review of 43 reconstructive cases. Plast Reconstr Surg. 2007 Jan;119(1):175–84.
37. Madsen MB, Hjortrup PB, Hansen MB, Lange T, Norrby-Teglund A, Hyldegaard O, et al. Immunoglobulin G for patients with necrotising soft tissue infection (INSTINCT): a randomized, blinded, placebo-controlled trial. Intensive Care Med. 2017 Nov;43(11):1585–93.
38. McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247–63.
39. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. STUDIES OF ILLNESS IN THE AGED. THE INDEX OF ADL: A STANDARDIZED MEASURE OF BIOLOGICAL AND PSYCHOSOCIAL FUNCTION. JAMA. 1963 Sep 21;185:914–9.

19 LIST OF ADDENDA

19.1 Addendum 1: List of investigators

N° centre	Address of the study location	Title	First name Surname	Telephone/E-mail
1	HOPITAL HENRI MONDOR, AP-HP Medical ICU 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil	Pr	Nicolas DE PROST	Tel: 01 49 81 21 11 E-mail: nicolas.de-prost@aphp.fr
2	HOPITAL HENRI MONDOR, AP-HP Surgical ICU 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil	Dr	Quentin DE ROUX	Tel: 01 49 81 21 11 E-mail: quentin.deroux@aphp.fr
3	HOPITAL HENRI MONDOR, AP-HP Dermatology 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil	Dr	Camille HUA	Tel : 01 49 81 21 11 E-mail : camille.hua@aphp.fr
4	HOPITAL SAINT-ANTOINE, AP-HP Medical ICU 184, rue du Faubourg Saint-Antoine 75012 Paris	Dr	Tomas URBINA	Tel : 01 49 28 20 00 E-mail : tomas.urbina@aphp.fr
5	HOPITAL BICHAT, AP-HP Medical ICU 46 rue Henri Huchard 75018 Paris	Pr	Romain SONNEVILLE	Tel: 01 40 25 77 02 E-mail: romain.sonneville@aphp.fr
6	HOPITAL BICHAT, AP-HP Surgical ICU 46 rue Henri Huchard 75018 Paris	Pr	Philippe MONTRAVERS	Tel: 01 40 25 83 55 E-mail: philippe.montravers@aphp.fr
7	HOPITAL COCHIN, AP-HP Medical ICU 27 rue du Faubourg Saint-Jacques 75014 Paris	Pr	Frédéric PENE	Tel: 01 58 41 46 77 E-mail: frederic.pene@aphp.fr
8	HOPITAL LOUIS-MOURIER, AP-HP ICU 178 rue des Renouillers 92700 Colombes	Pr	Damien ROUX	Tel: 01 47 60 68 33 E-mail: damien.roux@aphp.fr
9	HOPITAL AVICENNE, AP-HP ICU 125 rue de Stalingrad 93000 Bobigny	Pr	Stéphane GAUDRY	Tel: 01 47 60 68 55 E-mail: stephane.gaudry@aphp.fr
10	HOPITAL SAINT-LOUIS, AP-HP Burn ICU 1 avenue Claude Vellefaux 75010 Paris	Pr	Kevin SERROR	Tel: 01 42 49 98 07 E-mail: kserror@gmail.com
11	HOPITAL BICÊTRE, AP-HP Medical ICU 78 rue du Général Leclerc 94270 Le Kremlin-Bicêtre	Pr	Xavier MONNET	Tel: 01 45 21 30 61 E-mail: xavier.monnet@aphp.fr

12	HOPITAL AMBROISE PARE ICU 9, avenue Charles de Gaulle 92100 Boulogne-Billancourt	Pr	Antoine VIEILLARD-BARON	Tel : 01 49 09 50 00 E-mail : antoine.vieillard-baron@aphp.fr
13	CENTRE HOSPITALIER VICTOR DUPOUY ICU 101 rue du Lieutenant Colonel Prudhon 95100 Argenteuil	Dr	Damien CONTOU	Tel: 01 34 23 11 73 E-mail: damien.contou@ch-argenteuil.fr
14	HÔPITAL D'INSTRUCTION DES ARMEES BEGIN ICU 69 avenue de Paris 94160 Saint-Mandé	Dr	Clément DUBOST	Tel: 01 43 98 50 00 E-mail: clement.dubost@hotmail.fr
15	CENTRE HOSPITALIER SUD FRANCILIEN ICU 40 avenue Serge Dassault 91100 Corbeil-Essonnes	Dr	Guillaume CHEVREL	Tel: 01 61 69 61 69 E-mail: guillaume.chevrel@chsf.fr
16	CENTRE HOSPITALIER DE VERSAILLES ICU 177, rue de Versailles 78150 Le Chesnay-Rocquencourt	Dr	Fabrice BRUNEEL	Tel : 01 39 63 91 33 E-mail : FBRUNEEL@ch-versailles.fr
17	HOPITAL ROGER SALENGRO ICU Avenue du Professeur Emile Laine 59037 Lille	Dr	Thibault DUBURCQ	Tel: 03 20 44 62 31 E-mail: thibault.duburcq@chru-lille.fr
18	HOPITAL EDOUARD HERRIOT Medical ICU 5 place d'Arsonval 69003 Lyon	Pr	Jean-Christophe RICHARD	Tel: 04 72 11 11 01 E-mail: j-christophe.richard@chu-lyon.fr
19	HOPICES CIVILS DE LYON Medical ICU 3 quai des Célestins 69002 Lyon	Dr	Martin COUR	Tel: 08 25 08 25 69 E-mail: martin.cour@chu-lyon.fr

