Document title	**PROTOCOL FOR RESEARCH IN ROUTINE CARE**
Study title	**Comparison of the efficacy, safety and cost of Algosteril® *vs.* Negative Pressure Wound Therapy (NPWT) in preparation for skin grafting for surgical excision subsequent to surgery**
Acronym	ATEC study
ID RBM NO.	2013-A00815-40

Sponsor of the study

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V. 8 of 01 March 2016 approved by the CPP Ile-de-France IV le 31/03/2016

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V. 7 approved by CPP Ile-de-France IV on 28/01/2016

SIGNATURE PAGE

Comparison of the efficacy, safety and cost of Algosteril® *vs.* Negative Pressure Treatment (NPWT) in preparation for skin grafting for surgical excision

ATEC study

STUDY MANAGEMENT

Laboratoires Brothier

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Professional stamp:

COORDINATOR OF THE STUDY

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Head of the Department of Plastic surgery
1 Avenue Claude Vellefaux
75010 PARIS
Phone : 01 42 49 96 68

Date:

Signature:

Professional stamp:

Investigator's commitment

I the undersigned, ... hereby declare that
Surname First name

I have read the protocol and study entitled: "Comparison of the efficacy, safety and cost of Algosteril® *vs.* Negative Pressure Wound Therapy (NPWT) in preparation for skin grafting for surgical excision subsequent to surgery – "The ATEC study" and I agree to the following:

- To comply with the protocol for the ATEC study and to not make any change to it,
- To do what is necessary to collect good quality data justified by source documents,
- To conduct the study such that investigators and other qualified members of my team have access to copies of this protocol and to documents relating to conduct of the study in order to enable them to work in compliance with conditions appearing in these documents,
- To give the patient all information necessary so that he/she may take his/her decision to participate or not in this study in full knowledge of the facts and to inform him/her of his/her right not to participate in this study without incurring any responsibility nor any prejudgement of this fact,
- To include the patient in this study solely after obtaining his/her consent to participate in it,
- To comply with Good Clinical Practice, to accept periodic visits by the Brothier monitor and consultation by the monitor of the medical case report of the patient included in the trial,
- To accept the principle of a check by the health authorities without this being in breach of medical confidentiality,
- To save study data during a minimum of 15 years.

Issued in .....

On .....

Signature:

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1. ABBREVIATIONS

AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (*French National Agency for Medicines and Health Products Safety)*
APHP	Paris Hospitals-Public Assistance Group
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé *(Advisory Committee on Information Processing in Material Research in the Field of Health)*
CHU	University Hospital Centre
CNIL	Commission Nationale de l'Informatique et des Libertés *(National Commission for Computing and Liberties)*
CPP	Committee for the Protection of Persons (Ethics Committee)
CRF	Case Report Form
CRO	Contract Research Organisation
DC diary	Dressing change diary
GCP	Good Clinical Practice
GPEH	George Pompidou European Hospital
i.e.,	That is
MD	Medical Device
NPWT	Negative Pressure Treatment
ITT	Intention To Treat
PP	Per Protocol
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
URC	Clinical Research Unit

NB: in this document (protocol for evaluation in routine care), the persons who direct and monitor the study will be referred to as “investigators”.

2. ADMINISTRATIVE STRUCTURE OF THE STUDY

2.1. Coordinator and Scientific Committee

Role	Title/First name/Surname/Office phone number/E-mail
Coordinator	**Prof. Marc Revol** Hôpital St Louis, APHP Department of plastic surgery 1 Avenue Claude Vellefaux, 75010 PARIS Phone : 01 42 49 96 68/e-mail : marc@revol.org
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2.2. Sponsor's participants

Role	Title First Name Surname	Address and phone number
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2.3. Other participants not affiliated with the sponsor

Role	Title First name Surname	Address and phone number
Responsible for Biostatistics	**Frédéric Mistretta**	RCTs 38 rue du Plat 69002 Lyon Phone : 04 37 45 17 35
Study Director	**Jean-Sylvain Larguier**	RCTs 38 rue du Plat 69002 Lyon Phone : 04 37 45 17 18

3. STUDY SYNOPSIS

TITLE
Comparison of the efficacy, safety and of cost of Algosteril® *vs.* Negative Pressure Wound Therapy (NPWT) in preparation for split thickness skin graft (STSG) after surgical excision – The ATEC study
STUDY DESIGN
A randomised, multicentre, national, two parallel group, non-inferiority clinical study of routine care with blind evaluation of the primary outcome
STUDY RATIONALE

Surgical removal of skin and of underlying soft tissue are performed in plastic surgery for management of a tumour, traumatic or infectious reasons. If the resultant surgical excision bed is well-vascularised, it can be covered by a thin skin graft, either immediately or subsequently after a phase of granulation tissue formation and wound retraction. Granulation tissue occurs naturally and spontaneously within a few weeks. This phase, called healing by secondary intention, has the goal of reducing the dimensions of the surgical excision and obtaining optimal granulation tissue in order to receive a skin graft[1, 2].

This formation of granulation tissue can be promoted by medical devices (MD) among which Algosteril and NPWT are the most widely used with good results.

- **Algosteril** is obtained from brown seaweed, enriched with calcium ions. Thanks to its high drainage power, Algosteril eliminates the exudate from the surgical excision, traps bacteria in its fibres[3] and eliminates them when it is removed. Thanks to the release of its calcium ions, which activate key cells in healing, Algosteril accelerates granulation[4, 5].
  Comparative clinical studies have demonstrated the efficacy of Algosteril in surgical wounds healing by secondary intention (SWHSI) subsequent to surgery for pilonidal sinus[6], hidradenitis suppurativa[7] and radiotherapy-related necrosis on the head and neck[8]. In these studies, the time to obtainment of granulation tissue is shorter with Algosteril versus iodoform mesh, tulle gras and the combination use of anti-septic/tulle gras.
  Developed, produced and distributed by Brothier, an independent French pharmaceutical company, Algosteril has been marketed since 1991.
  Algosteril, reimbursed on the LPP under its tradename, is the only calcium alginate which has obtained class III EC marking for invasive use, for traumatic and surgical excision, infected or not.
  Algosteril daily cost is about €7[9] and wound dressings change requires only one nurse.
- **NPWT** consists of synthetic foam placed on the surgical excision and covered by an occlusive film to ensure the airtightness of the dressing. The entire system is connected by a tubing to a canister and to a negative pressure electrical generator. The concept of NPWT consists of placing the wound under pressure that is less than atmospheric pressure in order to drain the exudate, to increase the intra-tissue blood flow and to promote formation of granulation tissue.
  NPWT started to be used commercially in the 1990's world-wide[1]. Its efficacy in complex and acute wounds has been described in many publications[10, 11].
  NPWT has been distributed in France for about 15 years[1], by several companies (KCI/USA, Smith&Nephew/UK, Hartmann/Germany, Mölnlycke/Sweden, etc.).
  It is indicated among for surgery with surgical excision, infected or non-infected wounds[12].
  NPWT has a daily cost which can range up to €100[13, 14] and replacement of associated dressings often requires the intervention of several nurses.

Based on a survey of practice performed nationally by Brothier in 2012 on 983 French surgeons, Algosteril and NPWT are the two treatments most widely used in SWHSI [15], 98.1% and 53.6%, respectively.

In spite of routine use of these two treatment strategies (Algosteril and NPWT) in preparation of surgical excision for STSGsurgical excision, no randomised clinical trial has been conducted to compare their efficacy, safety and cost.

Furthermore, the authors of the Cochrane bibliographical review in 2012[11] have issued an alert on the need for randomised clinical trials with good levels of evidence which compared NPWT to other wound dressings in management of acute wounds, because the only 5 randomised clinical trials found have a low level of evidence due to multiple biases (selection, performance, detection, attrition, etc.).

17 plastic/reconstructive surgery expert centres are participating in conduct of a national randomised clinical trial. The objective is to obtain, for the first time, clinical and economic evidence of the place of Algosteril and NPWT in management of surgical excision subsequent to surgery. The aim of this study is to demonstrate similar efficacy of the two therapeutic strategies on the time for obtainment of optimum granulation tissue to receive a STSG.

To satisfy surgeons requests, and to help them, Brothier sponsored this trial whose status of a "research in routine care" is justified in light of the following elements:

- The two MD have EC marking and are routinely used in the indication concerned with similar results for efficacy on wound healing,
- Use of the two devices in the study will comply with guidelines in manufacturer's patient information leaflet,
- The specific modalities for monitoring during this study require negligible constraints for the patient and do not present any risk for the patient.

INTERVENTIONS

Algosteril

- Tradename/distributor in France: Algosteril® rope and Algosteril® compress 10x10 cm and 10x20cn from/Brothier
- Composition: calcium alginate fibres
- Indications class III/EC marking: surgical and traumatic surgical excision, infected lesions or not, etc.
- Protocol for use: according to the manufacturer's recommendations *(see product leaflet for use).*

NPWT

All NPWT systems *(without instillation, without PICO system),* used with or without interface according to the centre's practice.

- Tradename/distributor in France: Renasys®/ Smith &Nephew, VAC® Therapy/KCI Medical, etc.
- Composition: polyvinyl alcohol/polyurethane foam, occlusive film, tubing, reservoir and a negative pressure generator. *The most widely used practice with NPWT: black foam and pressure of -125 mmHg*
- Indications class IIb/EC marking: surgery with surgical excision, infected or not, etc.
- Protocol for use: according to the manufacturer's recommendations *(see product leaflet for use).*

OBJECTIVES

Primary objective: To demonstrate the non-inferiority between the two treatment strategies *(Algosteril vs. NPWT)* within the timeframe to obtain optimum granulation tissue to receive a STSG.

Secondary objectives:
To compare the two treatment strategies for:

- cost of management,
- impact of the studied MD on the daily life of patients,
- the occurrence of adverse events which may be potentially attributable to the study MD.

INCLUSION/NON-INCLUSION CRITERIA

Inclusion criteria – the following patients will be included:

- Patients 18 years of age or older,
- Who are to undergo:
  - Surgical excision or trimming of the skin and of soft tissue for tumour, traumatic or infectious causes *(*hidradenitis suppurativa*, Fournier's gangrene, necrotising fasciitis, skin traumatology damaged, suture breaking, abscess, pilonidal sinus, etc.)*
  - Or a skin flap.

  Surgical excision (minimum size 30 cm²) should be left to heal by secondary intention to obtaining optimum granulation tissue to receive a thin skin graft,
- Informed and who understand the information and provided consent by their non-opposition,
- Who can be followed throughout duration of the study,
- Who are beneficiaries of the French social security system.

Non-inclusion criteria – the following patients will not be included:

- With uncontrolled hyperglycaemia *(HbA1C>10%),*
- For whom skin excision is subsequent to a burn,
- For whom use of the studied MDs is contra-indicated,
- Treated within the 30 days prior to inclusion with immuno-suppressants, chemotherapy, or radiotherapy on the surgical site.
- Participating, or who have participated during the last 30 days prior to the procedure or who are scheduled to participate during this study in another interventional biomedical research study.

OUTCOMES MEASURES

Primary outcome: the time to obtain optimum granulation (defined as the number of days between the date of performing the surgical excision procedure and the date on which optimal granulation tissue was achieved.).

