Universitat de Girona
Facultat de Medicina

Final Degree Project

A comparative experimental trial between two Artificial Skin Substitutes: *Integra® bilayer* versus *Matriderm® 2 mm* to cover a full-thickness skin wound.

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1. ABSTRACT

Background

Artificial Skin Substitutes (ASS) are bioengineered materials designed as acellular scaffolds that act as substrate for cellular growth, proliferation and support for new tissue formation. ASS are indicated as alternatives to wound healing in circumstances when standard therapies are not feasible. ASS are a reality since 1981 and there currently are a huge range of matrix to choose. *Integra*® has been the first one and the most used worldwide. Nevertheless, there are other ASS with different characteristics than can improve it. *Matriderm® 2mm* is a new acellular scaffold similar to *Integra*®, but with a different material composition that allows an earlier cover of the skin loss with a skin autograft.

Objective

To compare the clinical outcomes between *Matriderm® 2 mm* versus *Integra® bilayer*, as a treatment to cover a full-thickness skin wound, using the clinical scales Vancouver Scar Scale (VSS) and Patient and Observes Scar Assessment Scale (POSAS).

Intervention

Both ASS will be performed in two-step grafting procedure. The wound will be covered at first with an ASS and there will be a second stage surgery to graft a split-thickness skin autograft.

Methods/Design

It is designed a multicenter, controlled, randomized and single blind trial. 154 patients with full-thickness skin wound that fulfill the inclusion and exclusion criteria will be included.

Keywords

Artificial skin substitutes, collagen scaffold, Matriderm, Integra, split-thickness skin autograft, wound healing

2. ABBREVIATIONS

ASS	Artificial skin substitutes
BSS	Bioengineered skin substitutes
ECM	Extracellular matrix
mm	millimeters
STSG	Split-thickness skin autograft
FTSG	Full-thickness skin autograft
FTSL	Full-thickness skin loss / Full-thickness skin wound
VSS	Vancouver Scar Scale
POSAS	Patient and Observer Scar Assessment Scale

3. INTRODUCTION

The skin is a dynamic and complex organ, an integrated organization of cells, tissues, and matrix elements that provides us an array of functions: it is our physical permeability barrier, it gives us protection from external pathogens, thermoregulation, exteroceptive sensation (touch, pain and temperature) (1,2), ultraviolet protection, wound repair and regeneration, and outward physical appearance (1).

Skin damage can occur for many causes, being the most frequent reasons the acute trauma, burn injury, chronic wounds or surgical interventions (3). The loss of skin is always a handicap and a weakness condition, even the loss of the integrity of large portions of the skin as a result of injury or illness may lead to major disability or even death (4).

3.1 Wound healing

The skin has capacity to regeneration by the epidermal stem-cells activity (5) and the stimulation of a complex wound healing process that results in the restoration of the anatomical continuity and its functions (6). That involves a physiological skin reaction that begins at the moment when the tissue is injured, starting a consecutive healing cascade with four overlapping phases, which each one is not entirely completed before the next begins (7):

I. Hemostasis: Tissue injury causes the disruption of blood vessels and extravasation of blood components (4). Immediately, injured vessels constrict to decrease blood loss. Injured tissue causes exposure of collagen that stimulates platelet

activation and adherence to form a blood clot (7,8) and stimulates the inflammatory cells activity (6).

II. Inflammatory phase: a few hours after injury, it begins the activation of complement and inflammatory cells, characterized by neutrophils and macrophages. Neutrophils are the predominant cell marker in the wound within 24 hours after injury (6). Those cells phagocytose the damaged and foreign substances and also activate local fibroblasts and keratinocytes (8).

III. Migration and Proliferative phase: lasts from 3 to 14 days, during which time the scar is formed, and comprise the proliferation and migration of fibroblasts into the wound defect. Fibroblasts synthesizes the matrix proteins fibronectin, hyaluronan, collagen and proteoglycans, forming a new extracellular matrix (ECM) and granulation tissue (7). ECM acts like a scaffold, it is essential for the repair process and supports cell migration. One to two days after injury, epidermal cell at the wound margin begin to proliferate behind the actively migrating cells (4). Meanwhile, the angiogenesis process starts with the stimulation and proliferation of microvascular endothelial cells from existing intact vessels, that migrate and induce the formation of new capillary vessels (4,8).

IV. Contraction and Remodeling phase: it starts with the grown of granulation tissue and lasts for over a year. Contraction occurs through the interactions between fibroblasts and the nearby ECM (7). Collagen in the ECM aids in locking the cells in place, thus augmenting the contraction process. Early collagen deposition is highly disorganized and it is realigned along tension lines, increasing in diameter and forming stable cross-links that gives wound tensile strength and stability (8). During the granulation tissue formation wounds gain only about 20% of their final strength, thereafter the rate of accumulation of collagen and remodeling is slow. The wound never attain the same breaking strength as uninjured skin, being at maximal strength only 70% as strong as normal skin (4).

Finally, excess collagen is degraded by matrix metalloproteinases produced by ECM cells (8). While maturation continues, blood flow to the area is reduced and metabolic activity in the area declines. An acellular, avascular scar is the final result of the acute wound healing process (6,7).

At the macroscopic level, skin healing ability depends on the damage proportion. The wound harm increases as the damage involves more skin deepness and extension, and the regeneration capacity is lower (3).

Wound can be classified depending on the depth of the affected tissue as follow:

- Superficial wound when it affects only the epidermis.
- Partial-thickness skin loss (PTSL) when it extends through the epidermis and into, but no trough the dermis.
- Full-thickness skin loss (FTSL) when it extends through the epidermis and dermis into the subcutaneous fat and deeper structures (9).

3.2 What is the ideal wound cover management?

The goal of the treatment of the patient with several loss of substance or FTSL is the substitution of the skin damaged by healthy skin as rapidly as possible and with the best aesthetic and functional outcomes (4). Nevertheless, in several situations depending on the wound location not only it is necessary to reach a cutaneous stable coverage, but also, a good quality of the skin (10). Consequently, the wound treatment has to be based on the characteristics of the injury that will guide the suitable healing approach, explained as follows:

3.2.1 Direct closure

Primary wound closure or healing by first intention is the wound direct suture. The wound closure is completed within hours after the injury is produced, prior to the formation of granulation tissue (11,12). Consequently, this is the fastest and easiest process and it gives the best esthetic outcome with minimal scarring result (3). The risk infection is minimum with an aseptic technique (11).

Delayed primary wound healing is the healing option when the wound edges can not be immediately approximated. This type of healing is indicated for contaminated wounds with purulent secretion and inflammation. The wound suture is delayed 3-4 days, meanwhile the wound is cleaned and debrided. By the fourth day the phagocytosis and re-epithelialization processes allow the wound suture (11,12).

Secondary wound closure or healing by second intention when the wound fails to heal by primary closure and is not sutured, the skin is allowed to close by itself. The wound may stay open and it should be cleaned and dressed. This healing results in an important inflammatory response with a lot of granulomatous tissue growth that results in pronounced contraction of wounds and bigger scars. Therefore, the aesthetic outcome is worse and the cicatrization time is longer than in the case of the primary and delayed wound healing (11,12).

3.2.2 Reconstructive surgery

Complex wounds or FTSL may not allow the direct closure, the next healing step are the skin reconstructive options that include from skin grafts to different types of flaps, primarily depending on the wound extension, location and depth. (13).

3.2.2.1 Skin grafts

A skin graft is a piece of skin harvested from an uninjured body area. The graft has not its own source of blood flow and its survival depends on the correct adhesion to the wound bed and the neovascularization growth (14).

The skin graft can be taken from the own patient body (**Autograft**), a donor or human cadaver tissue (**Allografts**) or taken from another species, being most used porcine or bovine cells (**Xenograft**). Allografts and xenografts may also be employed as temporary skin replacements, indicated to several burns, but later it must be covered by an autograft (15).

There are two kinds of graft depending on the skin thickness (Figure 1):

Split-thickness skin graft (STSG) it consists to harvest a piece of epidermis with a superficial part of the dermis typically 0.30–0.45 mm thick. It is taken with a dermatome from an undamaged skin donor site, most frequently taken from the patient's thigh. The donor areas heal in two weeks without or with minimum complications(11). This one represents the clinical "gold standard" in full-thickness wounds treatment (3).

Full-thickness skin graft (FTSG): It lies in a surgical excision of a piece of total dermal component is taken from a donor body area. It can only be performed if the injured area is small due to the donor skin scission is closed by first intention. Therefore it is indicated to cover small defects(16).

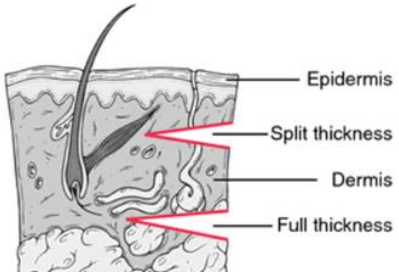


Figure 1- Image from http://medical-dictionary.thefreedictionary.com/split-thickness+graft

In addition, the grafts can be meshed and stretched to cover greater areas, and the donor skin areas can be smaller than the wound size. Although this method decreases mortality rates, the cosmetic and functional outcomes are inferior, with a bigger graft contraction, more scar tissue formation and marked 'crocodile skin' scar appearance (3).