19.2 Addendum 2: SURFAST (Structure d'URgence de prise en charge des FASciites Nécrosantes)

19.2.1 SURFAST presentation (French form)

INFORMER

Infections nécrosantes de la peau et des parties molles

Le réflexe SURFAST Structure d'URgences de prise en charge des FASciites nécrosanTes

- **Dermo-hypodermites bactériennes nécrosantes**
- **Fasciites nécrosantes**
- **Myosites nécrosantes**

Une prise en charge multidisciplinaire d'urgence pour les patients atteints de dermo-hypodermites bactériennes nécrosantes - fasciites nécrosantes (DHBN-FN).

Hôpital Henri-Mondor
pour les DHBN-FN des membres et périnée de l'adulte

Services de dermatologie, chirurgie plastique et réanimation médicale : Dr C. Hua, Dr E. Sbidian, Dr R. Bosc, Dr N. de Prost, Pr O. Chosidow
01 49 81 21 11 poste 36053

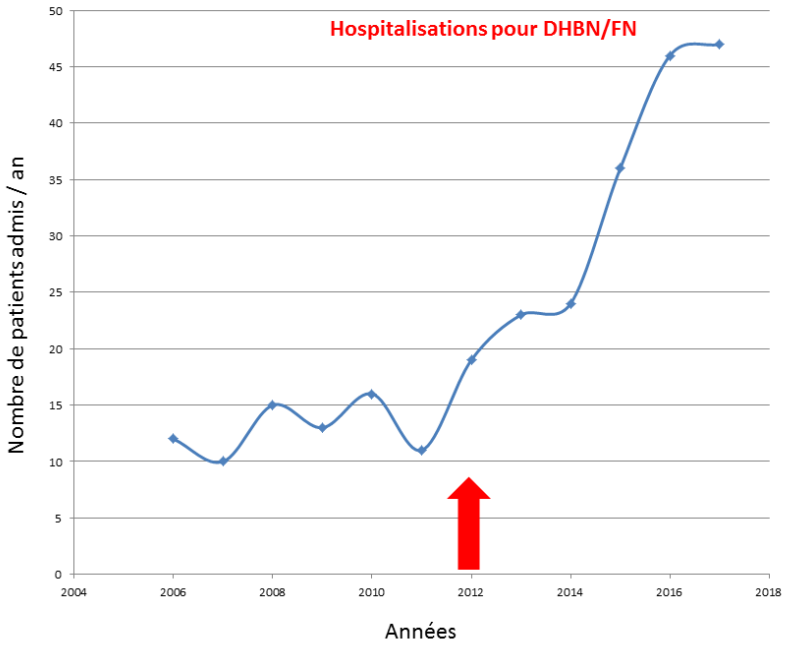
Hôpital Lariboisière
pour les DHBN-FN cervico-faciales de l'adulte