→ Definition of optimum granulation tissue: a homogeneous, pink and continuous, non-oozing, non-haemorrhagic, non-infected granulation tissue that is well-vascularised and uniformly covering the totality of the surgical excision.

surgical excision

→Evaluation of date of optimum granulation:
At each follow-up visit of each patient:
- The surgical excision will be photographed (and with a small ruler placed on the edge of the wound with the date, patient's initials, patient/centre no.)
- The graunulation tissue will be evaluated blinded by an evaluator different from the investigator who installed the studied MD
- The date when granulation tissue is considered optimum for a graft ($D_{optimum\ granulation}$) will be recorded in the CRF.

At the end of the study, anonymised photographs of the surgical excision, taken after obtainement of optimum granulation tissue and at the previous visit will be studied independently by 3 members of the Scientific Committee (Dr. Guerreschi, Prof. Hu, and Dr. Rousseau).

Each of them will validate the date of $D_{optimum\ granulation}$ recorded in the case report forms or will propose another date.
If a date has not been chosen by a majority opinion, the entire Scientific Committee will meet and will issue an opinion on the date of $D_{optimum\ granulation}$ for the concerned patient.

The statistical analysis will be based on the $D_{optimum\ granulation}$ (in the absence of photographs or if photographs are not evaluable, the dates chosen will be those proposed in the CRFs).

Secondary outcomes:
- Cost of management of surgical excision:
  - dressing changes: number, place, duration, quantity of products used, number of nurses,
  - Concomitant treatments: analgesics, local or general anaesthesia, antibiotics, etc.
- impact of MD on patient's daily life,
- Nature and frequency of adverse events potentially attributable to the studied medical devices.

- **Inclusion visit** (between D_{-15} and D_0): collection of patient non-opposition, inclusion, randomisation, ordering of NPWT if applicable
  CRFs: - validation of inclusion/non-inclusion criteria,
  - centralised randomisation,
  - patient data (age, gender, factors in delay in healing, previous medical conditions, etc.),
  - data on the disorder.

- **Interventional visit** (D_0): surgical excision procedure/wound trimming, photo of surgical excision, placement of the randomised MD
  CRFs: - data on surgical excision (size, location, etc.),
  - quantity of study products used.

- **Weekly follow-up visit:** (D_7, D_{14}…, D_X= $D_{optimum\ granulation}$): evaluation of granulation tissue, photos of surgical excision
  CRFs: - per cent granulation tissue,
  - concomitant treatments *(antibiotics, analgesics, local anaesthetics/GA, anti-coagulant, all other treatment which may have an impact on granulation)*,
  -dressing changes: number, place, duration, number of products used, number of nurses, etc.,
  - impact of MD on patient's daily life,
  - adverse events potentially attributable to the studied MD.

➔**End of study = date of optimum granulation**

SAMPLE SIZE

The primary outcome is the time (in days) between date of surgical excision procedure/wound trimming and date of optimum granulation tissue in order to receive a STSG.

This calculation is based on a search for non-inferiority of Algosteril *vs.* NPWT.

For this purpose, the number of patients to be analysed is 50 per group, taking the following elements as the starting hypothesis:

- A type 1 error $\alpha = 0.025$ *(one-sided p value)*
- Statistical power = 80%
- Expected difference in efficacy between the 2 groups = 0
- Standard-deviation = 7 days[17]
- Margin Δ of non-inferiority (higher loss of efficacy than can be tolerated) = 4 days *(validated by the study investigators).*

This calculation has been performed with the NQuery 7.0 software.
Two ANALYSIs will be performed, one On Intention To Treat (ITT) and the other Per Protocol (PP).

To take into account patients with a protocol major deviation, patients lost to follow-up, etc. (evaluated as 10% at most), 56 patients per group have to be included, i.e., a total of 112 patients. This total number of subjects to be included is compatible with feasibility of such a project by 15 plastic surgery/reconstructive surgery centres within a reasonable time period.

Concerning all secondary outcomes, the comparison between groups will be based on a search for the difference between the groups. Concerning comparison of the cost of management, no *a priori* calculation of power is possible. Calculation of power will be performed *post hoc* to demonstrate the actual statistical power to detect the difference observed, in light of number of patients in the study.

STATISTICAL ANALYSIS

The analysis will be performed by the RCTs company (an independent service provider) with SAS software version 9.2 or later, according to a statistical analysis plan which will be written based on all elements described in the protocol.

Two populations of analysis will be defined in this study:

- The "Intention To Treat" population (ITT): all randomised patients (including cases with a major protocol deviation) who received at least one of the studied MD,
- The "Per Protocol population" (PP): all patients included and who received at least one studied MD except for major protocol deviations

The type 1 error is set at $\alpha = 0.05$ two-sided P value. All evaluation end points will be analysis in the two populations of interest (ITTand "PP") populations.

Protocol deviations will be classified by the Scientific Committee as "major deviations" or as "minor deviations" at time of data review prior to locking of the database and blinded of the randomised strategy. Major deviations include significant deviations compared to criteria for inclusion/non-inclusion, in compliance with the study protocol, as well as protocols for use of the MD.

All parameters collected will be listed in tables containing descriptive statistics for each of the two groups, as well as the totality of the population analysis, according to the following modalities:

- For quantitative variables: number of missing values and of non-missing values, the mean, standard deviation, the 95% confidence interval, the median, 1st quartile, 3rd quartiles, the minimum and maximum,
- For qualitative variables: the number of missing values and of non-missing values, the frequencies, percentages and 95% confidence intervals for each of the modalities of the variable (excluding missing data from the denominator).

Analysis of the primary outcome:

Analysis of the primary outcome will be performed on the two populations of analysis defined without a hierarchy ("ITT" and "PP"). In order to be able to conclude, the conclusions obtained on these 2 populations must concur.
The primary outcome is the comparison of the time to obtain optimum granulation tissue with Algosteril and NPWT in non-inferiority.
The null hypothesis of inferiority will be tested: $\mu_{Algosteril} - \mu_{NPWT} \geq \Delta$.
A two-sided approach with a 95% confidence interval of the difference between the 2 groups $\mu_{Algosteril} - \mu_{NPWT}$ will be used.
If the upper limit of the 95% confidence interval is less than the margin of non-inferiority accepted ($\Delta = 4$ days), the null hypothesis will be rejected to the benefit of the alternative hypothesis of non-inferiority of Algosteril vs. NPWT ($\mu_{Algosteril} - \mu_{NPWT} < \Delta$).
If the upper limit of the 95% confidence interval is less than the margin of non-inferiority accepted ($\Delta = 4$ days) but also less than 0, the superiority of Algosteril vs. NPWT will be demonstrated with a level of significance $\alpha = 0.05$ (in conformity with the EMA guideline (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf).
The level of significance will be obtained with Student's t test.

Analysis of the secondary outcomes:

Analysis of secondary outcomes will be performed on the two populations of analysis defined without a hierarchy ("On ITT" and PP) and based on a search for a statistical difference between the two groups with a limit $\alpha=0.05$, two-sided tests. In order to be able to conclude, the conclusions obtained in these 2 populations must concur.

The secondary outcomes will be the comparison of Algosteril and of NPWT on their impact on the MD, on the patient's daily life and the cost of management. Iner-group comparison will be performed with an Analysis of Covariance model (for continuous variables) and logistic regression analysis (for binary values) incorporating the centre factor, as well as evaluation of the end point in initial evaluation (if available).

A description of adverse events potentially attributable to the studied medical devices (MDs) will be performed based on all of the "ITT" population and in each of the two groups.

TYPOLOGY OF THE STUDY AND TECHNICAL-REGULATORY ASPECTS

The two medical devices have EC marking and are routinely used in the indication. The use of the two studied MDs will be in conformity with their product patients leaflets with no change. The specific modalities for monitoring during this study:

- Generate negligible constraints for the patient,
- Do not present any risk for the patient.

In conformity with the regulation in force, the research study has been submitted for approval:

- To the CPP Ile-de-France IV,
- To the CCTIRS,
- To the CNIL.

ANSM RCB ID NO.: 2013-A00815-40

PARTICIPANTING CENTRES

- Sponsor of the study: Laboratoires Brothier
- Person responsible for directing and monitoring the study: Prof. Revol (Hôp. St Louis, APHP, Paris)
- Scientific Committee : Dr. Guerreschi (Lille), Prof. Hu (Brest), Prof. Revol (Paris), Dr. Rousseau (Angers)
  Methodologist: Prof. Chatellier (Paris)
- Study centres: 17 departments of Plastic and Reconstructive Surgery in the French University Hospital Centres
- Investigators:
  - Prof. Braye, Lyon
  - Prof. Bruant-Rodier, Strasbourg
  - Prof. Casanova, Marseille
  - Dr Chignon-Sicard, Nice
  - Prof. Rousseau, Angers
  - Prof. Duteille, Nantes
  - Prof. Hu, Brest
  - Dr Philandrianos, Marseille
  - Prof. Barthélémy, Clermont-Ferrand
  - Prof. Martinot-Duquesnoy, Lille
  - Prof. Casoli, Bordeaux
  - Prof. Revol, Paris
  - Dr Cambon, Paris (replacing Dr. Robert)
  - Prof. Sinna, Amiens
  - Prof. Tropet, Besançon
  - Prof. Watier, Rennes
  - Dr. Atlan, Paris
- Data Managers and Statisticians: RCTs company (Lyon)

PREVISIONNAL STUDY SCHEDULE

- Submission to the competent authorities: June 2013
- Set up of study: July 2014
- Period of inclusion: 12 months
- Maximum duration of the study per patient: up until optimum tissue granulation
- End of study: 30 June 2016
- Locking of the database: Nov. 2016
- 1st statistical result: Dec. 2016
- Final result: Jan. 2017
- Final report: March 2017

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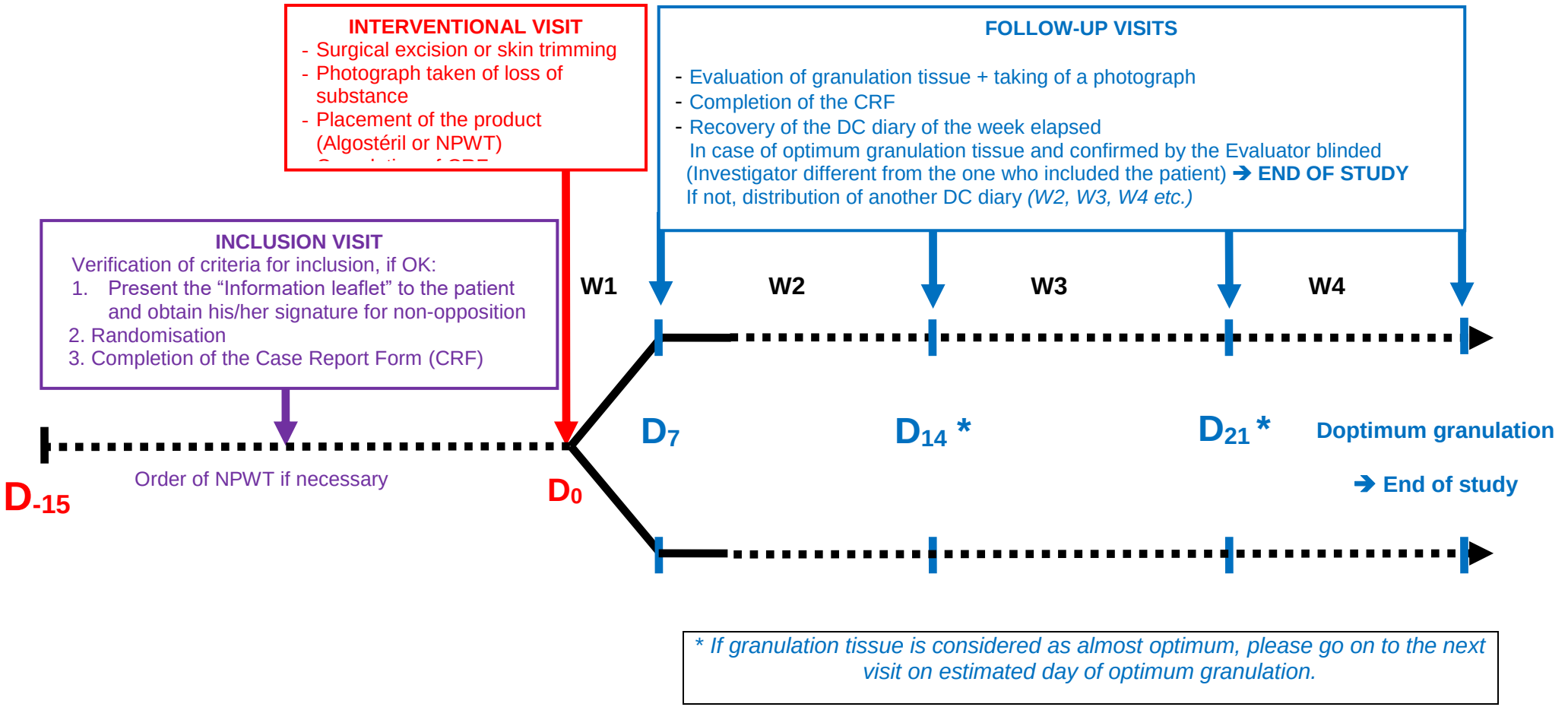
"ATEC" STUDY FLOWCHART