3.2.2.2 Flaps

A skin flap is a piece of not injured skin that is detached and moved to cover a wound, while keeping with its own vascularization source (17). A flap is indicated when the underlying tissue of various constituents is lost (13), due to the fact that a flap can be created from skin with its underlying subcutaneous tissue, fascia, or muscle, either individually or in some combination, depending on the wound damage (17).

There are several classifications of flaps depending on the perfusion source, the location of the donor site, the method of movement or their composition (18). Essentially, a local flap implies that the tissue is adjacent to the open wound and the skin is partly detached and locally moved, while in a distant or free flap, the tissue is totally detached and brought from an area away from the open wound and the vascular pedicle is microsurgically attached (17).

3.2.3 Bioengineered skin substitutes

Bioengineered skin substitutes (BSS) are a heterogeneous group of wound coverage materials, working as alternatives to wound healing in circumstances when standard therapies explained above are not possible(19) due to the characteristics of the wound, especially in case of exposed bone tissue or tendons.

The classic use of the BSS seeks to serve as a template for dermal repair in areas with total dermis destruction (20) working as a ECM scaffold to replace its basic properties that comprise the restoration of skin anatomy and physiological function, biocompatibility and provide resistance to shear forces (21,22).

BSS were designed at first as suitable materials to facilitate early burn excision regimes, to improve the wound care of severely burned patients, that may have not enough available skin for autograft harvesting, and to replace the classical use of allograft, and xenograft in burn management. Today, BSS are an essential part of burn care, but there are also an important part of the chronic wound management, to improve skin scars and other defects (21).

With the progress of biotechnology and tissue engineering, a huge rage of skin substitutes is now available in the international clinical market (15,23,24). There are many classifications (Annex 1), but depending on the nature of the main component there are classified as follows:

- Cultured epithelial autografts: sheets of skin cells
- Human skin allografts derived from donated human cadaver tissue.
- Allogeneic matrices derived from human neonatal fibroblasts.
- Composite matrices derived from human keratinocytes, fibroblasts, and bovine or porcine collagen (15).
- Artificial Skin Substitutes (ASS): Acellular matrices derived from porcine or bovine collagen, constructed out of non-biological molecules and polymers that are not present in normal human skin (19).

The acellular matrices (ASS) are the most widely used skin substitute and there are considered as a correct alternative to the standard wound healing. There are several trials which evaluate its clinical performance and biocompatibility (23,25–27).

Nowadays, there is no an ideal ASS in the market due to the fact that each kind of ASS has its own advantages and disadvantages. Their relevance lies on the fact that the ASS provide a fast wound coverage solution that may require less vascularized wound bed, decrease inhibitory factors of wound healing, reduce inflammatory response and consequent scarring(19). When the skin substitutes are combined with a temporary impermeable seal, enable immediate although temporary wound closure, slow fluid loss and create a physical barrier to external pathogens (26). They are structurally optimized to incorporate the surrounding tissue and to allow cell invasion by fibroblasts and capillaries for following dermal growth and remodeling (8).

Most part of ASS can be used in one or two-stage grafting procedure. It means that an epidermal graft (STSG) can be applied at the same time as applying the ASS (one-stage procedure) or some time after introducing the ASS (two-stage procedure). The decision to choose between one and the other technique depends on the wound bed condition. If the vascularization is severely damaged the STSG will not be perfused and two-stage grafting approach may aid vascularization growth and avoid STSG epidermal necrosis (16).

3.2.3.1 Integra® Dermal Regeneration Template

Integra® Dermal Regeneration Template is a bilayer membrane system (figure 2) for skin replacement that provides a dermal matrix and epidermal barrier for wound coverage(28).

The membrane, 2,1 mm thick, is composed by a dermal replacement layer and a epidermal substitute layer. The dermal replacement layer is composed by a three-dimensional matrix of purified cross-linked collagen acquired from bovine deep flexor

tendon; and glycosaminoglycan (chondroitin-6-sulfate) obtained from shark cartilage. Both matrix components are manufactured with a controlled porosity and defined degradation rate. The epidermal substitute layer is made of thin polysiloxane (silicone) layer that functions as a epidermis to control moisture loss from the wound (26,28–30). It is designed to be removed following vascularization of the dermal component, which usually takes approximately 2-3 weeks, allowing to graft a thin STSG (0,15 mm thick)(29). Although the epidermal component acts as a temporary barrier, the dermal layer incorporates into the wound and may therefore be considered as a permanent dermal substitute (21).

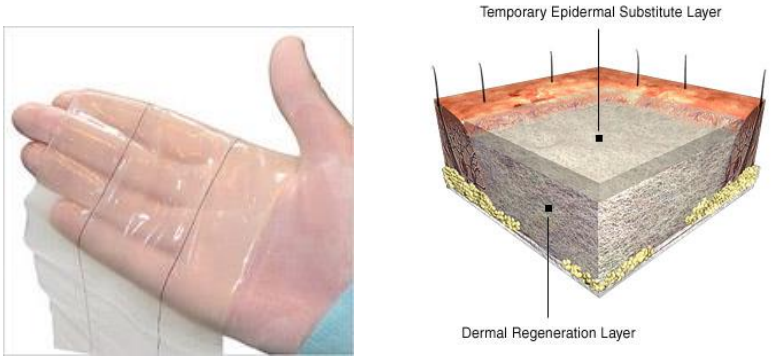


Figure 2- Images from http://www.ilstraining.com/idrt/idrt/brs_it_03.html ©Copyright 2010 Integra LifeSciences Corporation.

The main complication appears to be collection of hematomas and seromas under the ASS, which increases its susceptibility to infection, however this this has not been correlated with increased mortality risk and can be prevented with a careful surgical technique (21,28).

There are many publications, clinical trials and studies that prove the safety and efficacy of *Integra® bilayer*, being the most used ASS in the world(10). The first review about an ASS was published by Burke et al. on 1981 for the treatment of extensively burned

patients and describes the *Integra*® development (30). Heimbach et al. published on 1988 the first clinical trial using *Integra*® on 82 patients, of which 10 patients highlighted problems with hematoma and seroma formation and identification, and premature silicone separation, although they conclude that the long-term outcomes were comparable to using allograft (31).

In 1996, the *Food and Drug Administration* (FDA) approved *Integra*®, indicated for the treatment of potentially mortal burns and in 2002 it was approved to treat patients submitted to reconstructive surgeries to repair scar contractures (10).The last indication was communicated on January 2016 to treat certain diabetic foot ulcers, when used in conjunction with standard diabetic ulcer care (32).

The clinical sequence defined and recommended by the manufacturer for two-step grafting procedure is defined as follow:

- Day 1: *Integra*® *bilayer* surgical application to the wound bed.
- Day 7-14: new dermis formation: the synthetic collagen is replaced by collagen organically produced by new dermal skin cells.

  Generally, color changes through a progression from initial red to pink to orange/peach and then to yellow (neodermis stage) with occasional areas of light red, when the artificial dermis appears macroscopically revascularized.
- Day 14-28: the top silicone layer is easily removed from the underlying neodermis, then a thin STSG (0,15 mm) is applied over the new dermal skin.
- Day 25-56 the skin is completely regenerated (29).

3.2.3.2 Matriderm®

Matriderm® is an acellular scaffold composed of a native bovine type I, III and V collagen fibrils on a three-dimensional structurally intact matrix, supplemented by elastin hydrolysate from bovine nuchal ligament (16,19,33). The collagen matrix serves as a support structure that promotes and guide cell migration, proliferation and revascularization (19). The cells recognize binding sites on native collagen fiber and get activated by binding to them. Its elastin component improves the stability and elasticity of the regenerating tissue (21). As the healing process advances, the collagen-elastin matrix is absorbed, while fibroblast lays down the ECM and it is changed into native host collagen within weeks after application (19).

The matrix is commercially distributed in Europe since 2004, and is currently available in sheets of 0.5, 1 and 2 mm thickness. The 0.5 and 1mm thickness matrix may be graft with a STSG in a one-stage procedure (34) . Otherwise, sheets of 2 mm thickness are recommended for two-stage grafting procedure, delayed as soon as granulation tissue and vascularization have grown through the matrix, typically after 5 to 12 days (16).

In contrast to current most used *Integra*®, *Matriderm*® has been usually used in single stage grafting procedure (21). The first clinical reports were published by Haslik et al. who performed early debridement and immediate grafting of unmeshed STSG with *Matriderm*® *1mm* on 10 patients in a one-step procedure (35). This pilot study provided the initial evidence for its effectiveness. Afterwards, Cervelli et al. published a trial comparing the performance of *Matriderm*® *1mm* combined with STSG versus STSG alone with better aesthetic and scar characteristics results (34); they also evaluate the use of that ASS in diabetic ulcers with positive outcomes too (33). There are several trials evaluating the use of *Matriderm*® *1 mm* although, currently, there are no clinical trials published evaluating its use in two-step grafting procedure.