Service d'ORL : Pr Ph. Herman, Pr R. Kania
01 49 95 69 29

Hôpital Robert-Debré
pour les DHBN-FN des enfants

Service de réanimation pédiatrique : Dr M. Levy, Pr S. Dauger
01 40 03 22 87

19.2.2 Patient recruitment since SURFAST was created



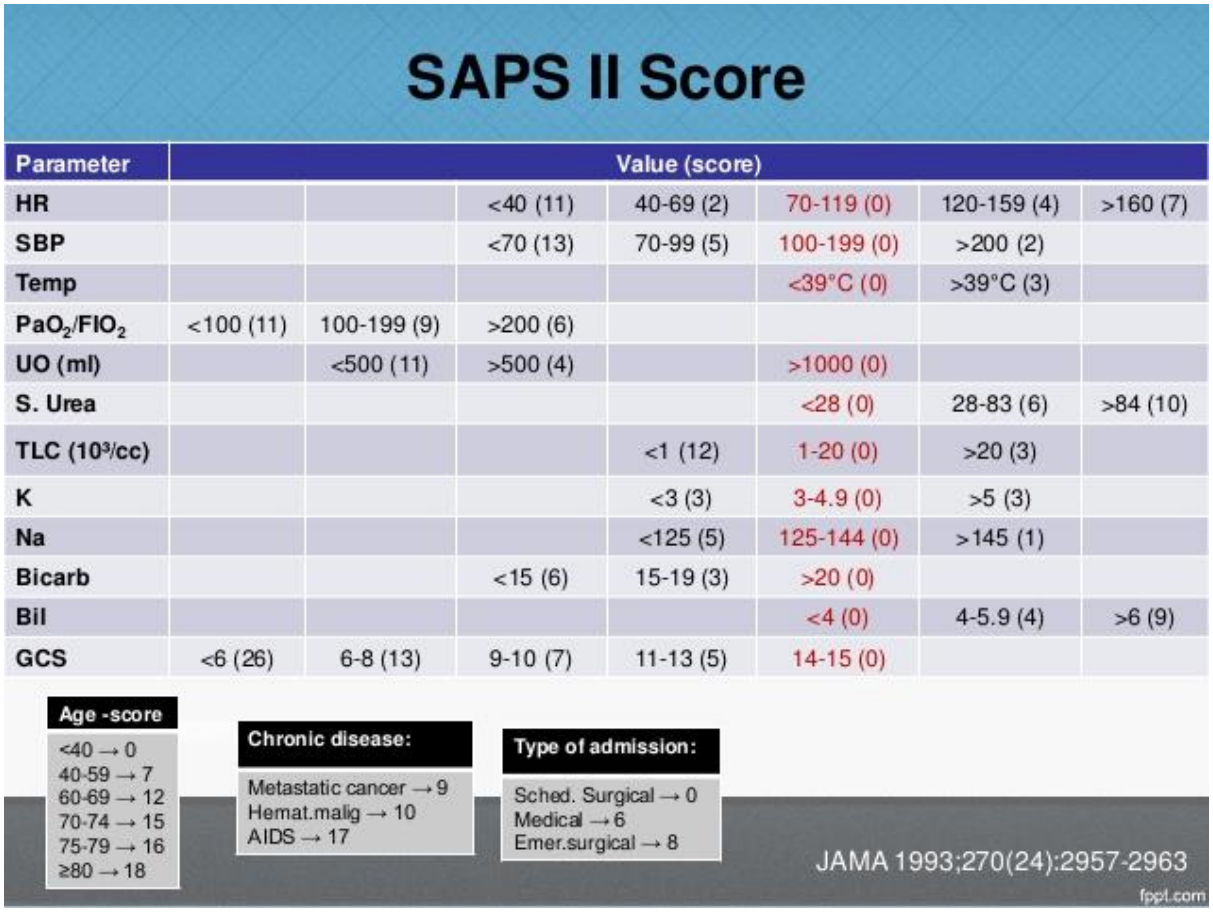
19.3 Addendum 3: scales and scores used

19.3.1 SOFA score

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	> 400	301–400	201–300	101–200	≤ 100
(kPa)	> 5.3)	(4.1–5.3)	(2.8–4.0)	(1.4–2.7)	≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl)	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	≥ 12.0
(µmol/l)	< 20)	(20–32)	(33–101)	(102–204)	≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
(µmol/l)	< 110)	(110–170)	(171–299)	(300–440)	> 440)
or urine output				< 500 ml/day	< 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in µg/kg/min)

19.3.2 SAPS II score



19.3.3 Behavioral Pain Scale

EXPRESSION DU VISAGE

1 : détendu

2 : plissement du front

3 : fermeture des yeux

4 : grimace

TONUS DES MEMBRES SUPERIEURS

1 : aucun

2 : flexion partielle

3 : flexion complète

4 : rétraction

ADAPTATION AU RESPIRATEUR

1 : adapté

2 : détachement ponctuel

3 : lutte contre le respirateur

4 : non ventilable

19.3.4 Clinical Frailty Scale

Clinical Frailty Scale*

1 **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 **Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 **Mildly Frail** – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 **Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 **Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

DALHOUSIE UNIVERSITY *Inspiring Minds*

19.3.5 SF-36 scores (French version)

1.- En général, diriez-vous que votre santé est : (cocher ce que vous ressentez)

Excellente __ Très bonne __ Bonne __ Satisfaisante __ Mauvaise ___

***2.- Par comparaison avec** il y a un an, **que diriez-vous sur votre santé** aujourd'hui ?*

Bien meilleure qu'il y a un an __ Un peu meilleure qu'il y a un an __
A peu près comme il y a un an __ Un peu moins bonne qu'il y a un an __
Pire qu'il y a un an __

3.- vous pourriez vous livrer aux activités suivantes le même jour. Est-ce que votre état de santé vous impose des limites dans ces activités ? Si oui, dans quelle mesure ? (entourez la flèche).

a.Activités intenses : courir, soulever des objets lourds, faire du sport.
Oui, très limité — oui, plutôt limité — pas limité du tout

b.Activités modérées :déplacer une table, passer l'aspirateur.
Oui, très limité — oui, plutôt limité — pas limité du tout

c.Soulever et transporter les achats d'alimentation.
Oui, très limité — oui, plutôt limité — pas limité du tout

d.Monter plusieurs étages à la suite.
Oui, très limité — oui, plutôt limité — pas limité du tout

e.Monter un seul étage.
Oui, très limité — oui, plutôt limité — pas limité du tout

f.Vous agenouiller, vous accroupir ou vous pencher très bas.
Oui, très limité — oui, plutôt limité — pas limité du tout

g.Marcher plus d'un kilomètre et demi.
Oui, très limité — oui, plutôt limité — pas limité du tout

h.Marcher plus de 500 mètres
Oui, très limité — oui, plutôt limité — pas limité du tout

i.Marcher seulement 100 mètres.
Oui, très limité — oui, plutôt limité — pas limité du tout

j.Prendre un bain, une douche ou vous habiller.