** If granulation tissue is considered as almost optimum, please go on to the next visit on estimated day of optimum granulation.*

4. STUDY RATIONALE

Surgical excision of skin and of underlying soft tissue is performed in plastic surgery for tumour, traumatic or infectious reasons. If the resultant surgical excision has a well-vascularised foundation, it can be covered by a thin skin graft, either at the outset or secondarily after a phase of granulation tissue formation and wound retraction. Granulation occurs naturally and spontaneously within a few weeks. This phase, called guided healing, has the goal of reducing the dimensions of this surgical excision and of obtaining optimum granulation tissue to receive a skin graft[1, 2].

Such granulation tissue can be promoted by medical devices (MD) among which Algosteril and NPWT are the most widely used with good results.

- **Algosteril** is obtained from brown seaweed, enriched in calcium ions. Thanks to its high drainage power, Algosteril eliminates the exudate from the lesion, traps bacteria in its fibres[3] and eliminates them when it is removed. Thanks to the release of its calcium ions, which activate key cells of healing, Algosteril accelerates granulation[4, 5].
  Comparative clinical studies have demonstrated the efficacy of Algosteril in healing of surgical excision subsequent to surgical excision of a pilonidal sinus[6], hidradenitis suppurativa [7] and radiotherapy-related necrosis of the head and neck[8]. In these studies, the time to obtain granulation tissue was shorter with Algosteril versus iodoform mesh, tulle gras and the combination antiseptic/tulle gras, respectively.
  Developed, produced and distributed by Brothier, an independent French pharmaceutical company, Algosteril has been on the market since 1991.
  Algosteril, reimbursed under its trade name on the LPP, is the only calcium alginate which has obtained class III EC marking, for invasive use, among other things for surgical and traumatic surgical excision infected or not.
  Its daily cost is about €7[9] and its changing of wound dressings requires a single nurse.
- **NPWT** consists of synthetic foam placed on the wound and covered by an occlusive film to ensure airtightness of the dressing. The entire system is connected by tubing to a reservoir and to a negative pressure electrical generator. The concept of NPWT consists of placing a wound under pressure less than atmospheric pressure in order to drain the exudate, to increase intra-tissue blood flow and to promote formation of granulation tissue.
  NPWT started to come into use commercially in the 1990s on a world-wide scale[1]. Its efficacy in complex and acute wounds has been described in many publications[10, 11].
  NPWT has been distributed in France for about 15 years[1], by several companies (KCI/USA, Smith&Nephew/UK, Hartmann/Germany, Mölnlycke/Sweden, etc.).
  It is indicated among other things in surgery with loss of infected substance or not[12].
  NPWT has a daily cost that can range up to €100[13, 14] and its renewal often requires the intervention of several nurses.

Based on a survey of practice performed on a national level by Brothier in 2012 on 983 French surgeons, Algosteril and NPWT are the two treatments most widely used in guided wound healing[15], 98.1% and 53.6%, respectively.

In spite of routine use of these two treatment strategies (Algosteril and NPWT) in preparation of surgical excision bed to skin grafting, no randomised clinical study has been conducted to compare their efficacy, their safety and their cost.

Furthermore, the authors of the Cochrane bibliographical review 2012[11] have issued an alert on the need for randomised clinical trials with good levels of evidence which compare NPWT to other dressings in acute wounds, because the only 5 randomised clinical trials found have a low level of evidence due to multiple biases (selection, performance, detection, attrition, etc.).

17 plastic/reconstructive surgery expert centres decide to conduct a national randomised clinical trial. The objective is to obtain, for the first time, clinical and economic evidence on the place of Algosteril and NPWT in the management of surgical excision. The aim of this study is to demonstrate similar efficacy of the two treatment strategies in the time to obtain optimum granulation tissue for skin grafting.

Brothier wishes to help them to conduct this trial whose status of "a research study on routine care" is justified in light of the following elements:

- The two MDs have EC marking and are routinely used in the indication concerned with similar results for efficacy on wound healing,
- Use of the two devices in the study will comply with recommendations of manufacturer's patient information leaflet, with no change,
- The specific modalities for monitoring during this study require negligible constraints for the patient and do not present any risk for the patient.

5. OBJECTIVES

5.1. Primary objective

To demonstrate the non-inferiority between the two treatment strategies (*Algosteril vs. NPWT*) within the timeframe to obtain optimum granulation tissue to receive a thin skin graft.

5.2. Secondary objectives

To compare the two treatment strategies for:

- cost of management,
-
- impact of the studied MD on the daily life of patients,
- the occurrence of adverse events which may be potentially attributable to the study MD.

6. DESIGN OF THE STUDY

6.1. Methods

A prospective clinical trial for evaluation of routine care: a multi-centre, national, randomised, two parallel group non-inferiority study with blinded evaluation of the primary outcome.
This study will compare the 2 treatment strategies in a 1:1 ratio.

6.1.1. Planned visits

- **Inclusion visit** (between D_{-15} and D_0): collection of the patient's non-opposition from, inclusion, randomisation, ordering of NPWT if applicable
  ⇨ CRFs:
  - validation of inclusion/non-inclusion criteria,
  - randomisation (IVRS or IWRS),
  - patient data (age, gender, factors in delay of healing, previous medical conditions, etc.),
  - data on the disorder.

- **Interventional visit** (D_0): surgical excision procedure /wound trimming, photo of surgical excision, placement of the randomised MD

⇨ CRFs:
- Data on surgical excision (size, location, etc.),
- Quantity of study products used.

- **Weekly follow-up visits** (D_7, D_{14}…, D_X = D $_{\text{optimum granulation}}$): evaluation of quality of granulation tissue, photos of surgical excision

⇨ CRFs:
- Quality of granulation tissue,
- Concomitant treatments *(anti-biotics, analgesics, local anaesthetics/GA anticoagulants, any other treatment having an impact on granulation),*
- Dressing changes: number, place, duration, quantity of products used, number of nurses, etc.,
- impact of product on patient's daily life,
- adverse events potentially attributable to the study MD.

➔ **End of study = date of optimum granulation**

6.1.2. Photographic record standard procedure

At the interventional visit (after skin excision) and at each follow-up visit (after removal of the study MD), the investigator will photograph the surgical excision.

1. Rinse the surgical excision with 0.9% sodium chloride and then blot it with a sterile compress to avoid any reflection,
2. Use a single colour surgical drape,
3. Place, at the opposite (below or above) of the surgical excision, small ruler (graduated in cm) on which are clearly noted: date of day, centre number, patient's initials and number,
4. Hold the digital camera perpendicular 30 cm from the surgical excision,
5. Photograph the surgical excision (take all photographs under the same conditions, with the same type of camera).

Photographs taken for each patient will be stored on the hard disc of the investigator's computer and on the memory card of the camera.
Photographs will be identified as follows: centre no./patient no./patient's initials/date of visit, /a, b, c, etc. in case of several photographs for a given patient at the same visit.
The Brothier Clinical Research Associate will recover them on a USB data stick at monitoring visits.

6.1.3. Blinded evaluation of optimum granulation

1. By an evaluator

The study MDs are marketed and have different presentations. Therefore, they are visually recognisable. The MD allocated to the patient will be known by the investigator who will have included, operated on the patient and placed the study MD.

For evaluation of the date of optimum granulation (primary outcome), a surgeon, not involved in placement of study MDs nor in follow-up of the patient called "an evaluator" will be invited to participate.

At weekly follow-up visits and once the study MD has been removed from surgical excision, the "evaluator" will be called upon to evaluate the granulation tissue and to judge if the latter is optimum to receive a thin skin graft and without knowing the MD allocated to the patient.

In order to determine as precisely as possible, the date of optimum granulation in surgical excision, an additional follow-up visit may be planned in addition to the planned weekly follow-up visits.

2. By the Scientific Committee

At the end of the study, anonymised photographs of the surgical excision taken at $D_{optimum\ granulation}$ and at the previous visit will be studied independently by 3 members of the Scientific Committee (Dr. Guerreschi, Prof. Hu and Dr. Rousseau).
Each of them will validate the date $D_{optimum\ granulation}$ recorded in the CRFs or will propose another date.
If a date has not been chosen by majority opinion, the entire Scientific Committee will meet and will issue a decision on the date $D_{optimum\ granulation}$ for the patient concerned.
The statistical analysis will be based on the dates $D_{optimum\ granulation}$ chosen by the Scientific Committee (in absence of the photograph or if photographs are not evaluable, the dates chosen will be those in the CRFs).