3.2.3.3 Comparative characteristics of the mentioned ASS

	Integra®	***Matriderm®***
Regulatory organism	FDA	CE mark
Preparations available	- Single layer 1,3mm - Bilayer: matrix + silicone layer - Meshed bilayer	- Single layer 0.5 mm - Single layer 1mm - Single layer 2mm
Matrix components	✓ Collagen type I ✓ Glucosaminoglycan (chondroitin-6-sulfate)	✓ Collagen type I, III, IV ✓ Elastin
1 step grafting procedure	*Integra® single layer* + STSG	*Matriderm® 1mm* + STSG
2 step grafting procedure	*Integra® bilayer* + STSG (delayed 14-28 days)	*Matriderm® 2mm* + STSG (delayed 5-12 days)

4. JUSTIFICATION

Based on the literature research about the ASS, there are some experimental trials evaluating the use of *Integra® bilayer* versus *Matriderm® 2mm*. Schneider et al. compared the dermal part of *Integra® bilayer* versus *Matriderm® 2mm* in rat models performed in two-step grafting procedure. The authors did not find significant differences regarding graft take, neodermis formation, and vascularization (25). Böttcher-Haberzeth et al. also compared those two ASS in a single step procedure on rats, and they conclude that both matrixes had a similar biological behavior early after transplantation, and they showed some particularities with neodermal thickness resulting from faster degradation of *Matriderm®* (36). Philandrianos et al. compared them in a porcine model and they conclude there was no long-term difference of scar qualities between the ASS compared to the control group (covered with a STSG and no ASS) (23).

The need to develop this project lies on the fact that we have not could find any specific study published at these moment, evaluating the ASS *Matriderm® 2mm* in two-step grafting procedures and there are a lack of information as regards to its clinical results. It could be explained due to *Matriderm® 2mm* is a new product, although we consider that is important to know its clinical behavior to indicate it as a good ASS to our patients.

We chose to compare *Matriderm® 2mm* versus *Integra® bilayer* due to last one could be considered as the ASS reference and there are a huge range of studies that support its use for several indications (3,10,15,21–23,25,27,31,37,38).

As explained above, the principal use of skin substitutes is the management of acute burn injury as well as post burn reconstructions, but this kind of injury is not treated at the *Hospital Universitari de Girona Dr. Josep Trueta* due to the patients are moved to *Hospital Universitari Vall d'Hebron* in Barcelona that has a specialized burn injury

department. Therefore, the principal use of ASS at the *Hospital Universitari de Girona Dr. Josep Trueta* is on reconstructive surgery, especially to cover loss of skin after surgical skin tumor excision and acute trauma.

At the *Hospital Universitari de Girona Dr. Josep Trueta*, the Department of Plastic Reconstructive and Aesthetic Surgery has not a protocolled use of the dermal substitutes. The hospital is provided with *Matriderm*® and *Integra*® and the decision to use one or the other is taken by the surgeons while the surgery is performing.

For these reasons and taking the experimental trials aforementioned (23,25,36) as a working guide, we expect to compare the two ASS and determinate which of them have the best clinical outcome and be able to develop a clinical protocol to take standard decisions and improve the wound healing management.

5. HYPOTHESIS

Matriderm® 2mm has better long-term functional and aesthetic skin outcomes compared to *Integra® bilayer*, due to the possibility to perform an earlier skin grafting of the wound.

6. OBJECTIVES

6.1 Primary objective

To compare the clinical results between *Matriderm® 2 mm* versus *Integra® bilayer*, as a skin substitute to cover a full-thickness skin wound, using the clinical scar scales Vancouver Scar Scale (VSS) and Patient and Observer Scar Assessment Scale (POSAS).

6.2 Secondary objectives

1. To compare the rates of the two ASS adhesion and the postoperative characteristics of the wound.
2. To determine the rates of adverse events including tissue inflammation, bleeding, hematoma, seroma and local infection.
3. To compare the scar and aesthetic outcome between the two ASS, including the patient satisfaction.
4. To compare the time to reach the complete skin cicatrization between the two ASS.

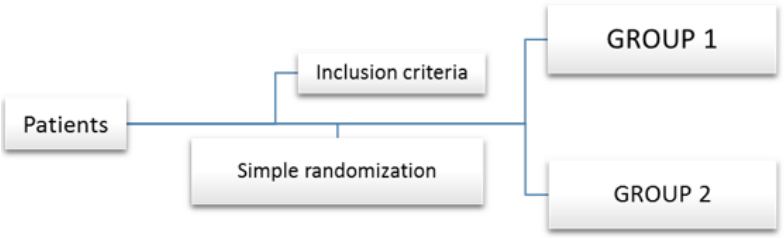
7. METHODOLOGY

7.1 Study design

It is designed a prospective, multicenter, randomized, controlled and single-blind clinical trial with two parallel groups that will receive two different ASS.

For a multicenter approach, all hospitals belonging to ICS Girona will be included in the sampling recruitment. Anyway, the surgical process will be performed at *Hospital Universitari de Girona Dr. Josep Trueta.*

Patient's randomization will be performed using the *Random Allocation Software 2.0,* getting simple randomization in two groups in proportion 1:1.



A single blind trial is designed as the best option. The patient will not be aware about the ASS used and they will not be informed about the different time between both surgeries depending on the ASS used.

7.2 Study Population

The target population will be patients with indications to cover a full-thickness wound with an ASS, admitted to *Hospital Universitari Dr. Josep Trueta de Girona*, *Hospital Santa Caterina de Salt*, *Hospital de Figueres*, *Hospital de Palamós* and *Hospital d'Olot*; between 2018 and 2021.

We will include patients with acute trauma injury with exposed bone and tendon structures and also, patients with indication to skin excision due to skin tumor (wide local excision).

The target patients who fulfill the inclusion criteria will compose the study population.

7.3 Inclusion criteria

- ✓ Age over 18 years.
- ✓ Wound size more than 1 cm x 1 cm and less than 10cm x 10cm.
- ✓ Wound characteristics (it has to fulfill one criteria):
  - Full-thickness skin loss with exposed bone tissue or tendons, that can not be closed with autologous graft or flap.
  - Patient with indication to skin excision due to skin tumor.

7.4 Exclusion criteria

- × Patients with known hypersensitivity to bovine collagen, elastin, chondroitin or silicon material.
- × Burn injury.
- × Infected wound, the wound has to be cleaned and debrided to be included.
- × Necrosis at the wound bed, the necrotic tissue has to be removed to be included.
- × Sepsis.
- × Long-term steroid therapy, due to the alteration of inflammatory and cicatrization process.
- × Venous or arterial occlusive disease.
- × Uncontrolled diabetes mellitus, as measured by HbA1c >9%.
- × Contraindication to any surgical process, defined as ASA classification ≥ IV Patient with severe systemic disease that is a constant threat to life.

The study population included have to fit all the inclusion criteria and the exclusion criteria to avoid the selection biases.

7.5 Sample size

The sample size is calculated with GRANMO Sample size and power calculator, version 7.12 April 2012 available at www.immim.cat.

Accepting an alpha risk of 0.05 and beta risk of 0.20 in a two-sided test, 77 subjects are necessary in first group and 77 in the second group to find as statistically significant a proportion difference, expected to be of 0.80 in group 1 and 0.95 in group 2.

It has been anticipated a drop-out rate of 10%.

In Girona area, including *Hospital Universitari Dr. Josep Trueta*, *Hospital Santa Caterina de Salt*, *Hospital de Palamós*, *Hospital de Figueres* and *Hospital d'Olot*, about 3-4 patients need an ASS every month. Consequently, we will need approximately 4 years to recruit the whole sample size.

The patients will be included following a non-probability consecutive sampling, selecting every patient that meets the inclusion criteria until we will get the required sample size. Afterwards, the patients included will be randomly divided in two groups.

7.6 Study variables

7.6.1 Independent variable

Each patient's wound will be covered with an ASS:

- Group 1 with *Matriderm® 2mm* + five days delayed STSG.
- Group 2 with *Integra® bilayer* + thirty days delayed STSG.

It is a dichotomous nominal qualitative variable.

7.6.2 Dependent variables

The goals of the wound management are to get a correct skin healing and a fast cicatrization with the best aesthetic scar outcome. Two dependent variables will be considered:

1. Short-term skin healing, attending on ASS and STSG correct adhesion and presence of adverse events: inflammation, hematoma, seroma, hemorrhage and wound infection, being those the most reported on literature.

   Results will be defined as correct adhesion (YES/NO), being a dichotomous nominal qualitative variable, and the presence of the adverse events as a nominal qualitative variable.

2. Long-term scar characteristics and aesthetic outcome. Both items will be evaluated with the VSS and POSAS scales. Results are expressed numerically, being a quantitative discrete variable.