Oui, très limité | oui, plutôt limité | pas limité du tout

4.- Au cours des 4 dernières semaines, avez-vous eu l'une des difficultés suivantes au travail ou lors des activités courantes, du fait de votre santé ? (réponse : oui ou non à chaque ligne)

	oui	non
Limiter le temps passé au travail, ou à d'autres activités ?		
Faire moins de choses que vous ne l'espériez ?		
Trouver des limites au type de travail ou d'activités possibles ?		
Arriver à tout faire, mais au prix d'un effort		

5.- Au cours des 4 dernières semaines, avez-vous eu des difficultés suivantes au travail ou lors des activités courantes parce que vous étiez déprimé ou anxieux ? (réponse : oui ou non à chaque ligne).

	oui	non
Limiter le temps passé au travail, ou à d'autres activités ?		
Faire moins de choses que vous n'espériez ?		
Ces activités n'ont pas été accomplies aussi soigneusement que d'habitude ?		

6.- Au cours des 4 dernières semaines, dans quelle mesure est-ce que votre état physique ou mental ont perturbé vos relations avec la famille, les amis, les voisins ou d'autres groupes ?

Pas du tout | très peu | assez fortement | énormément

7.- Avez-vous enduré des souffrances physiques au cours des 4 dernières semaines ?

Pas du tout | très peu | assez fortement | énormément

8.- Au cours des 4 dernières semaines la douleur a-t-elle gêné votre travail ou vos activités usuelles ?

Pas du tout | un peu | modérément | assez fortement | énormément

9.- Ces 9 questions concernent ce qui s'est passé au cours de ces dernières 4 semaines. Pour chaque question, donnez la réponse qui se rapproche le plus de ce que vous avez ressenti. Comment vous sentiez-vous au cours de ces 4 semaines :

a. vous sentiez-vous très enthousiaste ?

Tout le temps | très souvent | parfois | peu souvent | jamais

b. étiez-vous très nerveux ?

Tout le temps très souvent parfois peu souvent jamais

c. étiez-vous si triste que rien ne pouvait vous égayer ?

Tout le temps très souvent parfois peu souvent jamais

d. vous sentiez-vous au calme, en paix ?

Tout le temps très souvent parfois peu souvent jamais

e. aviez-vous beaucoup d'énergie ?

Tout le temps très souvent parfois peu souvent jamais

f. étiez-vous triste et maussade ?

Tout le temps très souvent parfois peu souvent jamais

g. aviez-vous l'impression d'être épuisé(e) ?

Tout le temps très souvent parfois peu souvent jamais

h. étiez-vous quelqu'un d'heureux ?

Tout le temps très souvent parfois peu souvent jamais

i. vous êtes-vous senti fatigué(e) ?

Tout le temps très souvent parfois peu souvent jamais

10.- Au cours des 4 dernières semaines, votre état physique ou mental a-t-il gêné vos activités sociales comme des visites aux amis, à la famille, etc ?

Tout le temps très souvent parfois peu souvent jamais

11.- Ces affirmations sont-elles vraies ou fausses dans votre cas ?

a. il me semble que je tombe malade plus facilement que d'autres.

Tout à fait vrai assez vrai ne sais pas plutôt faux faux

b. ma santé est aussi bonne que celle des gens que je connais.

Tout à fait vrai assez vrai ne sais pas plutôt faux faux

c. je m'attends à ce que mon état de santé s'aggrave.

Tout à fait vrai assez vrai ne sais pas plutôt faux faux

d. mon état de santé est excellent.

Tout à fait vrai assez vrai ne sais pas plutôt faux faux

Wade JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Medical Care 1992;30:473–483.

Activités quotidiennes (6 Items).

Merci d'entourer le chiffre correspondant à la situation actuelle de votre état de santé.