6.1.4. Collection of data

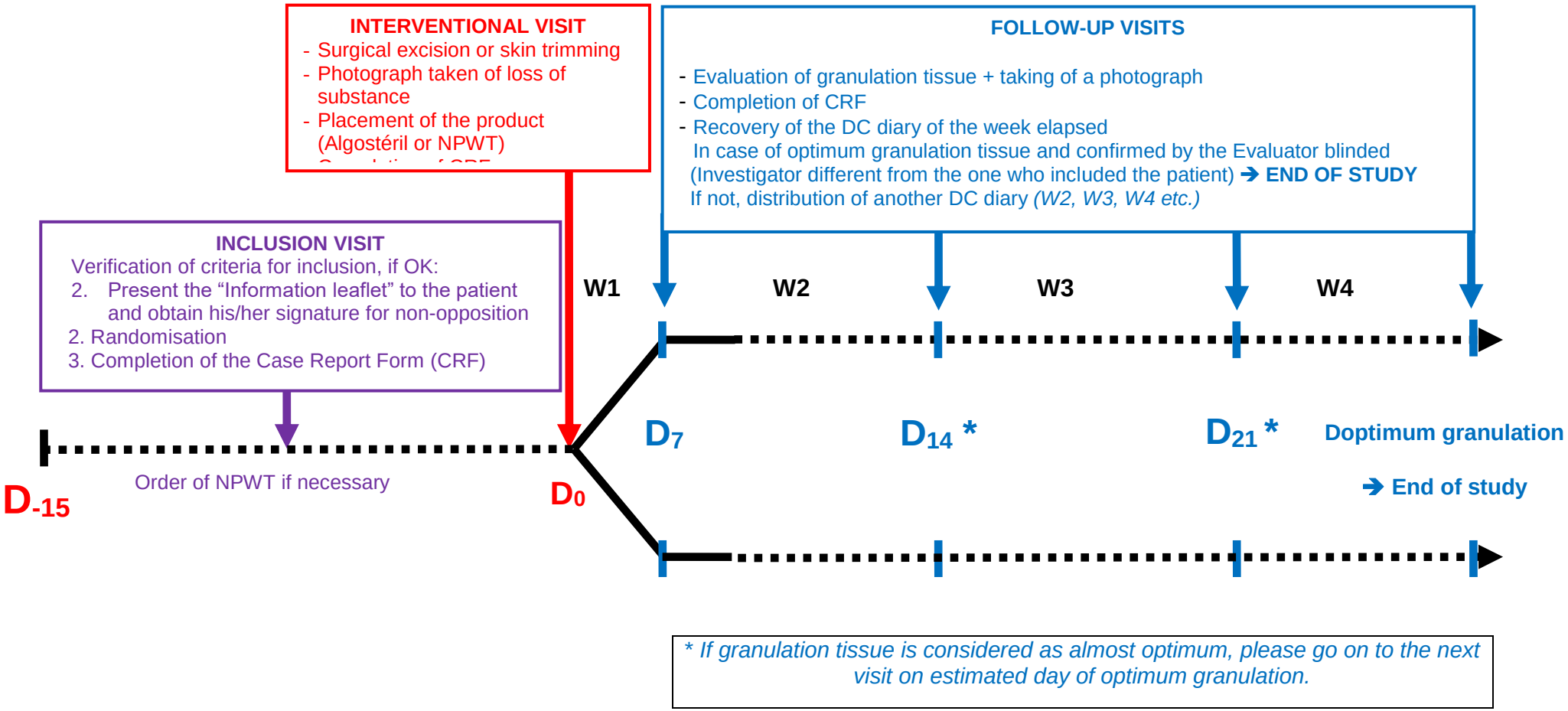
Case report forms (CRF)
For each patient and at each visit, the investigator must complete the CRF which will have been given to him.

Dressing change diary (DC diary)
For each patient and at each change of the wound dressing, the DC diary must complete this diary which records the patient's progress.

Specific diary discontinuation randomised treatment
In case of discontinuation of the randomised treatment, the information initially collected in the DC diary is collected in this specific diary which follows the patient.

NB: in the following pages, by "DC diary", it will be understood "dressing change diary" or "Specific diary discontinuation of randomised treatment" if applicable.

6.2. Overall study design



6.3. Randomisation

Technical modalities

At the inclusion visit (between D_{-15} and D_0), after verification of compliance with criteria for inclusion and non-inclusion and collection of non-opposition from the patient, the investigator may include the patient and randomise him/her to the medical device allocated:

By IVRS (phone): 01.40.88.66.10

By IWRS (internet): www.brothier-etude-atec.com

Person responsible for establishment of the randomisation list

The randomisation list will be pre-established by an independent company ABPlus.

Location of retention of randomisation list

- ABPlus company

7. INCLUSION AND NON-INCLUSION CRITERIA

7.1. Inclusion criteria

The following patients will be included:

- Patients 18 years of age or older,
- Who are to undergo:
  - Surgical excision or trimming of the skin and of the soft tissue for a tumour, trauma or infection *(hidradenitis suppurativa, Fournier's gangrene, necrotising fasciitis, traumatic skin damage, suture breaking, abscess, pilonidal sinus, etc.)*
  - Or a skin flap

  Surgical excision (minimum size of 30cm²) should be left in guided healing up until obtainment of optimum granulation tissue in order to receive a thin skin graft,
- Informed, who understand the information and consenting by non-opposition,
- Who can be followed throughout duration of the study,
- Who are beneficiaries of the social security system.

7.2. Non-inclusion criteria

The following patients will not be included:

- Patients with uncontrolled hyperglycaemia (HbA1C>10%),
- For whom excision is subsequent to a burn,
- For whom use of the study MDs is contra-indicated,
- Treated within 30 days prior to including with immuno-suppressant chemotherapy or radiotherapy on the site of excision.

7.3. Recruitment procedure

Recruitment will be done in departments of plastic surgery and traumatology. The investigator will verify at the pre-operative consultation (between D_{-15} and D_0) the eligibility of each patient while referring to the criteria for inclusion and of non-inclusion. If the patient is eligible, he will receive the "patient information leaflet".

A patient will be included only if he/she is not opposed to his/her participation in this study and the latter will last up until obtainment of optimum granulation in order to receive a thin skin graft. The total recruitment period will be 12 months.

8. NATURE OF THE MEDICAL DEVICES (MD) EVALUATED IN THE STUDY

Surgical excision of tumoural or traumatic infected/non-infected skin/sub-cutaneous tissue, (*hidradenitis suppurativa, Fournier's gangrene, necrotising fasciitis, traumatic skin damage, suture breaking, absces, pressure ulcer, pilonidal sinus, etc.)* will be performed in the OR according to the investigator's usual practice.

The randomised MD (Algosteril or NPWT) will be installed in the OR at the end of the procedure and then will be changed according to the product leaflet for use respectively up until obtainment of optimum granulation in order to receive a STSG.

8.1. Study medical devices

Algosteril

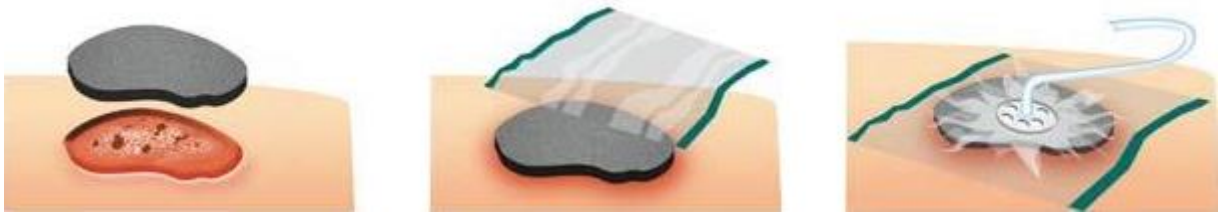
- Trade name (manufacturer and distributor in France): Algosteril flat mesh and Algosteril compress 10x20 (Brothier)
- Composition: calcium alginate fibres
- Mechanism of action: by means of its high drainage power, Algosteril eliminates the exudate from the lesion, traps bacteria in its fibres and eliminates them at time of its removal. Thanks to its release of its calcium ions which activate the key cells in healing, Algosteril accelerates granulation
- Indication/class III EC marking: surgical and traumatic surgical excision, infected lesion or not, etc.
- Protocol of use: refer strictly to manufacturer's recommendations *(see product leaflet for use).*
  - Cleanse the lesion
  - In case of a moderately exudative lesion or of stinging, moisten Algosteril using only 0.9% NaCl solution (or Ringer's solution)
  - Introduce Algosteril into the cavity of tissue loss without tamping
  - Cover the Algosteril with a secondary dressing
  - Dressing change:
    Infected wound → Twice a day up until disappearance of local signs of infection
    Exudative or fibrinous wound → once a day
    Clean wound → every 2 days

  Removal of Algosteril can be facilitated by moisturising with a 0.9% NaCl solution.

Negative pressure treatment (NPWT)

All NPWT systems *(without instillation, no PICO system)*, used with or without an interface according to practice of the centre

- Trade name (distributor in France): Renasys (Smith &Nephew), VAC Therapy (KCI Medical), etc.
- Composition: electrical generator source of controlled negative pressure, sterile dressing (polyvinyl alcohol/polyurethane foam), a drainage device, an adhesive drape, reservoir.
  Consumables delivered with different systems marketed are specific to each manufacturer and are not interchangeable.



Important:
- the most widely used practice with NPWT → black foam and pressure of -125 mmHg.
- the HAS does not recommend use of the hospital's central vacuum system as source of negative pressure.

- Method of action: the NPWT system promotes formation of granulation tissue by:
  - decrease of oedema and of exudates formed in the wound,
  - decrease in bacteria colonisation,
  - improvement of vascular and lymphatic circulation and of local oxygenation.
- Indications/class IIb EC marking: surgical excision with loss of infected substance or not.
- Protocol for use: refer strictly to manufacturer's recommendations *(see product leaflet for use).*
  - Cleanse wound and dry its edges
  - Cut and adjust the foam to the size of the wound, it is possible to use an interface between the wound and the foam
  - Cover it with adhesive film
  - Position the drainage device and connect it to the reservoir and to the electrical generator
  - Switch on the generator

  Changing of the dressing will be performed according to the usual practices and in conformity with the product leaflet for use.

8.2. Labelling, storage and MD distribution circuit

The study MDs are marketed products usually used by departments of surgery participating in the study. The products are paid for by the hospital as part of the study.

There is no specific labelling necessary in the setting of a study with routine care.
Products will be stored according to the manufacturer's recommendations and will follow the usual distribution circuit planned in the institution.

NB: In the centres where dispensing of NPWT is nominative and/or requires a period of time to be available, the investigator will take measures to reserve it in advance so that it is available in the operating room for the interventional visit at D0**.**

9. OUTCOMES

MEASURES

9.1. Primary outcome

The primary outcome is the time to obtain optimum granulation tissue, i.e., number of days between surgical excision/wound trimming and date of optimum granulation in order to receive a STSG.

→ Definition of optimum granulation tissue:
- granulation tissue which uniformly covers the foundation of the surgical excision,
- homogeneous, pink and continuous,
- not oozing, not haemorrhagic, not infected and well vascularised.

→Evaluation on date of optimum granulation:
At each follow-up visit of the patient:
- The surgical excision will be photographed (with a small ruler placed on the edge with date, initials, patient no./centre no.)
- The granulation tissue will be evaluated blindly by an evaluator different from the investigator who placed the study MD
- The date when granulation tissue is considered optimum for a graft ($D_{optimum\ granulation}$) will be recorded in the CRFs.

At the end of the study, anonymised photographs of the surgical excision taken at $D_{optimum\ granulation}$ and at the previous visit will be studied independently by four members of the Scientific Committee (Dr. Guerreschi, Prof. Hu, Prof. Moutet and Dr. Rousseau).
Each of them will validate the date $D_{optimum\ granulation}$ recorded in the CRF or will propose another date.
If a date has not been chosen by a majority, the entire Scientific Committee will meet and will issue a decision on the date $D_{optimum\ granulation}$ for the patient concerned.
The statistical analysis will be based on the $D_{optimum\ granulation}$ chosen by the Scientific Committee (in the absence of a photograph or if the photographs are not evaluable), the dates chosen will be those proposed in the CRF).

9.2. Secondary outcomes

9.2.1. Cost of management

Cost of management of surgical excision will be evaluated by taking into account:
- Number of healthcare interventions,
- Products used per case,
- The place where dressing change is performed (patient's bedside, OR, etc.),
- Duration of dressing change,
- Number of nurses,
- Concomitant treatments: antibiotics, analgesics, local anaesthetics or general anaesthesia, etc.

9.2.2. Impact of study product on patient's daily life

At each weekly follow-up visit, the following will be evaluated: the sound noises, background pain, discomfort during sleep and or movement.