7.6.3 Co-variables

- Age: getting older, the characteristics of the skin changes and the healing process may be affected. It modifies the inflammatory skin process, the collagen synthesis decreases, and the skin composition varies, both skin and muscle tissue lose their tone and elasticity, the vascularization may be impaired, and the skin composition varies (8). Those changes could affect the clinical outcome and we have to consider it and record the age. It is a quantitative discrete co-variable.

- Wound size: it is an inclusion criteria to avoid big size differences, nevertheless it has to be correctly measured and expressed in millimeters. It is a quantitative discrete co-variable.

- Wound location: Skin characteristics also changes depending on the body location. It will be differentiated between face, upper limbs, lower limbs and trunk. It is a nominal qualitative co-variable.

7.7 Measure instruments

The WOUND characteristics will be observed by two Plastic surgeons, once the wound will have been uncovered after the surgical processes. It will be registered:

- The color: normal, red, purple, white, black
- Post-operative ASS and STSG dehiscence or no adhesion: any separation between wound bed-ASS-STSG. It will be recorded as yes/no (being *"no"* the normal condition)
- Presence of adverse events: presence of hemorrhage, hematoma, seroma, purulent exudate or signs of infection.

It will be taken photographs of the wound at each appointment to support the recorded items.

To record the SCAR characteristics there are many scales available, such as the Vancouver Scare Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS), the Matching assessment of scars and photographs (MAPS), and the Manchester scar scale (MSS)(39). None of them really stands out or is generally accepted. Nevertheless the VSS and POSAS are the most widely used scales in daily practice (40) and we have choose them to evaluate the wound healing evolution and register the characteristics observed and measured.

All team research including surgeons and nurses will be previously taught and trained to know the questionnaire, the methodology of collecting data and how and when each item should be collected.

Vancouver Scar Assessment / VSS (Annex 2)

This scale categorizes the scar characteristics pigmentation, vascularization, pliability and height/thickness.

- Pigmentation and vascularization are evaluated by clinical observation.
- Pliability is evaluated by direct pressing on the examined area.
- Height and thickness are measured up to a millimeter rule.

Those parameters are expressed with a numerical value, giving a range of 0 to 14 points in the total score, being 0 points normality and 14 points the worst result (41,42).

POSAS version 2.0 scale (Patient Rating Scale Objective and Observer)(Annex 3)

The scale consists of two parts: a Patient Scale and an Observer Scale. Both scales contain six items that are scored numerically on a ten-step scale. Together they make up the 'Total Score' of the Patient and Observer Scale.

It allows to evaluate on a numerical measure the symptoms relative to pain, pruritus, irritation, color, inflexibility, thickness, irregularity and general state.

The observers interrogate the patients with specific and directed questions, and the results are classified with a minimal punctuation 1 (the best) to 10 (the worst), completing the list and the total score ranges from 0 to 90 points (40,41).

The Patient scale has been translated to Catalan language to ensure that the questions will be asked in the same way to the patients.

7.8 Methods of data collection

It is designed a Patient Data sheet (Annex 4) to collect on paper the clinical information that have been assumed as relevant for the clinical trial. This includes all the variables independent, dependent and co-variables items.

The Patient Data sheet has a simple design to provide an easy data register and avoid mistakes. The document includes:

- Patient anonymous information: codified number, age, gender and its assigned group.
- Wound characteristics
- Data table to full with the observed characteristics of the wound after both surgeries.
- Data table to full with the VSS and POSAS result and report any adverse event, at each appointment.

A computer database will be created to introduce all data collected from the Patient Data sheets when all data table will be completed at last appointment.

It will be taken photographs of the wound at each examination and it will be stored in a Patient's Digital photo database.

8. Execution plan

Patient recruitment

Currently, in the Spanish Health Care System, patients with loss of substance and patients with indication to skin excision (by a Dermatologist) are evaluated by a Plastic surgeon.

As soon as the Plastic surgeon indicates that the patient needs an ASS and the patient fulfill the inclusion and exclusion criteria, the Plastic surgeon will offer to him the possibility of participate in the clinical trial. The Plastic surgeon will explain the process and will give a Patient Information sheet (Annex 5) and the Informed consent sheets, one of the surgical process and the other one of the clinical trial participation (Annexes 6 and 7).

Once the patient sign the informed consent, the Plastic surgeon will fill the Patient Data sheet items (Annex 4) with a focused anamnesis. The patient will be randomly assigned to one of the two ASS groups and will start the surgical planning (figure 3).

First surgery: ASS cover (images at Annex 8)

The surgery will be performed as soon as possible, depending on the operation theatre availability. Acute wound trauma has priority and will not be delayed.

The surgical team will know the ASS assigned to be able to proceed with its suitable intervention and have total control of the process.

Patients will undergo this procedure in the operating theatre under general anesthesia. The process will start with the removal of affected and non-viable tissue with a deep

surgical debridement to assure a cleaned and uniform wound bed and a meticulous local hemostasis. (images 1 -3)

When the wound bed has been prepared, the next step will be putting the ASS in place. The sheet will be placed on the wound bed and it will be fixed to stapling the ASS sheet edges to the wound edges. (images 4-5)

Finally, the wound will be covered with an elastic and compression bandage to ensure the ASS adhesion and avoid hematoma or seroma accumulation. (image 6). After the procedure, the patient will be hospitalized.

Wound evaluation

At the patient's room, two surgeons will remove the bandage and will evaluate the wound. It will be recorded the wound characteristics, the ASS adhesion and the presence of adverse events such as hematoma, seroma or infection.

Second surgery: STSG cover

Depending on the ASS assigned to the patient, this procedure will be delayed 7 days (*Matriderm*®) or 30 days (*Integra*®) since the first surgery.

The objective is to cover the wound (covered at first with the ASS) with a split-thickness skin graft (STSG). The surgeon will harvest a thin STSG (0,13 mm) from patient's thigh using a dermatome (image 7). The STSG could be meshed if its size is smaller than the wound size. Then, the STSG will be attached and fixed by stapling edges and center.

The big difference between the two ASS is that *Integra*® has a top silicone layer that has to be removed before to STSG cover (Image 8).

The wound will be covered with the same kind of bandage used at the first surgery and the patient will be hospitalized at least for five days.

Postoperative and follow-up appointments

The wound will be uncovered again at 5 or 7 days (image 9) and the Plastic surgeon will record all the STSG characteristics in the Patient Data sheet.

If there are no complications during the process, patients will be called to evaluate the wound at 1, 3, 6 and 12 months after the hospital discharged. On those appointments, the Plastic surgeons will pass the VSS (Annex 2) and POSAS (Annex 3) scales and will register all the results in the Patient Data sheet.

	Day 0	Day 5-7	Day 14	Day 30	Day 37
Group 1 (M)	Inclusion in the clinical trial. Informed consent. **Surgery 1**: **ASS procedure.**	Wound examination **Surgery 2: STSG procedure**	STSG examination	-	-
Group 2 (I)		Wound examination	-	**Surgery 2:** Silicone layer removal + **STSG procedure**	STSG examination

Figure 3 – Surgical Planning

9. Statistical analysis

The results will be analyzed using *SPSS Statistic Software*, last version 24.0.0 .

9.1 Univariate analysis

For the qualitative variables (dependent and co-variable) the results will be expressed as proportions (percentages), presented for each group.

		Group 1	Group 2
ASS adhesion	YES		
	NO		
STSG adhesion	YES		
	NO		
Wound complications	Inflammation		
	Hematoma		
	Hemorrhage		
	Seroma		
	Local infection		
	Others		

Co-variable:

Wound location	Face		
	Upper limb		
	Lower limb		
	Trunk		

The quantitative variables (dependent and co-variables) will be described as means +/- standard deviation or it will be estimate a median if data is not normally distributed.

	Group 1	Group 2
VSS score		
POSAS score		

Co-variables:

Age		
Wound size (mm)		

9.2 Bivariate analysis

For qualitative variables It will be performed a *chi-squared-test* to compare the result and a contingency table will be created using VassarStats1 online software (http://vassarstats.net/).

Normal distribution will be checked using a *Kolmogorov-Smirnov test.*

It will be used a *Student's t-test* if data follow a normal distribution or a *Mann-Whitney test* for not normally distributed data.

9.3 Multivariate analysis

A multivariate analysis will be performed in order to establish the statistical association between the independent and both dependent variables, but controlling the effect of the co-variables that could act as confusion factors. It will be used a *logistic regression model* for the qualitative dependent variable and a *multiple lineal regression model* for the quantitative dependent variable.

Values of $P<0.05$ will be considered statistically significant in all tests.

10. Ethical Considerations

This project will be presented to *Comitè Ètic d'Investigació Clínica* (CEIC) of *Hospital Universitari de Girona Dr. Josep Trueta* in order to be examined and accepted to carry out.

This project is designed according to the ethical principles of the current Helsinki Declaration and the Medical Research Involving Human Subjects Act (last revision in 64th World Medical Association General Assembly, October 2013).

It is considered the Spanish legislation, specifically the "*Ley Orgánica 14/2007, de 3 de julio, de Investigación biomédica"* and the *"Real Decreto Legislativo 1/2015, de 24 de Julio"* that regulates the rational use of drugs and health products.

