Universitat de Girona
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FINAL DEGREE PROJECT

Optimizing Recovery: Investigating the Role of Early Postoperative Mobilisation in Free Flaps Surgery for Lower Leg Reconstruction

A MULTICENTRE, RANDOMIZED, CLINICAL TRIAL

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Girona, January 2024

Al Dr. Pau Bosacoma, per transmetre'm la seva dedicació i professionalitat des dels inicis. Pel seu suport, guia i consells en aquest procés.

Al Dr. Jordi Serracanta, per obrir-me un cop més les portes de la Unitat de Cremats de l'Hospital Universitari Vall d'Hebron.

A totes les professionals del servei de Cirurgia Plàstica de l'Hospital Universitari Josep Trueta i de l'Hospital Universitari Vall d'Hebron per la seva acollida. Especialment als seus residents, el Dr. Pau Martínez i Dra. Maria Bayona.

Al Marc Sáez, per la seva generositat i consells.

A les meves amigues, per fer aquest camí més fàcil i més bonic. Per cuidar-nos i recolzar-nos en tot moment.

A la meva família, per acompanyar-me i ajudar-me incondicionalment durant aquests 6 anys de carrera i en tot el que em proposo. Gràcies mama, papa, Mireia, Sergi i iaia. Us estimo

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1. ABSTRACT

BACKGROUND: Loss of soft tissue in the lower leg presents a significant challenge for reconstruction. In the field of plastic surgery, free tissue transfer has become a common solution for large or complex soft tissue defects. Following free flap reconstruction, patients typically undergo a post-operative dangling protocol to gradually acclimatise the lower leg free flaps to increased venous pressure. However, the criteria for these dangling protocols vary between surgeons and centres and are often based on individual experience. Due to the lack of scientific evidence, there is no consensus on when to start mobilisation of the reconstructed lower leg.

OBJECTIVES: The aim of this study is to compare the length of hospital stay after free flap lower leg reconstruction between patients undergoing early mobilisation (postoperative day 3) and those undergoing late mobilisation (postoperative day 10). Secondary objectives are to evaluate and compare the percentage of flap success, the incidence of complications, the need for rehabilitation and the direct economic costs between the two groups.

DESIGN: This study is designed as a multicentre, prospective, randomized, open-label, parallel-group trial involving patients undergoing free flap lower leg reconstruction in three hospitals across Catalonia.

METHODS: 140 participants undergoing free flap lower leg reconstructive surgery will be enrolled using a consecutive sampling method. Participants will be randomly assigned in a 1:1 ratio to the intervention group (early mobilization starting on postoperative day 3) and the control group (same protocol starting on day 10). The main outcome variable will be length of hospital stay. Flap success and complications will be evaluated during the hospital stay. Patients will be followed for 1 year, with periodic visits to evaluate flap success and to assess if rehabilitation is needed. After 1 year the economic direct costs will be calculated. All data on study variables and covariates will be collected and analysed to determine their statistical significance. The total duration of the study is estimated to be 5 years.

KEYWORDS: lower leg reconstruction, mobilisation starting time, free flap, free flap monitoring, dangling protocol, flap training, post-treatment complications, flap success, need of rehabilitation.

2. ABREVATIONS

ALT	Anterolateral Tight Flap
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CEIC	Clinical Research Ethics Committee
CS	Computer Scientist
DCS	Data Collection Sheet
ECPS	European Course in Plastic Surgery
ED	Economic Department
GC	General Coordinator
HC	Hospital Coordinator
HCP	Health Care Personnel
HIF	Hypoxia-Induced Factor
HUB	Hospital Universitari de Bellvitge
HUJT	Hospital Universitari Josep Trueta
HUVH	Hospital Universitari Vall d'Hebron
LEFS	Lower Extremity Functional Scale
MESS	Mangled Extremity Severity Score
MI	Main Investigator
PCO_2	Partial Pressure if carbon dioxide
POD	Post-Operative Day
SECPRE	Sociedad Española de Cirugía Plástica Reparadora y Estética
ST	Statistician
StO_2	Arterial Oxygen Saturation
SPSS	Statistical Package for Social Sciences
TP	Training Personnel
VAR	Venoarteriolar Response
VEGF	Vascular Endothelial Growth Factor

3. BACKGROUND

3.1. ANATOMY OF THE LOWER LEG

The components and characteristics of the lower extremity differ greatly as one moves from proximal to distal regions. For this reason, the anatomical representation of the lower extremity is divided into thigh, knee, lower leg (or leg) and foot (1). In this study we will focus on the **lower leg**.

The lower leg is the region of the lower extremity between the knee and the foot. It consists of two bones: the tibia and the fibula, which provide stability and support for the rest of the body and allow walking (2).

The entire arterial blood supply to the lower leg is provided by the popliteal artery, which is an extension of the femoral artery. The popliteal artery continues into its terminal branches: the anterior tibial, posterior tibial and peroneal arteries (*Figure 1*) (3). These three major arteries are in closed compartments and have no significant communication between them (4). Each artery has a paired vena comitans in the deep venous system. At the superficial level, the small and great saphenous veins are important in draining blood from the lower leg (3).