9.2.3. Safety

Safety will be evaluated by the nature and frequency of adverse events potentially attributable to the study MD.

10. CONDUCT OF THE STUDY

Role of the Scientific Committee

The Scientific Committee, comprised of clinicians, will be consulted by the sponsor for:

- Drafting of study documents (synopsis, protocol and CRFs)
- Meeting requests for information not developed in the protocol from doctors participating in this study.
- Participating in the application of results (end of study report, summary of results sent to doctors participating in this study)

Different meetings will be organised:
- in order to establish a consensus of date of optimum granulation,
- for the review of statistical results.

10.1. Provisional study schedule

- Submission to the competent authorities: June 2013
- Set up of study: July 2014
- Inclusion period: up to 30 March 2016
- Maximum duration of study per patient: up to optimum granulation
- End of study: 30 June 2016
- Locking of the database: Nov. 2016
- 1st statistical results: Dec. 2016
- Final results: Jan. 2017
- Final report: March 2017

10.2. Summary table of patient follow-up

Visits	INCLUSION	INTERVENTION	WEEKLY FOLLOW-UP *			
Dates	D_{-15} to D_0 Pre-operative consultation	D_0	**Follow-up 1** $D_7 \pm 2d$	**Follow-up 2** $D_{14} \pm 2d$	...	**Follow-up X** End of study
• Validation of criteria for inclusion and non-inclusion • Information for the patient • Signature by the investigator of patient non-opposition • Inclusion • Randomisation (ordering of NPWT if applicable**) • Collection: patient data, data on the disorder	✓					
• Surgical excision/wound trimming • Placement of randomised MD (Algosteril or NPWT) • Collection: data on surgical excision, quantity of study products used		✓				
Photographs of surgical excision		✓	✓	✓	✓	✓
Collection: concomitant treatments, adverse events potentially attributable to the study MD		✓	✓	✓	✓	✓
• Evaluation of the quality of granulation by an evaluator different from the investigator • Dressing change: quantity of products used for + duration/location + number of nurses + analgesics and local anaesthetics or general anaesthesia			✓	✓	✓	✓
Verification of completion of the DC diary			✓	✓	✓	✓
Date of optimum granulation (end of study)						✓

***** When the date of optimum granulation appears to be near, an **additional follow-up visit** may be planned.

**** Important:** In centres where dispensing of NPWT is by name and/or requires a time period, the investigator will take the measures necessary to reserve it in advance so that it is available in the OR for the intervention visit at D0.

10.3. Inclusion Visit (D-15 to D0)

Collection of non-opposition from patient
The inclusion visit will take place at the pre-operative consultation, at most 15 days before the surgical procedure.
The investigator:

- Will verify the criteria for inclusion and for non-inclusion of the patient. If the patient complies with all criteria for inclusion and non-inclusion, the investigator will invite him/her to participate in the study and will give him/her the "Information leaflet", will give him/her all information necessary on the study (explanation of the study objectives, the MDs compared, conduct and constraints of the study, etc.) and will answer all his/her questions.

➔ If the patient is not opposed to his/her participation, the investigator will complete and sign the "Information leaflet".

Inclusion and randomisation
Once the patient has been included, the investigator may perform randomisation of the patient. Randomisation will be done by phone or by internet. The patient number and the study product will be allocated.

Data to be recorded in the CRF

- validation of criteria for inclusion/non-inclusion,
- patient data (age, gender, factors on time to healing, previous medical disorders, etc.),
- data on the disorder.

Ordering of the NPWT, if applicable
In centres where dispensing of a NPWT requires a period of time, the investigator will take the necessary measures so that NPWT is available in the OR on day of the intervention (D0).

10.4. Interventional visit (at D0)

The "Interventional visit" may take place on the same day as the "Inclusion visit".

Surgical excision or wound trimming in the OR
Algosteril and NPWT should be available in the OR before start of the intervention.
Surgical excision or wound trimming will be performed by the investigator according his/her usual practice. A photograph of the surgical excision will be taken at the end of the procedure and before placement of the allocated MD.

Placement of the randomised MD
The MD to be applied in the OR, at the end of the intervention, will be the one indicated by randomisation (*Algosteril or NPWT*)
The protocols for placement will be in conformity with the product leaflets for use.

Data to be collected in the CRF

- Data on surgical excision (size, location, etc.)
- Quantity of study products used.

10.5. Dressing change performed by the registered nurse between the follow-up visits

Wound dressings will be changed up until obtainment of granulation tissue suitable to receive a skin graft. Changing of dressings will be done in compliance with manufacturer's recommendations.

The protocols for changing of wound dressings *(during hospitalisation or in the patient's home)* will be in conformity with usual practice and the manufacturer's recommendations.

At each changing of the dressing, the nurse will collect in the DC diary, the following data:

- Treatments for dressing change: *analgesics, local anaesthetics/GA, etc.*
- Number of dressing changes, place, duration, quantity of products used, number of nurses, etc.

In case of discontinuation of the randomised treatment, the information initially collected in the DC diary will be collected in the Specific diary as well as the date and reasons for discontinuation of treatment.

10.6. Follow-up visits by the investigator (at D_7, D_{14}…, $D_X = D_{optimum\ granulation}$)

Evaluation of optimum granulation tissue in the surgical excision area

The patient will be seen again by the investigator every 7 days (± 1 day) with the principal objective being an evaluation of the quality of granulation tissue of surgical excision.

If the granulation tissue appears to be close to optimum granulation tissue in order to receive a thin skin graft, the investigator may schedule intermediate visits.

At each follow-up visit, the investigator, after removal of the wound dressing, should call the evaluator who will evaluate if the quality of the granulation tissue is optimum in order to receive a thin skin graft. If it is, the date of optimum granulation tissue will be recorded.
Optimum granulation tissue is defined as follows:

- Granulation tissue which covers the totality of the foundation of the surgical excision,
- Homogenous, pink and continuous,
- Non-oozing, non-haemorrhagic, not infected and well vascularised.

Photograph of the surgical excision

At each follow-up visit, the investigator will take a photo of the surgical excision.

Data to be collected in the CRFs

- Quality of the granulation tissue,
- concomitant treatments *(antibiotics, analgesics, local anaesthetics/GA, anti-coagulants, all other treatment which have an impact on granulation),*
- number of dressing changes, place, duration, quantity of products used, number of nurses, etc.
- adverse events potentially attributable to the study MD.

The investigator will verify completion of the DC diary.

10.7. Evaluation of the primary outcome by the Scientific Committee

At the end of the study, anonymised photographs of the surgical excision taken at $D_{optimum\ granulation}$ and at the previous visit will be studied independently by four members of the Scientific Committee (Dr. Guerreschi, Prof. Hu, Prof. Moutet and Dr. Rousseau).

Each of them will validate the date $D_{optimum\ granulation}$ recorded in the CRF or will propose another date.

If a date has not been chosen by a majority opinion, the entire Scientific Committee will meet and will issue a decision on the date $D_{optimum\ granulation}$ for the patient concerned.

The statistical analysis will be based on the $D_{optimum\ granulation}$ chosen by the Scientific Committee (in the absence of a photograph or if the photographs are not evaluable), the dates chosen will be those proposed in the CRF).

10.8. Criteria for withdrawal of patients

Withdrawal of a patient from the study may occur:

- At the request of a patient, who can withdraw from the study at any time without affecting the quality of care to which he/she is entitled,
- If the patient is lost to follow-up. Whenever the investigator no longer has any news from the patient, he/she should make every effort to contact the patient in order to determine his/her reason for withdrawal from the study and to offer him/her an end of study visit. If all attempts to contact a participant fail, the investigator then declares the patient "lost to follow-up". The investigator must document all attempts in the corresponding medical dossier.
- Whenever the investigator considers the continuation of the patient in the study as harmful, in particular, in case of occurrence of a serious case event.
- In case of a protocol violation.
- At the request of the sponsor/person responsible for the study.
- Study withdrawals can become effective only after confirmation by the investigator ***AND*** the sponsor of the study. Such withdrawals from the study are always final.

In all cases, the reason for withdrawal from the study must be indicated in the CRFs. Subjects who are withdrawals from the study will not be replaced.

11. MANAGEMENT OF SERIOUS AND NON-SERIOUS ADVERSE EVENTS

Adverse events must follow the usual channel for reporting planned by regulation in force:

- adverse events that may be related to a medicinal product are to be reported to the pharmacovigilance regional centre
- incidents or risks of incidents resulting from use of a medical device are to be reported to the material vigilance local contact
- other (reporting of nosocomial infections, etc.)

No procedure for management of serious adverse events is required by this type of study.

In the setting of the study, nevertheless the investigator will be asked to mention in the CRFs all serious or non-serious adverse events considered as likely to be related to the study MD *(that is for which in the opinion of the investigator or the sponsor, it is reasonably possible that is directly or indirectly related to the randomised MD).*

Reminder:
Serious adverse event = all adverse events which:

- Are fatal,
- Are life-threatening for the person who is the subject of the research,
- Require hospitalisation for more than 24 hours or result in prolongation of hospitalisation,
- Result in incapacity or an important or durable disability,
- Are manifest by a congenital anomaly or a malformation.

12. DATA MANAGEMENT AND STATISTICS

12.1. Determination of sample size

The primary outcome is the time (in days) between the date of surgical excision/wound trimming and date of optimum granulation in order to receive a thin skin graft.

The calculation is based on a study of non-inferiority of Algosteril *vs* NPWT.

For this purpose, the number of patients to be analysed is 50 per group taking as the hypothesis the following elements:

- Type 1 error $\alpha = 0.025$ *(one-sided p value)*
- Statistical power = 80%
- Expected difference in efficacy between the 2 groups = 0
- Standard deviation = 7 days [17]
- Margin Δ non-inferiority (a greater loss of efficacy than can be tolerated) = 4 days *(validated by the study investigators).*

This calculation has been performed with the NQuery 7.0 software.
Two analysis will be performed, one on ITT and the other Per PP.
In order to take into account patients with a protocol major deviation, who are lost to follow-up, etc. (evaluated as a maximum of 10%), 56 patients per group must be included, i.e., a total of 112. This total number of subjects to be included is compatible with feasibility of such a project by 17 plastic surgery/reconstructive surgery centres within a reasonable time period.

Considering all secondary outcomes, the comparison between groups will be based on the search for a difference between the groups.

Concerning comparison of cost of management, no calculation of power *a priori* is possible. Calculation of power will be performed *post hoc* to determine the effect of statistical power in order to detect the difference observed, considering the number of patients in the study.

12.2. Statistical analysis

The analysis will be performed by RCTs (an independent company) under the SAS software version 9.2 or later according to a statistical analysis plan (SAP) which will be written based on all elements described in the protocol.

Two populations of analysis will be defined in this study:

- ITT Population: all randomised patients (including all cases of protocol major deviation) who received at least on one day one of the study MD,
- "Per Protocol" (PP) Population: all patients included and who received one of the study MD, except for protocol major deviations.

The type 1 error is set at $\alpha = 0.05$ two-sided. All evaluation end points will be analysed in the two populations of interest ITT and PP.

Protocol deviations will be classified by the Scientific Committee as "major deviations" or "minor deviations" at time of review of data prior to locking of the database and blinded to the randomised strategy. Major deviations include significant deviations compared to

inclusion/non-inclusion criteria, non-compliance with the study protocol, as well as for protocols for use of the MD.