1. **Soins d'hygiène personnels** : faites vous votre toilette au lavabo, baignoire ou douche :
   - 1 : sans aide ;
   - 0.5 : avec aide pour certaines parties du corps (jambe/dos, pieds) ;
   - 0 : Avec aide pour toute la toilette ;
2. **Habillage :** prendre les habits de l'armoire/ tiroirs, y compris sous-vêtements, saît manipuler fermetures et bretelles.
   - 1 : Prend les vêtements et s'habille complètement sans aide ;
   - 0.5 : Prend les habits et s'habille sans aide sauf pour les chaussures ;
   - 0 : Reçoit de l'aide pour prendre les habits et/ou s'habiller ou reste partiellement ou totalement dévêtu ;
3. **Aller aux toilettes :**
   - 1 : Va aux toilettes, se nettoie et arrange ses vêtements sans aide (peut s'aider d'un support comme une canne, un déambulateur, une chaise roulante et peut utiliser un bassin ou une chaise percée avec nettoyage par lui-même) ;
   - 0.5 : Reçoit de l'aide pour aller aux toilettes, se nettoyer ou arranger ses vêtements ou dans l'utilisation du bassin ou d'une chaise percée ;
   - 0 : ne va pas aux toilettes ;
4. **Déplacements :**
   - 1 : Se couche et se lève du lit aussi bien qu il s'assoit ou se lève d'une chaise, sans aide (peut s'aider d'un support comme un déambulateur ou une canne) ;
   - 0.5 : Se couche (ou s'assoit) ou se lève avec aide ;
   - 0 : reste alité ;
5. **Continence :**
   - 1 : Contrôle parfaitement seul son élimination ;
   - 0.5 : A quelques « accidents », ou n'assure plus seul le contrôle de son élimination ;
   - 0 : utilisation d'une sonde ou incontinence complète ;
6. **Alimentation :**
   - 1 : mange sans aide ;
   - 0.5 : Mange seul mais a besoin d'une aide pour couper la viande ou pour beurrer les tartines ou reçoit de l'aide pour manger ou est nourri partiellement ;
   - 0 : est nourri totalement ou à l'aide d'une sonde ou de solutés intraveineux ;

Date : ..... TOTAL : .....

19.4 Addendum 4: list of dressings available for the control group

PANSEMENTS 2020 - Liste des spécialités (adapted from Dr Patricia Senet, Dorosz 2020)

19.4.1 Hydrocolloïdes

Comfeel Plus, Duoderm E, Algoplaque HP, Askina Biofilm Suprasorb H, Hydrocoll standard , Tegaderm Hydrocolloid, Ultec pro, Askina Hydro	Plaques adhésives épaisses. Généralement 10 x 10 cm ; 15 x 15 et 20 x 20	1 application tous les 2 à 7 jours sans pansement secondaire
Comfeel Plus Transparent, Comfeel Plus Brûlures, Comfeel Ovale, Duoderm Extramince, Duoderm Extramince Ovale, Algoplaque Film, Hydrocoll thin Askina Transparent, Urgomed, Tegaderm Hydrocolloid Thin	Plaques adhésives minces, translucides Généralement : 5 x 5, 10 x 10 cm; 15 x 15 et 20 x 20	1 application tous les 2 à 7 jours sans pansement secondaire
Comfeel Plus plaque mousse (talon, coude), Suprasorb H sacrum, Algoplaque Sacrum Duoderm Signal (talon, sacrum) Hydrocoll Sacral, Hydrocoll concave (talon, coude)	Formes spécifiques anatomiques adhésives	1 application tous les 2 à 7 jours sans pansement secondaire
Algoplaque Bordé Comfeel Plus Plaque Contour Duoderm E Bordé Duoder E bordé triangulaire	Plaques adhésives, renforcées en périphérie : 14 x 14 Standard, large 15 x 18 ; 20 x 23	1 application tous les 2 à 7 jours sans pansement secondaire
Comfeel Pâte, Comfeel Poudre, Duoderm Pâte, Algoplaque Pâte	Tubes de 30 gr	1 application sous un hydrocolloïde en plaque

Contre-indications :
Infection, hypersensibilité à un des composants, plaie hyperbourgeonnante, brûlures 2ème degré profond et 3ème degré, peau péri-lésionnelle altérée ou fragile, plaie nécrotique.

Propriétés :
Pansements composés de polymères modérément absorbants, dont les propriétés physico-chimiques sont majoritairement liées à la présence de carboxyméthylcellulose (CMC). Ils se présentent sous forme de poudre, de pâte ou de plaques adhésives sur toute leur surface dont la face externe est imperméable aux liquides, Au contact des exsudats, formation d'un gel en général malodorant.

Indications et mode d'emploi :
Plaies chroniques sans distinction de phase. Si traitement séquentiel, plaies chroniques en phase d'épidermisation.
Pour formes minces : escarre au stade de rougeur pour protéger si besoin la peau (urines, macération).
NB : Forme mince pour les brûlures, dermabrasions, plaies superficielles.
Plaques découpables. Forme pâte pour les plaies cavitaires.

Effets secondaires :
Macération, allergie de contact/dermite irritative (si changement trop fréquent), odeur désagréable (délitement du gel de CMC au contact des exsudats)