The patient's information will be confidential data treated according to the Spanish legislation, concretely the "*Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal",* to guarantee the anonymity and no names will be published.

The research professionals will inform the patients about the clinical trial and will give them the Patient Information sheet "*Full d'informació al pacient*" (Annex 5).

Patients must sign the Clinical trial Informed Consent sheet "*Consentiment informat*" (Annex 7) before being included in the trial. The document is formulated in accordance with the Catalan law "*Llei 21/2000, del 29 de desembre, sobre els drets d'informació concernent la salut i l'autonomia del pacient, i la documentació clínica".*

Both documents are written in Catalan language, the official language, to facilitate its understanding to the patient and avoid mistakes.

The investigators of this project declare that there are no conflicts of interests.

11. Study Limitations and Biases

There are some limitations that must be explained and be considered at the phase of results interpretation:

- It is designed a single blind trial and only the patient will be unconscious of the used ASS. It is not conceivable to reach a double blind due to the fact that the surgical team must know the assigned ASS to manage it correctly. There will be training meeting for the research team, to ensure a correct and standard examination of the wounds, to minimize a possible detection bias.

- The sample studied will be performed with non-probability recruitment, and this sample will not represent the general population, therefore, the conclusions could not be applied to patients with other characteristics wounds.

- The sample size was calculated according the previous data from literature clinical trials with *Integra® bilayer*, but there is no information about *Matriderm® 2 mm*, therefore it has been used the information found of *Matriderm® 1mm*, being conscious that the results between the two *Matriderm®* products may not be the same.

- The sample size required to be statistically significant is large enough and the time to collect it will be long. The literature studies analyzed have taken smaller sample size. This means that the dropout rate may be bigger than we expect.

- The planning designed is to program two wound examinations at the hospital and four appointments at the Outpatient Care Center, being the last one a year after the second surgical intervention. This could mean an appreciable lost to follow-up patients.

- The instrument measure Vancouver Scar Scale was designed to evaluate burn scars and its validity and reliability to rate postsurgical scars is criticized in some studies. Notwithstanding this scale is the most used worldwide and has been used also to rate postsurgical scars with acceptable outcomes.

12. Work plan

12.1 Personnel of the research team

The research team will be composed by:

- Surgical team: composed by five Plastic surgeons, being one of them the First investigator.

  Each surgeon is assigned to one of the five hospitals involved in the trial and all of them compose the surgical team of *Hospital Universitari de Girona Dr. Josep Trueta.*
- Nursing team: composed by five nurses, each one will work coordinated with one Plastic surgeons.
- A computer technician
- A biostatistician expert

12.2 Study stages

The project is designed in 5 phases schematized in a Chronogram box at Annex 9 and is described as follows:

1- Preparation phase: 2 months
   - The first investigator will make an extensive literature research to know the updated reviews and current knowledge about the bioengineered skin substitutes.
   - After doing a critical analysis of the literature, the first investigator will develop the protocol of the study. In addition, he will design the Patient Information

sheet (Annex 5), the Patient Data sheet (Annex 4) and the Clinical Trial Informed Consent sheet (Annex 7).

- The computer technician will design the computer database and a Patient Digital Photo file, and will design a security system to ensure its confidentiality. Besides, the computer technician will obtain and get used to the randomization software and statistical software that has been chosen.

2- Coordination phase: 2 months

- The first investigator will take on responsibility to present the protocol to the *Comitè d'Ètica Investigació clínica* (CEIC) to obtain the approval to carry out the project.
- There will be a first organization meeting to establish the coordination of the hospitals involved and the staff collaboration; and to inform about the main guideline of the clinical trial, the background and the research objectives.
- A Training meeting will be performed to all the clinical staff to explain the ASS characteristics, the surgical process and the postoperative care. Besides, it will include a VSS and POSAS practice session.

3- Field work: about 4 years, although this will be finally determined by the time to achieve the whole sample size.

- It will carry out the patient recruitment, the surgical interventions and the follow up appointments.
- All the process will be recorded with the Patient Data sheet and photographs of the wound will be taken.

4- Data analysis and results interpretation: 2 months

- Database will be processed by a computer technician and then will be analyzed by a biostatistician using the appropriate statistical test.
- The first investigator and the surgical team will interpret and discuss the results and will write the final conclusion.

5- Publication and dissemination of research findings: 1 year

- An article will be edited and published in the journal *Revista de Cirugía plástica ibero-latinoamericana*
- The first investigator and a Plastic surgeon will present the results and conclusions in the National Congresses of SECPRE (*Sociedad Española de Cirugía Plástica Reparadora y Estética*)

All the process will take an approximate duration of six years, from 2017 to 2022.

13. Feasibility

The project will be carried out at the ICS Girona hospitals, involving hospitals from Girona, Salt, Figueres, Palamós and Olot. Currently, one day a week, one of the Plastic surgeons moves to one of those hospitals and visit local outpatients. This will be the way to contact with those patients to recruit them for the study.

The surgical processes will be performed at *Hospital Universitari de Girona Dr. Josep Trueta* where there will be provided with all means for developing the study, set up operation theatre and surgical instrumental needed to the surgical processes.

The research team, including surgeons and nurses are working at the involved hospitals and their participation will not imply extra work hours or additional travels.

It will need to hire a biostatistician and a computer expert which will be included in the budget.

The hospital will provide the computer equipment for design and process database. A digital camera to take the wound photographs will be lend by the first investigator, at his own responsibility.

All extra needs are detailed in the budget box (figure 4).

14. Impact on the National Health Care System

The ASS were a revolutionary approach to the wound heal management but with the disadvantage of the high cost (37). The chosen ASS used on this trial are expensive too, although *Matriderm*® is cheaper than *Integra*®.

If the hypothesis that Matriderm® has better or even the same clinical outcomes than *Integra*® we will be allow to recommend the use of *Matriderm*® instead of *Integra*® saving money.

The study will provide clinical evidence to develop a decision protocol to use one ASS or the other, choosing the one that get better clinical outcomes.

15. Budget

		Work hours	Cost/hour (€)	Total (€)
Staff	Biostatistician	45h	30€/h	1.350
	Computer technician	40h	30€/h	1.200
		Unit	Cost/unit (€)	
Materials	*Matriderm®*	77	850	65.450
	Integra®	77	1.000	77.000
	Sheets print out	2.160	0,05	108
Others	Insurance policy			15.000
Results dissemination	Congress inscription SECPRE	2	250	500
	Travels and diets	2	300	600
	Journal publication	1	1000	1000
				162.208 €

Figure 4- Budget Box

Notes and specifications:

- The prices of *Integra*® and *Matriderm*® are an estimation, considering that the price will be modified depending on the sheet size indicated for each patient.
- Surgeons and nurses team will not receive extra money compensation for their participation in the trial.
- The surgeries, operation room material and maintenance are included in Spanish Nathional Health Care System budget.

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17. Annexes

17.1 - Annex 1 Bioengineered Skin Substitutes classification

BSS CLASSIFICATION BASED ON COMPOSITION (19):

Class I: **Temporary impervious dressing materials**

a) single layer materials

- naturally occurring or biological dressing substitute, e.g. amniotic membrane, potato peel
- synthetic dressing substitute, e.g. synthetic polymer sheet (Tegaderm®, Opsite®), polymer foam or spray

b) bi-layered tissue engineered materials, e.g. TransCyte®

Class II: **Single layer durable skin substitutes**

a. Epidermal substitutes, e.g. cultured epithelial autograft (CEA), Apligraft®
b. Dermal substitutes

- bovine collagen sheet, e.g. Kollagen®
- porcine collagen sheet
- bovine dermal matrix, e.g. Matriderm®
- human dermal matrix, e.g. Alloderm®

Class III: **Composite skin substitutes**

a) Skin graft

- Allograft
- Xenograft

b) Tissue engineered skin

- Dermal regeneration template, e.g. Integra®
- Biobrane®

17.2 - Annex 2 Vancouver Scar scale

VANCOUVER SCAR SCALE

VASCULARITY			
0		Normal	Closely resembles color of rest of body
1		Pink	
2		Red	
3		Purple	
PIGMENTATION			
0		Normal	Closely remembers color of rest of body
1		Hypopigmentation	
2		Hyperpigmentation	
PLIABILITY			
0		Normal	
1		Supple	Flexible with minimal resistance
2		Yielding	Giving way to pressure
3		Firm	Inflexible, not easily moved, resistant to manual pressure
4		Banding	Rope-like tissue that blanches with extension of the scar
5		Contracture	Permanent shortering of scar producing deformity or distorsion
HEIGHT			
0		Normal- flat	
1		< 2 mm	
2		2-5 mm	
3		> 5 mm	

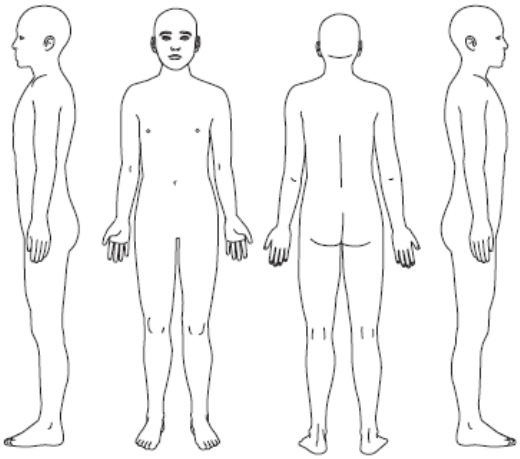
Mark a X beside the punctuation.