All parameters collected will be presented in tables containing descriptive statistics for each of the two groups, as well as the totality of the population analysed, according to the following modalities:

- For quantitative variables: number of missing values and of non-missing values, mean, standard deviation, 95% confidence interval, median, 1st quartile, 3rd quartile, minimum and maximum,
- For qualitative variables: number of missing values and of non-missing values, frequencies, percentages and 95% confidence intervals for each of the modalities of the variable (excluding missing data from the denominator).

Analysis of the primary outcome:

Analysis of the primary outcome will involve the two populations of analysis defined without a hierarchy on ITT and PP. In order to be able to conclude, conclusions obtained in these 2 populations should concur.

The primary outcome is comparison of the time to optimum granulation of Algosteril and of NPWT in non-inferiority.

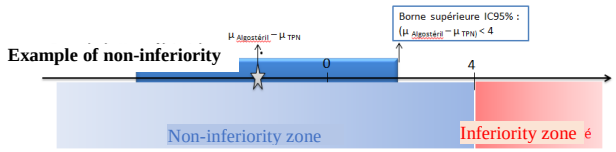
The null hypothesis of inferiority will be tested: $\mu_{Algosteril} - \mu_{NPWT} \geq \Delta$.

An approach with a two-sided 95% confidence interval of the difference between the 2 groups $\mu_{Algosteril} - \mu_{NPWT}$ will be performed.

If the upper limit of the 95% confidence interval is less than the margin of non-inferiority consented (Δ = 4 days), the null hypothesis will be rejected to the benefit of the alternative hypothesis of non-inferiority of Algosteril vs. NPWT ($\mu_{Algosteril} - \mu_{NPWT} < \Delta$).

If the upper limit of the 95% confidence level is less than the margin of non-inferiority consented (Δ = 4 days), but also less than 0, the superiority of Algosteril vs. NPWT will be demonstrated at level of significance α = 0.05 (in conformity with the EMA guideline (http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf).

The level of significance will be obtained with Student's t test.



Analysis of secondary outcomes:

Analysis of secondary outcomes will be performed on the two populations of analysis defined without a hierarchy on (ITT and PP) and based on a search for a statistical difference between the two groups at the limit α=0.05, two-sided. In order to be able to conclude, the conclusions obtained in the 2 populations should concur.

The secondary outcomes will be evaluated by the comparison of Algosteril and of NPWT on quality of life, pain and cost of management. Comparison between groups will be performed using the Analysis of Covariance model (for continuous variables) and logistic regression analysis (for binary variables) incorporating a centre factor, as well as evaluation of the criterion at time of the initial evaluation (if available).

A description of adverse events potentially attributable to the study medical devices (MD) will be performed on the entire on ITT population and in each of the two groups.

13. RIGHT OF ACCESS TO DATA AND SOURCE DATA

13.1. Access to data

The sponsor is in charge of obtaining the agreement of all parties involved in the study in order to ensure direct access to all places of conduct of the study, to source data, to source documents and to reports for the purpose of quality control and of an audit.
The investigators will make available documents and individual data strictly necessary for follow-up, for quality control and for an audit of the study, to the persons who have access to these documents in conformity with legislative and regulatory conditions in force.

13.2. Source data

All documents or original objects enabling to demonstrate the existence or accuracy of data or of a fact recorded during the study are defined as source documents (medical record, original of laboratory test results, imaging reports, etc.).

13.3. Confidentiality of data

In conformity with legislative conditions in force, persons who have direct access to source data will take all precautions necessary in order to ensure confidentiality of information relating to this study, to persons who are subjects in it, and in particular concerning their identity, as well as the results obtained. Such persons in the same capacity as the investigators are subject to professional secrecy.

During this study or at its end, data collected on persons who are subjects in it and sent to the sponsor by investigators (or all other specialised participants) will be coded. They must not in any case clearly show the names of persons concerned or their address (only the first letters of the patient's surname and of the first name will be recorded, together with the specific code for the study indicating the order of inclusion of patients).

The sponsor will ensure that each person who is a subject in the study has been informed about access to his/her individual data and is strictly necessary for quality control of this study.

14. QUALITY CONTROL AND INSURANCE

14.1. Instructions for data collection

All information required by the protocol will be recorded in the CRFs, the DC diaries (paper documents). Data should be collected progressively as they are obtained and recorded in the case report forms and the DC diaries, clearly and legibly.

Data collected in the DC diary and certain data in the "CRF" (percentage of granulation of the wound and impact of the studied product on the patient's daily life will be considered as source data.
Erroneous data recorded in CRFs and DC diaries will be crossed out clearly and the new data will be copied next to the crossed-out information, together with the reviewer's initials, the date and possibly the reason given by the investigator or by the authorised person who have made the correction.
Whenever the investigator no longer has any news from a patient, he/she should make every effort to contact him/her in order to determine the reason for the patient's withdrawal from the study and to invite him/her to attend an end of study visit. If all attempts to contact the participant fail, the investigator can then declare the patient as "***lost to follow-up***". The investigator should document all attempts in the corresponding medical dossier.

14.2. Study follow-up and quality control

➢ A visit to set up the study will be performed in each centre participating in the study by the Study project leader. The purpose of this visit is to:

- Present to the study centre the protocol, the conditions for providing information and obtaining of non-opposition from the patient to participate in this study, to present the CRFs and the DC diary,
- To recover study documents (such as the protocol signature page signed by the principal investigator, the form on the "On-site staff participating in this study", etc.),
- To distribute the study documents (protocol, CRFs, DC diary, investigator binder, etc.),

➢ A monitor mandated by Brothier will ensure regularly, in each centre, the proper conduct of the study, the collection of data generated in writing, their documentation, recording and report, in agreement with Standard Operating Procedures applied at Brothier and in conformity with Good Clinical Practice, as well as with legislative and regulatory conditions in force.

On-site monitoring visits will be organised after making an appointment with the investigator. The investigator and members of his/her team accept to make him/herself available at such visits performed at regular intervals by the Brothier monitor.

The frequency of visits performed will depend on number of patients included, the rate of inclusions and on difficulties encountered in conduct of this study.

At these visits, the following items will be reviewed:
- compliance with the study protocol, the procedures defined in it and regulatory text in force,
- signature by the investigator of the information leaflet certifying non-opposition of the patient,
- the quality of data collected in the CRFs: accuracy, missing data, consistency of data with source documents (medical records, appointment logbooks, originals of laboratory test results, etc.).

Each visit will be the subject of a written report (monitoring visit form).

CRFs and DC diaries completed will be recovered progressively in the study in order to be sent to RCTs in charge of data entry and of data management. Requests for corrections issued from RCTs will be sent to the investigator.

➢ At the closing visit, the Brothier monitor will recover the last requests for corrections completed and signed by the investigator, the end of study documents (list of patients included, etc.).

The investigator agrees to make available to the Brothier monitor at the monitoring visits the following:

- the patient's medical dossiers (source dossiers),

- the CRFs,
- the DC diaries recovered,
- the information leaflets signed certifying non-opposition of patients.

The visit will be the subject of a written report (closing visit form).

14.3. Audit – Inspection

An audit can be performed at any time by persons mandated by the sponsor and independent of the person responsible for the study. Its objective is to ensure the quality of the study, the validity of its results and compliance with law and regulations in force.
Investigators agree to comply with requirements from the sponsor and from the competent authority regarding an audit or an inspection of the study.
The audit may be applied to all stages of the study, from development of the protocol to publication of results and to classification of data used or produced as part of the study.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Conformity with reference texts

Since the techniques and methods used in the study are usually performed, it can enter in the setting of a **study designed to evaluate routine care** as defined by law no. 2004-806 of 9 August 2004 (article L1121-1, line 2 and article R1121-3 of the public health code).

The sponsor (Brothier) and the investigators agree that this study will be conducted in conformity with law no. 2004-806 of 9 August 2004, as well as in agreement with Good Clinical Practice (ICH version 4 of 1 May 1996) and the declaration of Helsinki (Ethical practices applicable to medical research on human subjects, Tokyo 2004, see 22.1. Appendix 1).
The study will be conducted in conformity with the present protocol. Apart from emergency situations requiring the set up of precise therapeutic actions, the investigators agree with the protocol in all points.
This study has received a favourable opinion from the Committee for the Protection of Persons (CPP) (Ethics Committee) Ile de France IV on 15/07/2013, from the Consultative Committee for Data Processing in Research in the field of Health (CCTIRS) on xx/xx/2013 and authorisation from the National Commission on Data Processing and Freedoms (CNIL) on xx/xx/2013.

Data compiled and recorded at the time of this study will be subject to data processing by RCTs, an independent CRO specialising in data entry, processing and data analysis in the field of health in compliance with law no. 78-17 of 6 January 1978 relating to data processing, computer files and freedoms modified by law no. 2004-801 of 6 August 2004.

15.2. Information leaflet

At time of the pre-operative consultation, the investigator will invite the patient to participate in this study. The investigator will make known to the patient, in particular, the objective, methodology and duration of the study, as well as the expected benefits, the constraints and foreseeable risks. The investigator will also inform the patient of his/her right to oppose to participate in this study.

The investigator will give the patient the information leaflet which will first have been submitted to the CPP for an opinion.

The investigator can include a patient in the study only if the latter is not opposed to his/her participation in the study.
The investigator will complete, date and sign the information leaflet in three copies (one copy is given to the patient, one copy is kept by the investigator and one copy will be recovered by the sponsor) thus validating non-opposition of the patient.

In compliance with law no. 2002-303 of 4 March 2002, patients are informed, upon their request, of the overall results of the study.

15.3. Protocol amendment

Any substantial change, that is, any change of a nature so as to have a significant impact on protection of persons, on conditions of validity and on results of the study, on interpretation of scientific documents which support conduct of the study or on modalities of its conduct, is the subject of a written amendment which is submitted to the sponsor and to the Centre for Methodology and Management of data, if applicable, and the latter must obtain, prior to its implementation a favourable opinion of the CPP.

Non-substantial changes, that is, those which do not have a significant impact on whatever aspect of the study whatsoever, are communicated to the CPP for information.

All protocol amendments must be brought to the knowledge of all healthcare professionals participating in the study and who agree to comply with their content.

16. DATA PROCESSING AND RETENTION OF DOCUMENTS AND DATA RELATING TO THE STUDY

16.1. Data processing

After monitoring, management and retention of data will be performed based on SAS data version 9.2 or later.
A data-management plan built jointly by the data-manager RCTs and the Brothier Project Leader will be drafted.
After correction of errors that this plan has identified, the database will locked for analysis.

16.2. Retention of documents relating to the study

The following documents relating to the study will be archived in conformity with Good Clinical Practice **for a duration of 15 years after the end of the study:**

- By the investigator:
  - The protocol and possible protocol amendments,
  - The CRFs and DC diaries,
  - The source data of participants,
  - Information leaflets certifying non-opposition from patients,
  - All other documents and correspondence relating to the study.
- By the sponsor:
  - The protocol and possible protocol amendments,
  - The original of CRFs and of DC diaries,
  - Information leaflets certifying non-opposition of patients,

• All other documents and correspondence relating to the study.

Any transfer or destruction cannot be performed without the agreement of the sponsor. At the end of the regulatory duration of archiving, the sponsor will be consulted for destruction and will give his/her written agreement.

All data, all documents and reports may be the subject of an audit or inspection.