19.4.2 Hydrocellulaires

Allevyn Adhésive, Aquacel Foam, Biatain adhésif, UrgoTul Absorb Border, Combiderm, Permafoam Comfort, HydroTac Comfort ; Suprasorb P, Tielle, Tegaderm Foam Adhesive, Kendall *foam, Askina Transorbent, Cutinova Hydro, Hydrophar, Versiva XC adhésif*	Plaques adhésives en périphérie, généralement 12,5 x 12,5; 12,5 x 22,5, 17,5 x 17,5, 22,5 x 22,5 (pour certains : 7,5 x 7,5)	1 application tous les 2 à 7 jours sans pansement secondaire
Allevyn Gentle Biatain Contact, Mepilex XT	Plaques microadhérentes siliconées 5 x 5 ; 12,5 x 12,5 ; 10 x 20 ; 15 x 15 ou 21,5 x 21,5	1 application tous les 2 à 7 jours (pansement secondaire nécessaire)
Allevyn Life Mépilex Border Biatain Silicone	Plaques microadhérentes siliconées renforcées en périphérie 7,5x8,5 ; 12,5 x 12,5	1 application tous les 2 à 7 jours (pas de pansement secondaire nécessaire)
Allevyn Gentle Border Lite, Allevyn Gentle border Lite oval, Biatain Silicone Lite Mépilex em, Mépilex Border em, Mepilex Transfer, Mepilex Border Flex, UrgoTul Lite Border, Suprasorb P	Plaques plus fines, adhésives ou microadhérentes (siliconées ou non), généralement 5 x 10; 7,5 x 8,5 ; 10 x 10 ; 10 x 20 ; 15 x 20	1 application tous les 2 à 7 jours sans pansement secondaire
Allevyn Non Adhésive, Aquacel Foam non adhésif, Biatain non adhésif, Biatain Soft Hold *UrgoTul Absorb* *Combiderm Non Adhésif, Suprasorb P Non adhésif, Tielle S, Tegaderm Foam, UrgoTul Lite, Permafoam, HydroTac, Kendall Foam, Askina Foam, Versiva XC non adhésif*	Plaques non adhésives (découpables), ou microadhérentes généralement 11 x 11 ; 10 x 20 ; 21,5 x 21,5 (pour certains : 5 x 5 ; 7,5 x 7,5)	1 application tous les 2 à 7 jours (pansement secondaire nécessaire)
Allevyn Heel ou sacrum, Allevyn Life Heel ou Sacrum, Allevyn Gentle Border Multisite, Biatain Talon, Aquacel Foam Talon ou Sacrum, Urgotul Absorb talon, Mepilex Talon, Mepilex Border sacrum, Permafoam Sacral, Permafoam Concave (talon, coude) Tielle Sacrum, Tielle Talon	Formes spécifiques anatomiques adhésives ou non (Allevyn Heel), ou microadhérentes (Mépilex, Allevyn Gentle, UrgotulAbsorb)	1 application tous les 2 à 7 jours
Permafoam Cavity, Tielle Packing, Biatain Cavity	Mousse sphérique 5 cm ou tubulaire, non adhésive, pour plaie cavitaire	1 application tous les 2 à 7 jours (pansement secondaire nécessaire)
Cutimed Sorbion Mextra Superabsorbent Resposorb Super ou Silicone Tegaderm Superabsorber Vliwasorb Pro, Sorbact superabsorber, 3M, Vliwasorb Pro	Plaques non adhésives, très absorbantes de dimensions variables, souvent indiquées en pansements secondaires si exsudats majeurs Non découpables	1 application tous les 2 à 7 jours (pansement secondaire nécessaire)

Contre-indications :
Infection, hypersensibilité à un des composants, plaies sèches.

Propriétés :
Pansements composés de polymères présentés notamment sous forme de mousse. Ils ne se délitent pas dans la plaie, sont très absorbants, comportant une couche hydrophile.
Seules les formes « superabsorbantes » n'ont pas de film semi perméable à la surface, ressemblent à des pansements dits américains et sont utilisées en pansement secondaire en cas d'exsudat majeur.
Les autres formes sont des plaques adhésives ou non ou des formes anatomiques ou adaptées au remplissage des plaies cavitaires. Les formes microadhérentes ont une interface (silicone ou lipido-colloïde) au contact de la plaie et de la peau périphérique.

Indications et mode d'emploi :
Plaies aiguës sans distinction de phase. Traitement séquentiel, plaies chroniques en phase de bourgeonnement. Plaies traumatiques ou post opératoires.
Plaques adhésives non découpables, plaques non adhésives ou microadhérentes découpables.

19.4.3 Pansement avec composant anti-protéase

Urgostart interface	Interface non adhésive, non occlusive, non adhérente	1 application tous les 2 à 4 jours
Urgostart	Plaques hydrocellulaires non adhésives découpables 13 x 12 et 15 x 20 cm	1application tous les 2 à 7 jours (pansement secondaire nécessaire)
Urgostart microadhérent	Plaques hydrocellulaires micro adhérentes découpables 13 x 12 et 15 x 20 cm Forme talon 12 x 19	1application tous les 2 à 7 jours (pansement secondaire nécessaire)
Urgostart Plus Border, Urgostart Border	Plaques contenant des fibres polyacrylate absorbantes, adhésives ou non en périphérie 8 x 8; 13 x 13 et 15 x 20 cm	1application tous les 2 à 7 jours

Propriétés :
Pansement hydrocellulaire imprégné de substance ayant des propriétés anti-protéasiques.
La forme « Plus » a des capacités de détersion et d'absorption, est utilisée quelque soit le stade de la plaie et a montré une accélération de la cicatrisation dans les ulcères du pied diabétique neuro-ischémiques.

Indications :
Ulcères de jambe veineux ou mixtes à prédominance veineuse (traitement séquentiel).
Ulcères du pied diabétique d'origine neuro-ischémique, non infectés (traitement séquentiel).