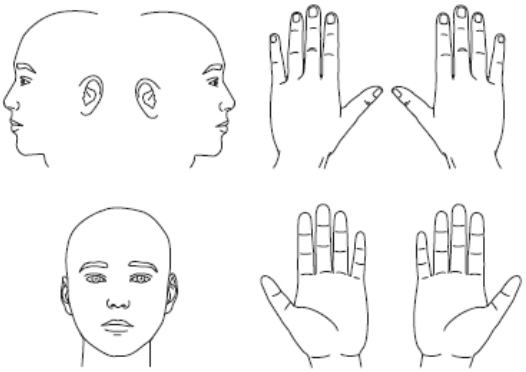
17.3 - Annex 3 Patient and Observer Scar Assessment Scales

POSAS Observer scale

The Patient and Observer Scar Assessment Scale v 2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**





	1 = normal skin									worst scar imaginable = 10	
PARAMETER	1	2	3	4	5	6	7	8	9	10	**CATEGORY**
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable').
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

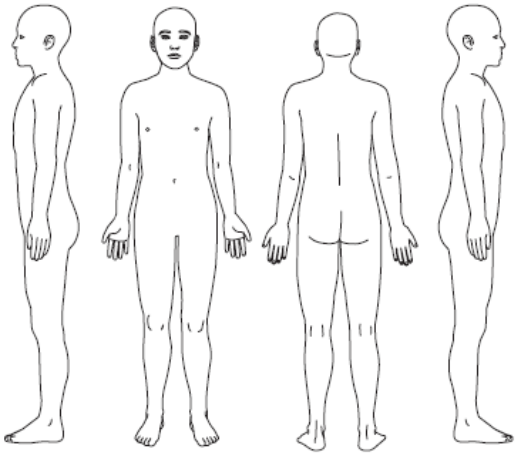
Explanatory notes on the items:

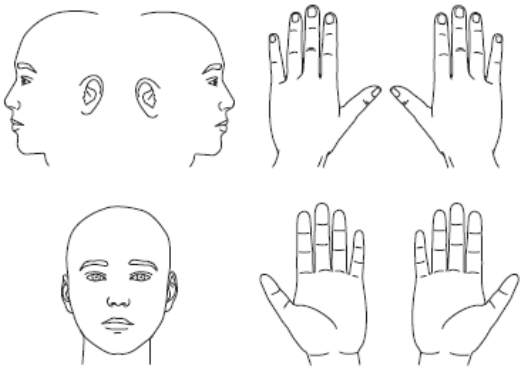
- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

POSAS Patient scale

The Patient and Observer Scar Assessment Scale v 2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**





	1 = no, en absolut … si, molt = 10
LI FA MAL LA CICATRIU?	1 2 3 4 5 6 7 8 9 10
LI PICA LA CICATRIU?	1 2 3 4 5 6 7 8 9 10

	1 = no, com la pell normal … si, molt diferent = 10
TÉ LA CICATRIU UN COLOR DIFERENT AL DE LA SEVA PELL NORMAL?	1 2 3 4 5 6 7 8 9 10
ÉS LA CICATRIU MÉS RÍGIDA QUE LA SEVA PELL NORMAL?	1 2 3 4 5 6 7 8 9 10
TÉ LA CICATRIU UN GRUIX DIFERENT AL DE LA SEVA PELL NORMAL?	1 2 3 4 5 6 7 8 9 10
ÉS LA CICATRIU MES IRREGULAR QUE LA SEVA PELL NORMAL?	1 2 3 4 5 6 7 8 9 10

	1 = com la pell normal … molt diferent = 10
QUINA ÉS LA SEVA OPINIÓ GENERAL DE LA CICATRIU COMPARADA AMB LA SEVA PELL NORMAL?	1 2 3 4 5 6 7 8 9 10

Both POSAS scales are taken from http://www.posas.org/the-posas/the-scale/

17.4 - Annex 4 Patient data sheet

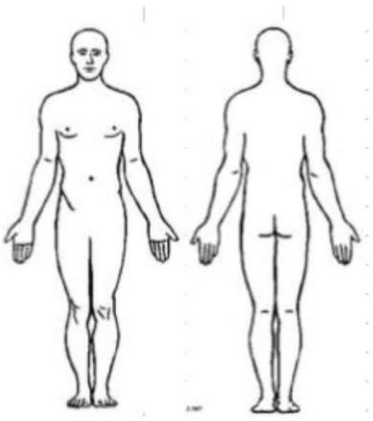
Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

A comparative experimental trial between two Artificial Skin Substitutes:
***Integra® bilayer* versus *MatriDerm® 2 mm* to cover a full-thickness skin wound.**

PATIENT DATA SHEET

PATIENT NUMBER	_ _ _ _ _
GROUP	☐ 1 (M) ☐ 2 (I)
Age	_ _
Gender	☐ male ☐ female



WOUND CHARACTERISTICS:

Size	____mm x ____mm
Location	
Etiology	☐Trauma ☐ Skin Excision
Exposed tissue	

ASS Surgery	
Date	__/__/____
Surgeons (number)	____ ____
Sheet size	
Sheet set number	
Complications	

ASS examination	
Date	__/__/____
Surgeons (number)	____ ____
Color	
ASS adhesion	
Adverse events	

1

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

A comparative experimental trial between two Artificial Skin Substitutes: *Integra® bilayer* versus *MatriDerm® 2 mm* to close a full-thickness skin wound.

ASS Surgery	
Date	__/__/____
Surgeons (number)	____ ____
Sheet size	
Sheet set number	
Complications	

ASS examination	
Date	__/__/____
Surgeons (number)	____ ____
Color	
ASS adhesion	
Adverse events	

APPOINTMENTS	DATE	Observer (number)	VSS	POSAS observer	POSAS patient	Wound complications*
Appointment 1 1 month	__/__/____					
Appointment 2 3 months	__/__/____					
Appointment 3 6 months	__/__/____					
Appointment 4 12 months	__/__/____					
		MEAN SCORE				

* Complete with the abbreviations: hematoma (**HM**), local Infection (**IF**), seroma (**S**), dehiscence (**DH**), ASS separation (**AS**), or others (specify it)

2

17.5 - Annex 5 Patient information Sheet

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

FULL D'INFORMACIÓ AL PACIENT

Ens dirigim a vostè per informar-li sobre un estudi d'investigació en el què se li convida a participar.
L'estudi ha estat aprovat pel Comitè Ètic d'Investigació Clínica i l'Agència Espanyola del Medicament i Productes Sanitaris, d'acord amb la legislació vigent, el Reial Decret 1/2015, de 4 de juliol, pel qual es regulen els assajos clínics amb medicaments i productes sanitaris.
La nostra intenció és tan sols que vostè rebi la informació correcta i suficient perquè pugui avaluar i jutjar si vol o no participar en aquest estudi. Per a això li demanem que llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir.

Ha de saber que la seva participació en aquest estudi és voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense que per això s'alteri la relació amb el seu metge ni es produeixi cap perjudici en la seva tractament.

TÍTOL DE L'ESTUDI: " **Assaig clínic comparatiu entre dos substituts dèrmics artificials: *Integra® bilayer* versus *Matriderm® 2 mm* per cobrir una ferida de gruix total.** "

Per què fem aquest estudi?
L'objectiu de l'estudi és avaluar el resultat clínic de 2 substituts dèrmics artificials i veure quin dels dos té millors resultats a curt i llarg termini.
Els substituts dèrmics artificials estan indicats per cobrir lesions extenses a la pell que no poden ser suturades de forma directa ni utilitzant la pròpia pell del pacient. Són materials que s'han fet servir des de fa més de 20 anys i es té molta experiència en el seu ús. S'ha demostrat en estudis previs la seva seguretat i el seu risc no excedeix el riscos propis d'una intervenció quirúrgica.
L'estudi compararà aquets 2 materials sintètics en 154 pacients que compleixin una sèrie de criteris d'inclusió.

Que li demanem que faci?
Davant la situació de necessitar un substitut dèrmic artificial per cobrir una lesió cutània, se li assignarà de forma aleatòria un dels dos materials i es procedirà a cobrir la lesió a quiròfan, sota anestesia general.
Quedarà ingressat a l'hospital uns dies i posteriorment se li cobrirà de nou la lesió amb un empelt. L'empelt consisteix en una fina capa de pell que s'agafa de la cuixa, a quiròfan i sota anestesia general. La lesió de la cuixa serà similar a la produïda per una rascada, que cicatritzarà en unes 2 setmanes.
Un cop realitzats els 2 procediments quirúrgics, se li demanarà que compleixi una sèrie de visites de control a Consultes Externes de Cirurgia Plàstica per avaluar la ferida als 1, 3, 6 i 12 mesos.