17. STUDY RESULTS

The sponsor will be in charge of writing a study report in collaboration with the members of the Scientific Committee and the coordinating investigator. The latter must certify, by his/her signature, that he/she has read the report and confirm that, to his/her knowledge, the latter accurately describes the conduct and results of the study.
When the data collected from all study centres has been entirely analysed by the sponsor, the latter will communicate the results of the study to the investigators, as well as the overall results of the study intended to be communicated to patients who accepted to participate, if they so request.
During the year following the end of the study, the sponsor will send the study synopsis to the Ethics committee and to the Regulatory authorities in the form of a final report summary.

18. FINANCIAL CONTRACT AND INSURANCE

Financing of investigators is detailed in each study agreement concluded with the latter.
Agreements will also be concluded with the directorate of the institutions participating in the study.
This study does not carry any additional risk. Therefore, it is common law which applies: insurance will be that of the institution responsible for healthcare (art L.1142-2).

19. RULES RELATING TO PUBLICATION

Brothier adheres to the process of circulation of scientific information.
The rights of Brothier and of investigators concerning publication of results are described in the research contracts established with the investigators.
By signing the protocol, the investigator accepts that the results of the study can be used for purposes of national and international registration, for purposes of publication and information of medical and pharmaceutical healthcare professionals.
If necessary: name, address, qualification and role in the study of investigators will be reported to the authorities.

20. PROPRIETARY RIGHTS

All information, materials and documents provided by the sponsor or its representative will be and will remain the exclusive property of the sponsor.
All results, documents, all data and inventions which result directly or indirectly from the study in whatever format become the immediate and exclusive property of the sponsor.
The sponsor will be free to utilise all results as it sees fit, without any restriction regarding proprietary rights (territory, field, duration). The sponsor will not be held to any obligation to patent, develop, market or to otherwise use results of the study.

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22. APPENDICES

22.1. Appendix 1: Declaration of Helsinki

ASSOCIATION MEDICALE MONDIALE
DECLARATION D'HELSINKI
Principes éthiques applicables à la recherche médicale impliquant des êtres humains

Adoptée par la 18e Assemblée générale de l'AMM, Helsinki, Finlande, Juin 1964 et amendée par les
29e Assemblée générale de l'AMM, Tokyo, Octobre 1975
35e Assemblée générale de l'AMM, Venise, Octobre 1983
41e Assemblée générale de l'AMM, Hong Kong, Septembre 1989
48e Assemblée générale de l'AMM, Somerset West (Afrique du Sud), Octobre 1996
52e Assemblée générale de l'AMM, Edimbourg, Ecosse, Octobre 2000
53e Assemblée générale de l'AMM, Washington, Etats Unis, 2002 (ajout d'une note de clarification pour le paragraphe 29)
55e Assemblée générale de l'AMM, Tokyo, Japon 2004 (ajout d'une note de clarification concernant le paragraphe 30)
59e Assemblée générale de l'AMM, Séoul, Corée, Octobre 2008

A. INTRODUCTION

1. L'Association Médicale Mondiale (AMM) a élaboré la Déclaration d'Helsinki comme un énoncé de principes éthiques applicables à la recherche médicale impliquant des êtres humains, y compris la recherche sur du matériel biologique humain et sur des données identifiables.

   La Déclaration est conçue comme un tout indissociable. Aucun paragraphe ne peut être appliqué sans tenir compte de tous les autres paragraphes pertinents.

2. Cette Déclaration s'adresse principalement aux médecins. L'AMM invite cependant les autres participants à la recherche médicale impliquant des êtres humains à adopter ces principes.

3. Le devoir du médecin est de promouvoir et de sauvegarder la santé des patients, y compris celles des personnes impliquées dans la recherche médicale. Le médecin consacre son savoir et sa conscience à l'accomplissement de ce devoir.

4. La Déclaration de Genève de l'AMM engage les médecins en ces termes: «La santé de mon patient prévaudra sur toutes les autres considérations » et le Code International d'Ethique Médicale déclare qu'un «médecin doit agir dans le meilleur intérêt du patient lorsqu'il le soigne».

5. Le progrès médical est basé sur la recherche qui, en définitive, doit comprendre des études impliquant des êtres humains. Des possibilités appropriées de participer à la recherche médicale devraient être offertes aux populations qui y sont sous-représentées.

6. Dans la recherche médicale impliquant des êtres humains, le bien-être de chaque personne impliquée dans la recherche doit prévaloir sur tous les autres intérêts.

7. L'objectif premier de la recherche médicale impliquant des êtres humains est de comprendre les causes, le développement et les effets des maladies et d'améliorer les

15. Le protocole de recherche doit être soumis à un comité d'éthique de la recherche pour évaluation, commentaires, conseils et approbation avant que l'étude ne commence. Ce comité doit être indépendant du chercheur, du promoteur et de toute autre influence indue. Il doit prendre en considération les lois et réglementations du ou des pays où se déroule la recherche, ainsi que les normes et standards internationaux, mais ceux-ci ne doivent pas permettre de restreindre ou exclure l'une des protections garanties par la présente Déclaration aux personnes impliquées dans la recherche. Le comité doit avoir un droit de suivi sur les études en cours. Le chercheur doit fournir au comité des informations sur le suivi, notamment concernant tout évènement indésirable grave. Aucune modification ne peut être apportée au protocole sans évaluation et approbation par le comité.

16. La recherche médicale impliquant des êtres humains doit être conduite uniquement par des personnes scientifiquement qualifiées et expérimentées. La recherche impliquant des patients ou des volontaires en bonne santé nécessite la supervision d'un médecin ou d'un autre professionnel de santé qualifié et compétent. La responsabilité de protéger les personnes impliquées dans la recherche doit toujours incomber à un médecin ou à un autre professionnel de santé et jamais aux personnes impliquées dans la recherche même si celles-ci ont donné leur consentement.

17. La recherche médicale impliquant une population ou une communauté défavorisée ou vulnérable se justifie uniquement si la recherche répond aux besoins et priorités sanitaires de cette population ou communauté et si, selon toute vraisemblance, les résultats de la recherche seront bénéfiques à cette population ou communauté.

18. Toute recherche médicale impliquant des êtres humains doit préalablement faire l'objet d'une évaluation soigneuse des risques et des inconvénients prévisibles pour les personnes et les communautés impliquées dans la recherche, par rapport aux bénéfices prévisibles pour elles et les autres personnes ou communautés affectées par la pathologie étudiée.

19. Tout essai clinique doit être enregistré dans une banque de données accessible au public avant que ne soit recruté la première personne impliquée dans la recherche.

20. Les médecins ne sont pas autorisés à participer à une recherche impliquant des êtres humains sans avoir la certitude que les risques inhérents ont été correctement évalués et pourront être gérés de manière satisfaisante. Les médecins doivent cesser immédiatement une étude dès que les risques s'avèrent dépasser les bénéfices potentiels ou dès l'instant où des résultats positifs et bénéfiques ont été démontrés.

21. Une recherche médicale impliquant des êtres humains ne peut être conduite que si l'importance de l'objectif dépasse les risques et inconvénients inhérents pour les personnes impliquées dans la recherche.

22. La participation de personnes capables à une recherche médicale doit être un acte volontaire. Bien qu'il puisse être opportun de consulter les membres de la famille ou les responsables de la communauté, aucune personne capable ne peut être impliquée dans une étude sans qu'elle ait donné librement son consentement.

23. Toutes les précautions doivent être prises pour protéger la vie privée et la confidentialité des informations personnelles concernant les personnes impliquées dans la recherche, et pour minimiser l'impact de l'étude sur leur intégrité physique, mentale et sociale.

24. Dans la recherche médicale impliquant des personnes capables, toute personne pouvant potentiellement être impliquée dans la recherche doit être correctement informé des objectifs, des méthodes, des sources de financement, de tout éventuel conflit d'intérêts, des affiliations institutionnelles du chercheur, des bénéfices escomptés et des risques potentiels de l'étude, des désagréments qu'elle peut engendrer et de tout autre aspect pertinent de l'étude. La personne pouvant potentiellement être impliquée dans la recherche doit être informé de son droit de refuser de participer à l'étude ou de s'en retirer à tout moment sans mesure de rétorsion. Une attention particulière devrait être accordée aux besoins d'informations spécifiques de chaque personne pouvant potentiellement être impliquée dans la recherche ainsi qu'aux méthodes adoptées pour fournir les informations. Lorsque le médecin ou une autre personne qualifiée en la matière a la certitude que la personne concernée a compris les informations, il doit alors solliciter son consentement libre et éclairé, de préférence par écrit. Si le consentement ne peut pas être donné par écrit, le consentement non écrit doit être formellement documenté en présence d'un témoin.

25. Pour la recherche médicale utilisant des tissus ou des données d'origine humaine, les médecins doivent normalement solliciter le consentement pour le prélèvement, l'analyse, le stockage et/ou la réutilisation. Il peut se présenter des situations où il est impraticable, voire impossible d'obtenir le consentement ou que cela mettrait en péril la validité de la recherche. Dans de telles situations, la recherche peut être entreprise uniquement après évaluation et approbation d'un comité d'éthique de la recherche.

26. Lorsqu'il sollicite le consentement éclairé d'une personne pour sa participation à une recherche, le médecin devrait être particulièrement attentif lorsque cette dernière est dans une relation de dépendance avec lui ou pourrait donner son consentement sous la contrainte. Dans ce cas, le consentement éclairé devrait être sollicité par une personne qualifiée en la matière et complètement indépendante de cette relation.

27. Lorsque la recherche implique des personnes incapables, le médecin doit solliciter le consentement éclairé de leur représentant légal. Les personnes incapables ne doivent pas être inclues dans une étude qui n'a aucune chance de leur être bénéfique sauf si cette étude vise à améliorer la santé de la population qu'elles représentent, qu'elle ne peut pas être réalisée avec des personnes capables et qu'elle ne comporte que des risques et des inconvénients minimes.

28. Lorsqu'une personne considérée comme incapable est en mesure de donner son assentiment concernant sa participation à la recherche, le médecin doit solliciter cet assentiment en complément du consentement de son représentant légal. Le refus de la personne pouvant potentiellement être impliquée dans la recherche devrait être respecté.

29. La recherche impliquant des personnes physiquement ou mentalement incapables de donner leur consentement, par exemple des patients inconscients, peut être menée uniquement si l'état physique ou mental empêchant de donner un consentement éclairé

est une caractéristique nécessaire de la population sur laquelle porte cette recherche. Dans de telles circonstances, le médecin devrait solliciter le consentement éclairé du représentant légal. En l'absence d'un représentant légal et si la recherche ne peut pas être retardée, l'étude peut être lancée sans le consentement éclairé. Dans ce cas, le protocole de recherche doit mentionner les raisons spécifiques d'impliquer des personnes dont l'état les rend incapables de donner leur consentement éclairé et l'étude doit être approuvée par un comité d'éthique de la recherche. Le consentement pour maintenir la personne concernée dans la recherche devrait, dès que possible, être obtenu de la personne elle-même ou de son représentant légal.

30. Les auteurs, rédacteurs et éditeurs ont tous des obligations éthiques concernant la publication des résultats de recherche. Les auteurs ont le devoir de mettre à la disposition du public les résultats de leurs recherches sur les êtres humains. Ils ont la responsabilité de fournir des rapports complets et précis. Ils devraient se conformer aux directives acceptées en matière d'éthique pour la rédaction de rapports. Les résultats aussi bien négatifs et non concluants que positifs devraient être publiés ou rendus publics par un autre moyen. La publication devrait mentionner les sources de financement, les affiliations institutionnelles et les conflits d'intérêts. Les rapports de recherche non-conformes aux principes de la présente Déclaration ne devraient pas être acceptés pour publication.