19.4.4 Alginates

Algostéril, Melgisorb Plus, Biatain Alginate pansement, Sorbalgon Plus, Urgosorb, Algisite M, Tegaderm Alginate, Curasorb, Suprasorb A, Sorbalgon, Kendall Alginate, Askina sorb, Comfeel Seasorb, Kaltostat	Compresses stériles, généralement: 5 x5, 10 x 10, 10 x 20 cm; 15 x15 Mèches pour plaies cavitaires 30 cm à 44 cm	1 application tous les 1 à 3 jours (pansement secondaire nécessaire)

Contre-indications :
Plaie non exsudative

Propriétés :
Pansements composés majoritairement (> 50%) d'alginates, associés ou non à de la carboxyméthylcellulose. Ils sont caractérisés par leur capacité d'absorption et leurs propriétés hémostatiques. Ils peuvent laisser des fibres sur la plaie au retrait et rester en place 5 à 10 jours sur les sites donneurs de greffe.

Indications et mode d'emploi :
Plaies hémorragiques. Traitement séquentiel plaies chroniques en phase de détersion.
Pansements découpables.
Intérêt dans les plaies modérément à fortement exsudatives, fibrineuses, infectées.

19.4.5 Hydrogels

Duoderm Hydrogel, Burn Free plaque; IntraSite Gel ou Conformable, Normlgel, Purilon gel, Tegaderm Hydrogel, Curafil Gel, Hydrosorb gel, Urgo Hydrogel Advance, Hydroclean cavity, Hydrotac transparent, Suprasorb gel Hydroclean,, Aquaflo, Askina gel	Plaques 10 x 10 Tubes, applicateur doseur, seringue pré-remplie ou sachet de 15 gr	1 application toutes les 48 h, pansement secondaire nécessaire peu absorbant et imperméable (film de polyuréthane, hydrocolloïde mince)

Contre-indications :
Plaie exsudative. Hypersensibilité à un des composants (notamment propylene glycol contenu dans certains hydrogels). Fistules.

Propriétés :
Gels contenant majoritairement (> 50%) de l'eau. Ils sont caractérisés par leur capacité à humidifier les plaies ; ils se présentent sous forme de plaques, de compresses imprégnées, de gels. Ils peuvent entraîner une macération de la peau autour de la plaie.

Indications et mode d'emploi :
Traitement séquentiel, plaies chroniques en phase de détersion (plaie sèche).
NB : Les formes plaques sont plutôt utilisées pour les radiodermites.

19.4.6 Pansements en fibres de carboxyméthylcellulose (ou hydrofibres) ou fibres de polyacrylate

Aquacel Extra Urgoclean	Compresses épaisses 10 x 12; 13,5 x 15; 15 x 20 cm Compresses 6 x 10; 13 x 12; 15 x 20 cm	1 application tous les 1 à 2 jours (pansement secondaire nécessaire)
Aquacel mèche Urgoclean mèche	Mèche 2,5 x 40 cm Mèche 5 x 40 cm	

Contre-indications :
Plaie faiblement exsudative. Hypersensibilité à un des composants. Brûlures du 2ème degré profond ou 3ème degré.

Propriétés :
Pansements composés majoritairement (> 50%) de fibres non tissées de carboxyméthylcellulose pure ou de polyacrylate. Ils se présentent sous forme de compresses ou de mèches. Ces fibres se transforment en gel cohésif au contact des exsudats (retrait non douloureux). Ces pansements sont caractérisés par leur haute capacité d'absorption.

Indications et mode d'emploi :
Plaies aiguës sans distinction de phase. Utilisés également à la phase de détersion des plaies chroniques exsudatives.
Pansements découpables, non adhérents au retrait.

19.4.7 Pansements à base de charbon

Carbonet, Askina Carbosorb,	Compresses 10 x 10 ou 10 x 20 cm	1 application tous les 2 à 3 jours (pansement secondaire nécessaire)
Actisorb , Vliwactiv Carboflex	Compresses non découpables 10,5 x 10,5; 10,5 x 19 cm	1 application tous les 2 à 3 jours (pansement secondaire nécessaire)

Contre-indications :
Hypersensibilité à un des composants.

Propriétés :
Pansements composés de différents supports auxquels a été ajouté du charbon actif, à visée d'absorption des molécules responsables des mauvaises odeurs des plaies. Se présentent sous forme de plaques et de compresses. Absorption des exsudats plus ou moins importante selon la marque.

Indications et mode d'emploi :
Plaies aigües ou chroniques malodorantes. Plaies cancéreuses.

19.4.8 Pansements interface

Adaptic, Urgotul, Physiotulle, Hydrotul, Mépitel, Mepitel One	Plaques de tulle enduite ou imprégnée, généralement 7,5 x 10; 10 x 12; 15 x 20; 10 x 40 cm	1 application tous les 1 à 7 jours (pansement secondaire nécessaire)
Urgotul Lite	Plaque de tulle avec compresse absorbante 10 x12 et 15 x 20 cm	1 application tous les 1 à 7 jours (pansement secondaire nécessaire)
Urgotul Lite Border	Plaque de tulle avec compresse absorbante et adhésif 6,5 x 10; 8 x 8; 10 x12 ;10 x 20; 15 x 20 cm	1 application tous les 1 à 7 jours (pas de pansement secondaire nécessaire)

Contre-indications :
Hypersensibilité à un des composants.