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Hospital Universitari de Girona Doctor Josep Trueta

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Quins són els beneficis?

Per vostè com a participant voluntari, el benefici principal serà la cobertura òptima de la seva lesió amb material de qualitat i un seguiment exhaustiu de l'evolució de la seva lesió.

La seva participació és voluntària i no serà remunerada.

Quins són els riscos i/o inconvenients que se'n poden derivar?

Els riscos del substituts dèrmics són els riscos generals del tancament quirúrgic d'una lesió, que inclou hematoma, infecció local, sagnat, dehiscència de la ferida o no adhesió del substitut dèrmic.

Altres riscs són els derivats de l'ús d'anestèsia general, que inclouen reaccions al·lèrgiques, alteracions cardíaques, respiratòries, metabòliques i neurològiques, en casos excepcionals.

Quins són els seus drets com a participant en l'estudi ?

- Dret a la revocació del consentiment i els seus efectes, inclosa la possibilitat de la destrucció o de l'anonimització de la mostra i que aquests efectes no s'estendran a les dades resultants de les investigacions que ja s'hagin dut a terme.
- Dret a revocar el consentiment en qualsevol moment, sense perjudici del seu tractament mèdic.
- Possibilitat de contactar amb els investigadors en cas d'aparició d'efecte advers imprevist.
- Dret a decidir la destinació de les seves dades en cas de decidir retirar-se de l'estudi.
- Dret a que es torni a demanar el seu consentiment si es vol utilitzar les seves dades en estudis posteriors.
- Segur o altres mesures que existeixin per assegurar una compensació adequada en el cas que el subjecte pateixi algun dany.
- Garantia de confidencialitat de la informació obtinguda, indicant l'existència del fitxer, la finalitat de la recollida de les dades i destinataris de la informació, del caràcter obligatori o facultatiu de les respostes, de la possibilitat i on exercir els drets d'accés, rectificació, cancel·lació i oposició, de la identitat i adreça del responsable del fitxer, la manera en què es manejaran les bases de dades i la identitat de les persones que tindran accés a les dades de caràcter personal del pacient.

A qui pot contactar per demanar més informació?

Si té qualsevol dubte, pregunta o necessita més informació respecte a l'estudi, no dubti en consultar-ho amb qualsevol membre de l'equip de Cirurgia plàstica, que formen part activa de l'estudi.

Unitat de Cirurgia Plàstica, Estètica i Reparadora Hospital Universitari Josep Trueta de Girona

Telèfon atenció a usuari: 972 94 02 00

Moltes gràcies.

17.6 - Annex 6 Surgery Informed Consent

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom	
Segon cognom	
Nom	
Data de naixement	Sexe
NHC	DNI
CIP	
Episodi origen	

Consentiment informat

Cognoms i nom de la persona responsable del pacient sigui menor o incapaç de donar el seu consentiment | DNI* | Relació amb el/la pacient*

Nom del procediment

Tancament quirúrgic de lesió cutània.

DESCRIPCIÓ DEL PROCEDIMENT

Aquest procediment consisteix en cobrir un defecte cutani. De vegades, pel correcte tancament del defecte cutani, és necessari l'ús d'empelts, penjolls o substituts dèrmics artificials temporals.

L'anestesia que s'utilitza és la denominada general, això significa que se li injectarà un fàrmac que li produirà una sedació temporal, amb la finalitat d'evitar el dolor.
Es necessari informar al metge responsable de l'existència de possibles al·lèrgies a medicaments, alteracions en la coagulació, malalties cardiopulmonars, existència de pròtesi, marcapàs, medicació actual, o qualsevol altra circumstància que pugui augmentar el risc de complicacions.

D'AQUESTA INTERVENCIÓ S'ESPEREN ELS SEGÜENTS BENEFICIS:
Realitzar un estudi anatomopatològic (biòpsia) per diagnosticar la malaltia, facilitant-ne el possible tractament o sent pròpiament el tractament definitiu per a aquesta.

RISCOS GENERALS

Qualsevol exploració, tractament o intervenció quirúrgica presenta uns riscos generals. El més greu és la possibilitat d'una parada cardíaca. Altres complicacions són les hemorràgies i les infeccions. En cas d'urgència vital, caldrà actuar sobre aquestes complicacions amb els mitjans oportuns per al bé del pacient, dels quals s'informarà (sempre que les circumstancies ho permetin) el malalt o la persona que en sigui responsable.

RISCOS ESPECIFICS D'AQUEST PROCEDIMENT

D'AQUESTA INTERVENCIÓ ÉS POSSIBLE QUE ES PRODUEIXIN ELS SEGUENTS EFECTES SECUNDARIS O COMPLICACIONS:

La intervenció, independentment de la perfecta execució comporta una cicatriu residual.
Compren que malgrat l'adequada elecció de la tècnica i de la seva correcta realització poden presentar-se efectes indesitjables o complicacions com:

Pàgina 1 | 2

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom	
Segon cognom	
Nom	
Data de naixement	Sexe
NHC	DNI
CIP	
Episodi origen	

Consentiment informat

Infecció, sagnat o alteracions de la cicatrització de la ferida quirúrgica. Dolor prolongat en la zona de l'operació.
Aquest tipus de intervenció, tant per la seva pròpia tècnica comprèn la situació vital de cada pacient, pot portar implícites una sèrie de complicacions que podrien requerir tractaments complementaris tant mèdics com quirúrgics.

AUTORITZACIÓ

He rebut la suficient informació i he llegit el full informatiu sobre la exploració, el tractament i/o la intervenció quirúrgica que em realitzaran. He pogut fer preguntes sobre aquest procediment. Puc canviar d'opció en qualsevol moment, abans de la realització del procediment, si així ho crec convenient. He comprès la informació que m'ha estat donada, i per això conscientment autoritzo que es porti a terme el dit procediment.
Aquest consentiment es formula d'acord amb allò que estableix la Llei 21/2000 de 29 de desembre publicada en el DOGC nº 3303 de l'11 de gener 2001.

Servei	Professional que informa	Numero d'identificació
CIRUGIA PLÀSTICA I	AGUILERA GARCIA, JÈSSICA	12569548

Signatura del/la pacient o responsable	Data	Signatura del professional

□ Accepta

□ No accepta

Revocació de consentiment informat.

Jo, En/Na _____ revoco el consentiment prestat en data __ /__ /____ i declaro per tant que, després de la informació rebuda, no autoritzo a sotmetre'm al procediment de Tancament quirúrgic de lesió cutània.

Pàgina 2 | 2

17.7 - Annex 7 Clinical trial Informed Consent

Hospital Universitari de Girona Doctor Josep Trueta

Institut Català de la Salut

Primer cognom	
Segon cognom	
Nom	
Data de naixement	Sexe

Consentiment informat Assaig clínic

Nom de l'estudi: **Assaig clínic comparatiu entre dos substituts dèrmics artificials: *Integra® bilayer* versus *Matriderm® 2 mm* per cobrir una ferida de gruix total.**

AUTORITZACIÓ

He rebut la suficient informació i he llegit el full informatiu sobre la exploració, el tractament i/o la intervenció quirúrgica que em realitzaran.

He pogut fer preguntes sobre aquest procediment.

Puc canviar d'opció en qualsevol moment, abans de la realització del procediment, si així ho crec convenient.

He comprès la informació que m'ha estat donada.

Per això conscientment autoritzo que es porti a terme el dit procediment.

Aquest consentiment es formula d'acord amb allò que estableix la Llei 21/2000 de 29 de desembre publicada en el DOGC nº 3303 de l'11 de gener 2001.

Servei	Professional que informa	Numero d'identificació
CIRUGIA PLÀSTICA I	AGUILERA GARCIA, JÈSSICA	12569548

Signatura del/la pacient o responsable	Data	Signatura del professional

□ Accepta

□ No accepta

Revocació de consentiment informat.

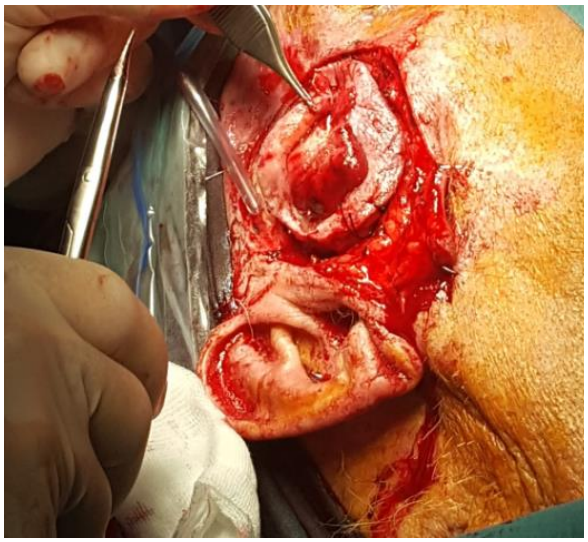
Jo, En/Na _____ revoco el consentiment prestat en data __ /__ /____ i declaro per tant que, després de la informació rebuda, no autoritzo a sotmetre'm al procediment de Tancament quirúrgic de lesió cutània.