C. PRINCIPES ADDITIONNELS POUR LA RECHERCHE MEDICALE ASSOCIEE A DES SOINS MEDICAUX

31. Le médecin peut associer la recherche médicale à des soins médicaux uniquement dans la mesure où la recherche se justifie par sa valeur potentielle en matière de prévention, de diagnostic ou de traitement et si le médecin a de bonnes raisons de penser que la participation à l'étude ne portera pas atteinte à la santé des patients concernés.

32. Les bénéfices, les risques, les inconvénients, ainsi que l'efficacité d'une nouvelle intervention doivent être testés et comparés à ceux de la meilleure intervention courante avérée, sauf dans les circonstances suivantes :
    - L'utilisation de placebo, ou le fait de ne pas administrer de traitement, est acceptable lorsqu'il n'existe pas d'intervention courante avérée; ou
    - l'utilisation d'un placebo afin de déterminer l'efficacité ou la sécurité d'une intervention est nécessaire pour des raisons de méthodologie incontournables et scientifiquement fondées, et les patients recevant le placebo ou aucun traitement ne courent aucun risque de préjudices graves ou irréversibles. Le plus grand soin doit être apporté afin d'éviter tout abus de cette option.

33. A la fin de l'étude, les patients impliqués ont le droit d'être informés des conclusions de l'étude et de profiter de tout bénéfice en résultant, par exemple, d'un accès aux interventions identifiées comme bénéfiques dans le cadre de l'étude ou à d'autres soins ou bénéfices appropriés.

34. Le médecin doit fournir des informations complètes au patient sur la nature des soins liés à la recherche. Le refus d'un patient de participer à une étude ou sa décision de s'en retirer ne doit jamais interférer avec la relation patient-médecin.

35. Dans le cadre du traitement d'un patient, faute d'interventions avérées ou faute d'efficacité de ces interventions, le médecin, après avoir sollicité les conseils d'experts et avec le consentement éclairé du patient ou de son représentant légal, peut recourir à une intervention non avérée si, selon son appréciation professionnelle, elle offre une chance de sauver la vie, rétablir la santé ou alléger les souffrances du patient. Dans toute la mesure du possible, cette intervention devrait faire l'objet d'une recherche pour en évaluer la sécurité et l'efficacité. Dans tous les cas, les nouvelles informations devraient être enregistrées et, le cas échéant, rendues publiques.

22.2. Appendix 2: Information note

Comparison of the efficacy, safety and cost of Algosteril® *vs.* Negative Pressure Wound Therapy (NPWT) in preparation for skin grafting for surgical excision subsequent to surgical excision

SHORT TITLE: ATEC Study - **RCB ID N.:** 2013-A00815-40

Document in triplicate to be given to the patient (yellow sheet), to the investigator and to the sponsor of the study (original)

Dear Sir or Madam,
Your Surgeon, Prof./Dr ..... is inviting you to participate in a clinical study, for which the sponsor is Brothier (*Pharmaceutical company located at 41 rue de Neuilly - 92375 Nanterre)* and national coordinator is Prof. Marc Revol (*Department of Plastic Surgery in Hôpital Saint Louis, Paris*).
Your participation in this study is entirely voluntary and you will have the right to oppose your pariticipation in it. In this case, your decision will not carry any prejudgement for the quality of your subsequent medical managment.
In order to enable you to take your decision, you will find in the following the information on conduct of the study. Please take the necessary time of reflection that you may need depending on degree of urgency of your intervention. Do not hesitate to ask your Surgeon all questions which you consider useful.

Why this study?
You are invited to participate in this study because your health condition requires a surgical procedure for which follow-up requires use of wound dressings which are the subject of this study.
The surgical procedure that you are going to undergo has the purpose of removing damaged skin and results in surgical excision (a wound) which requires in a second phase a skin graft. Wound dressings for healing are applied up until your wound is estimated as suitable to receive this graft.
For this purpose, the two dressings routinely used are those which are the subject of the study: Algosteril and Negative Pressure Wound Therapy (NPWT). Their healing efficacy and safety have been demonstrated by many clinical studies and they have obtained all approvals necessary for their implementation.
Algosteril (mesh or compress) is a vegetable wound dressing (marine seaweed) enriched with calcium ions.
NPWT consists of a foam placed on the wound and covered with an occlusive film. The entire system is connected by a tubing to a reservoir and to a suction pump with negative atmospheric pressure.
To date, no clinical study has been conducted to compare these two dressings to each other.
The clincian's experience suggests that these two wound dressings have similar healing efficacy and safety. In light of the fact that differences may exist regarding impact of intervention in patient daily life and the overall cost of management, it is important to conduct a comparative clinical study which will guide the choice of the treatment strategy.

Objective of this study?
The objective of this study is:
- To demonstrate that the two wound dressings make it possible to perform the skin graft within a similar time period,
- To evaluate the impact of your wound dressing on your daily life and cost of your management.

How will this study be conducted?
17 French departments of plastic surgery are participating in this study. It is planned to include 112 patients.

Patients participating in this study will be divided into two groups of dressings: "Algosteril group" and "NPWT group".

Your participation in this study involves:
A pre-operative consultation (today): your Surgeon, after examining you, has explained to you the purpose and conduct of the study. If you are not opposed to participating in it, he/she records this at the end of this document, he/she gives you a copy of it and includes you in the study.
Your assignment to one of the wound dressing groups or the other is determined by randomisation, that is, randomly. You have as much chance of being in the "Algosteril group" as well as in the "NPWT group".
Day of procedure: your Surgeon performs surgery according to usual practice and at the end of the procedure installs the dressing which has been allocated to you.
Throughout the study: your dressing is changed regularly (in the hospital or in your home).
Weekly follow-up visits: these take place until your wound is estimated as ready to receive a skin graft. In order to be as objective as possible, this estimate is performed in the presence of your surgeon or by another surgeon who does not know the type of dressing which has been allocated to you.
An additional follow-up visit may be planned if your wound appears ready to receive a skin graft before the next follow-up visit.
Photographs of your wound are taken by your Surgeon.
End of study/end of your participation: corresponds to the day when your wound is estimated as ready to receive a skin graft.

What are the possible disadvantages and what are your asked to do?
The constraints related to your participation in this study are negligeable and do not present any specific risk for you.
The possible disadvantages of NPWT are: dependence on the device, the sound of the motor and pain when it is removed.
No laboratory test (X-ray, blood test, etc.) is ordered for you and no restriction is imposed on you in the setting of this study.

What are the modalities of your management in case of withdrawal from the study?
If you have to discontinue your participation before the normal end of the study, whatever the reason, your Surgeon will enable you to receive the best possible management appropriate for your condition.

Confidentiality and use of your medical data
In the setting of this study, computer processing of your personal data will be performed to analyse the results with regard to the objective which has been presented to you. Your name will not appear on the different documents, it will be replaced by a number and by your initials.
Your personal medical data will be sent to Brothier or to persons or companies acting on its behalf in France. These data can also, under conditions ensuring their confidentiality, be sent to the health authorities.
In conformity with conditions of the law on data processing, computer files and freedoms, you have at all times the right of access and correction of your computerised personal data (law no. 2004-801 of 6 August 2004 modifying law no. 78-17 of 6 January 1978 relating to data processing, computer files and freedoms).
You also have the right to oppose transmission of your data, covered by professional secrecy that may be used in the seting of this study and may be processed.
You can also access directly or through the doctor of your choice all your medical data in application of conditions of article L1111-7 of the French Public Health Code. If you so desire, you will be informed by your Surgeon of the overall results of the study.
In conformity with the law on Public Health Policy on studies to evaluate routine care:

- The study protocol is recorded under the number 2013-A00815-40, as well as the non-opposition form.
- This study has obtained a favourable opinion:
  - From the Committee for the Protection of Persons Ile-de-France IV on 15/07/2013,

- From the Consultative Committee on Data Processing in Research in the Field of Health (CCTIRS) on 24/10/2013,
- Authorisation from the French National Commission on Data Processing and Freedoms (CNIL) on 12/06/2014.

Thank you for your contribution that you will provide to this study by participating in it.

COLLECTION OF NON-OPPOSITION FROM THE PATIENT

I, the undersigned, Dr./Prof. (Surname/First name): .....……..……..., Department: ……Hospital: ……....., hereby certify that Mr./Mrs. (Surname/First name): ..... is not opposed to participate in the ATEC study.

The patient has been informed on: .....

Surgeon's Signature: Patient's Signature:

22.3. Appendix 3 – Protocol for excision photography

- Rinse the surgical excision with 0.9% sodium chloride and then gently dab it with a sterile compress to avoid any reflection; use only one colour surgical drape.
- Place a small ruler calibrated in centimetres opposite the area of excision. Note on this ruler the date, centre number, patient's initials and inclusion number.
- Hold the digital camera perpendicular to the excision at a distance of 30 cm.
- Photograph all excisions under the same conditions and using the same type of camera.
- The photographs taken should be kept on both the memory card of the camera and the hard disk of the investigator's computer. The photographs should be identified with the following information: centre number/patient number/patient's initials/date of visit plus the order of the photographs (a, b, c,…) if several photographs are taken of a patient at the same visit.
- A clinical research associate will retrieve the photographs during monitoring visits.

22.4. Appendix 4 – list and contact information of study centres

SURNAME	FIRST NAME	INSTITUTION	ADDRESS	CITY
REVOL	Marc	APHP - HOPITAL SAINT LOUIS	1 av Claude Vellefaux	PARIS
BRAYE	Fabienne	HCL - HOPITAL EDOUARD HERRIOT	1 place d'Arsonval	LYON
ROUSSEAU	Pascal	CHU ANGERS	5 rue larrey	ANGERS
GUERRESCHI	Pierre	CHRU HOP SALENGRO	Av du Prof. Emile Laine	LILLE
PLUVY	Isabelle	CHR JEAN MINJOZ	Bld Fleming	BESANCON
DUTEILLE	Franck	CHU NANTES	30 bld Jean-Monnet	NANTES
BRUANT-RODIER	Catherine	CHU - HOPITAL CIVIL	1 place de l'Hôpital	STRASBOURG
HU	Weiguo	CHU LA CAVALE BLANCHE	Bld Tanguy Prigent	BREST
CASOLI	Vincent	GROUPE HOSPITALIER PELLEGRIN	Place Amélie Raba-Léon	BORDEAUX
SINNA	Raphaël	CHU AMIENS - HOP NORD	Place victor Pauchet	AMIENS
CASANOVA	Dominique	APHM - HOPITAL DE LA CONCEPTION	147 bld Baille	MARSEILLE
SIMON	Etienne	CHU NANCY - HOPITAL CENTRAL	29 av du Maréchal de Lattre de Tassigny	NANCY
WATIER	Eric	CHU RENNES	16 bld de Bulgarie	RENNES
CAMBON	Adeline	APHP-HOP ST. ANTOINE	184 rue du faubourg St Antoine	PARIS
CHIGNON-SICARD	Bérengère	HOP. PASTEUR	30 voie Romaine	NICE
PHILANDRIANOS (replacing Dr Moullot.)	Cécile	HOP. NORD	Chemin des Bourrely	MARSEILLE
BARTHELEMY	Isabelle	CHU ESTAING	1 Place Lucie et Raymond Aubrac	CLERMONT-FERRAND
ATLAN	Mickael	HOPITAL TENON	4 rue de la Chine	PARIS