Propriétés :
Pansements possédant une adhérence faible, persistante tout au long de l'utilisation au contact directe de la plaie (absence de migration de la substance imprégnée ou enduite), visant à limiter les traumatismes et les douleurs induits par le retrait des pansements.

Indications et mode d'emploi :
Peau fragile (maladies bulleuses). Traitement séquentiel plaies aiguës en phase d'épidermisation, plaies chroniques en phases de bourgeonnement ou d'épidermisation.
Découpables et conformables sauf Urgotul Lite Border®.

19.4.9 Pansements à l'argent

UrgoTul Ag , UrgoTul Ag Lite, UrgoTul Ag Lite Border	Interface (± compresse; ± adhésive en périphérie) 6,5 x 10; 8 x 8; 10 x 12; 15 x 20 cm	1 application tous les 2 à 7 jours (pansement secondaire nécessaire sauf forme Border)
UrgoClean Ag	Pansement avec fibres poly-absorbantes 6 x10; 13 x 12; 15 x 20	1 application tous les 1 à 7 jours (pansement secondaire nécessaire)

Contre-indications :
Hypersensibilité à un des composants

Propriétés :
Pansements constitués de différents supports auxquels a été ajouté de l'argent sous forme variable à visée antibactérienne ou anti-inflammatoire.

Indication (reconnue pour gammes UrgoTul Ag et UrgoCell Ag) :
Traitement séquentiel de 4 semaines des ulcères de jambe à caractère inflammatoire, ayant au moins 3 des signes cliniques suivants : douleur entre 2 changements de pansements, érythème péri lésionnel, œdème, plaie malodorante, exsudat abondant.

19.4.10 Pansements à l'acide hyaluronique

Ialuset Ialuset Plus (contient sulfadiazine argentique en plus)	Tube crème 100 gr, Flacon pressurisé 100 gr, Compresses tulle imprégné 10x10 cm	1application/jour (pansement secondaire nécessaire)
Ialuset Hydro	Plaque d'hydrocolloïde adhésive 10x10 cm	1application tous les 2 à 7 jours (pas de pansement secondaire)

Contre-indications :
Hypersensibilité à un des composants

Propriétés :
Pansements contenant de l'acide hyaluronique à des concentrations variables, avec de la sulfadiazine argentique (famille des sulfamides antibactériens) dans la forme Ialuset Plus. L'acide hyaluronique appartient à la famille des glycosaminoglycanes. Les pansements se présentent sous différentes formes : compresses imprégnées, crèmes.
Proposés pour les ulcères de jambe peu ou pas exsudatifs (épidermisation, bourgeonnement), en traitement court (4 semaines)

19.4.11 Pansements gras

Grassolind neutral, Jelonet, Jelonet Plus,Vaselitulle, Tulle gras MS; Cuticell	Plaques, généralement 10 x 10 ou 20 x 20 cm	1application tous les 1 à 2 jours (pansement secondaire nécessaire)

Contre-indications :
Hypersensibilité à un des composants

Propriétés :
Pansements constitués d'une trame imprégnée ou enduite de substance neutre (vaseline, paraffine)
Proposés pour les plaies peu ou pas exsudatives (phases d'épidermisation, de bourgeonnement), en traitement court séquentiel (4 semaines).

19.4.12 Films adhésifs semi perméables. Remboursements LPPR

Clip Derm, Hydrofilm, Lumiderm 6000, Opsite Flexigrid, Optiskin, Tégaderm , Suprasorb F, Polyskin II Mepiform, Mepitel Film	Plaques adhésives, généralement 6 x 7; 10 x 12; 15 x 20 cm	1application tous les 1 à 7 jours
Hydrofilm Plus, Opsite Post-Op Tégaderm + Pad, Viasorb	Plaques adhésives avec compresses intégrées 7 x 5; 9 x 10; 15 x 9; 25 x 10 cm	1application tous les 1 à 7 jours

Contre-indications :
Hypersensibilité à un des composants. Plaies infectées. Plaies exsudatives.

Propriétés :
Pansements constitués d'un film transparent plastique, le plus souvent à base de polyuréthane, enduit d'une masse adhésive. Ils sont extensibles, souples, perméables à l'air et à la vapeur d'eau, imperméables aux bactéries et aux liquides. Ils sont encore appelés films autoadhéssifs transparents, films adhésifs extensibles, pansements de maintien transparents ou pansements transparents adhésifs.
Utilisés comme pansements primaires sur la peau saine ou lésée, non infectée, ou comme pansements secondaires.
NB: Opsite Flexigrid : grille placée sur la face extérieure du pansement, pouvant servir de calque pour la mesure de surface.

Proposés dans les plaies chroniques de cicatrisation difficile.