Pàgina 1 | 1

17.8 - Annex 8 Surgical process images

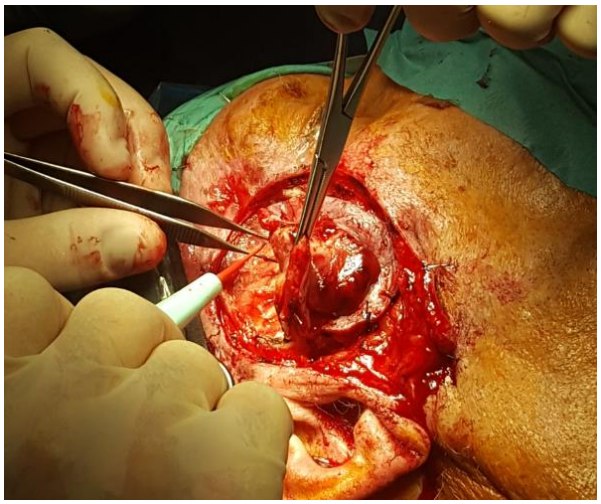
All images are ceded by Plastic and Aesthetic Surgery Department H. Trueta, with the patient approbation.

Image 1



Tumor excision

Image 2



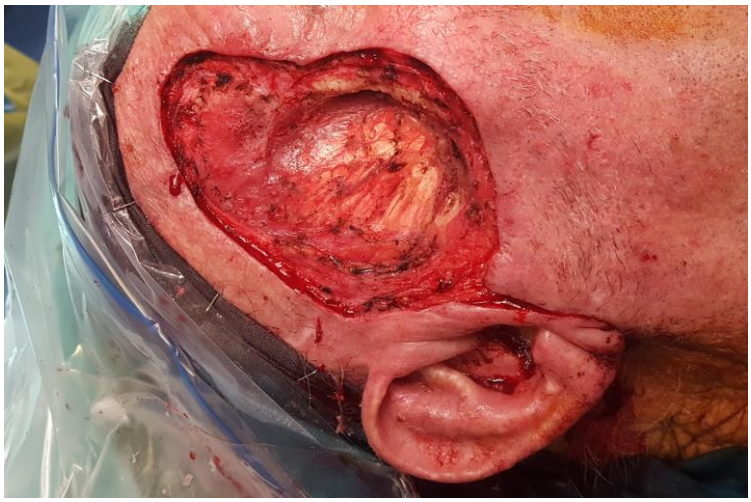


Image 3

Wound bed remodeling and hemostasis

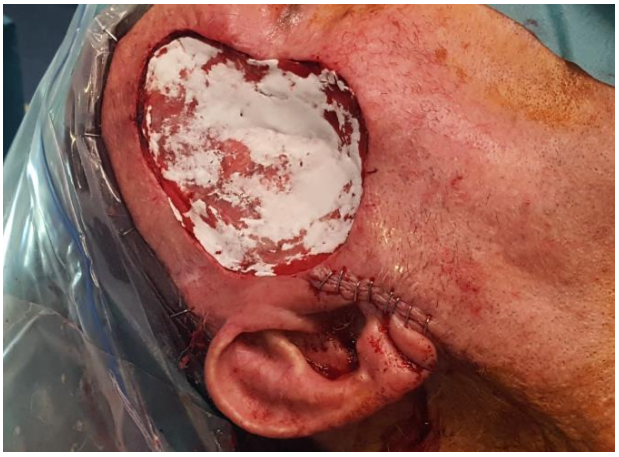


Image 4

ASS application (*Matriderm*®)

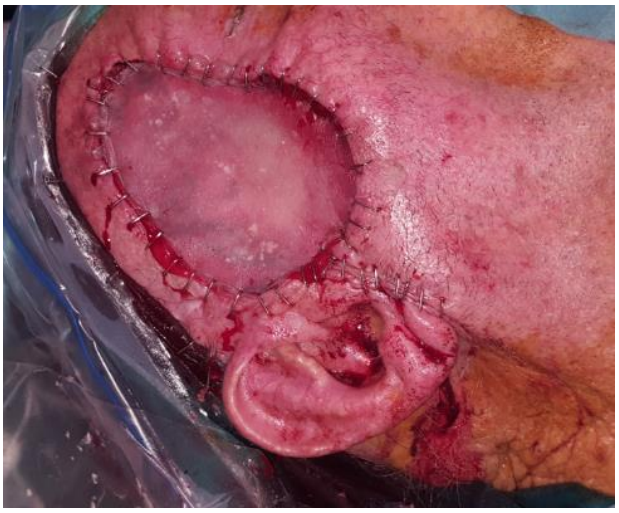


Image 5

ASS Fixation

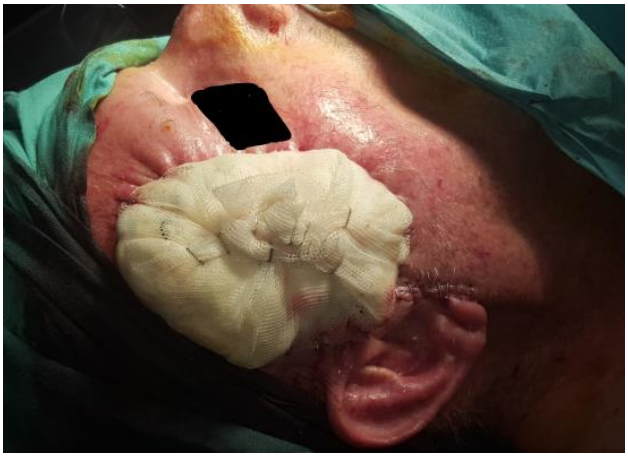


Image 6

Compressive bandage

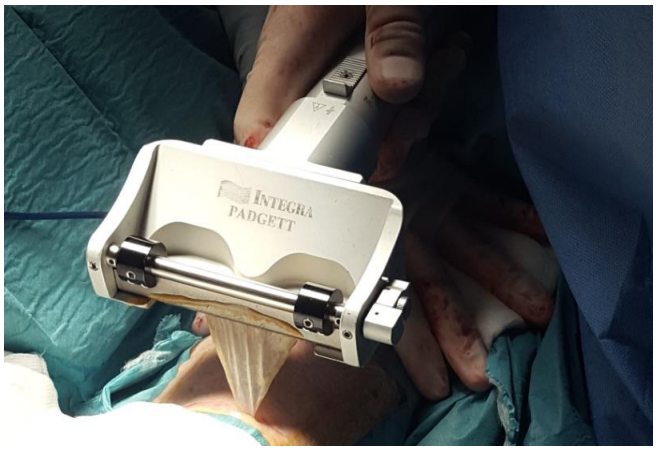


Image 7

STSG harvested with a dermatome

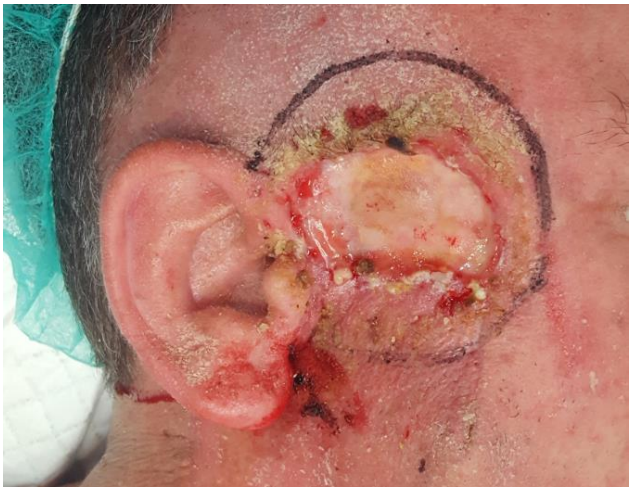


Image 8

Integra® after the silicone layer

removal (33 days post-surgery)

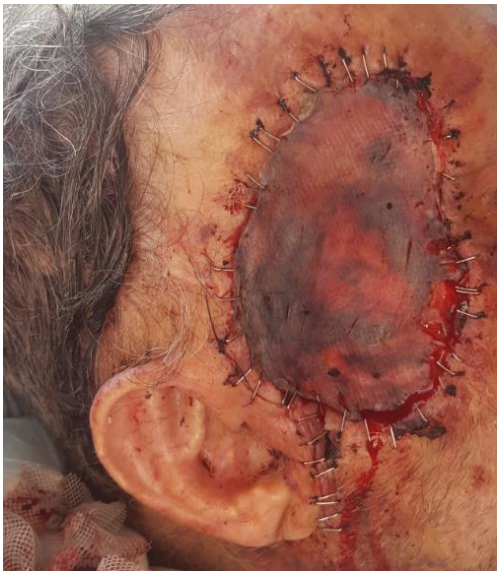


Image 9

Matriderm® + STSG after 5 days

17.9 - Annex 9 Chronogram