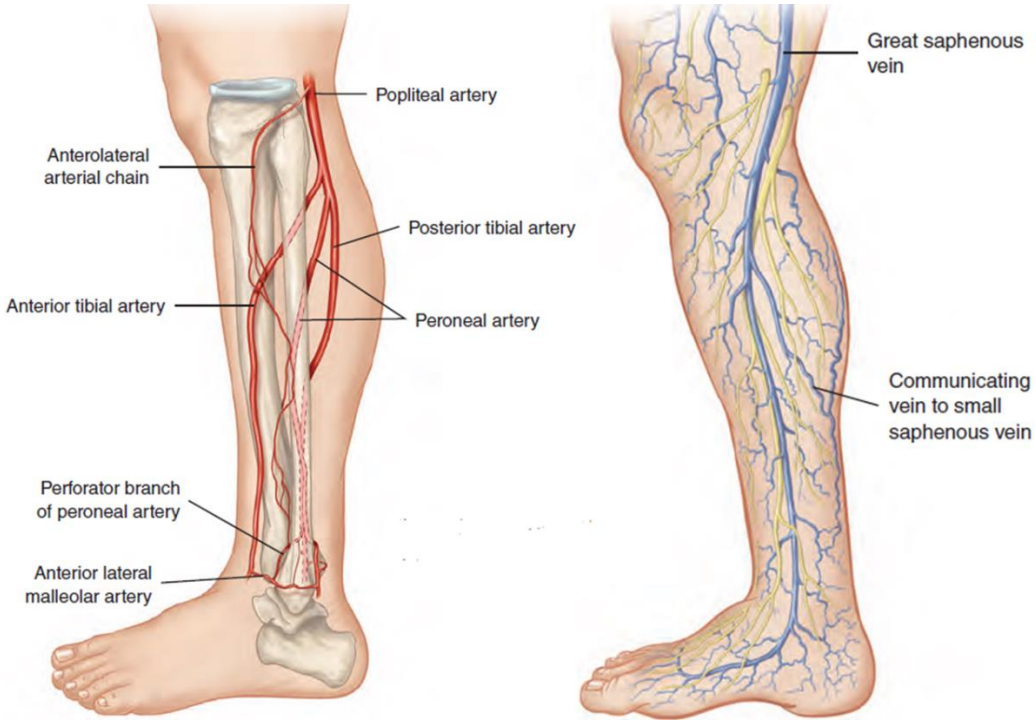

Figure 1 – Arterial and venous circulation of the lower leg (3)

There are 14 muscles in the lower leg, which are divided into four compartments: anterior, lateral, deep posterior, and superficial posterior *(Figure 2).* All muscles, except the popliteus, are involved in the movement of the ankle, foot or toes (1).

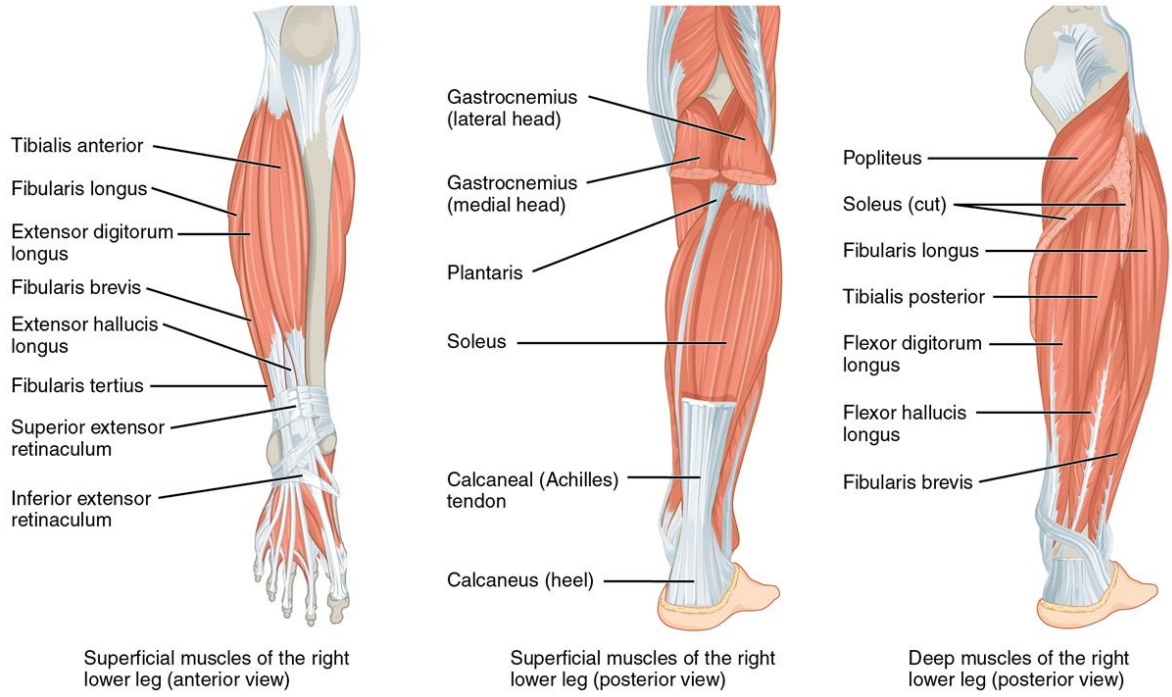

Figure 2 – Muscles of the lower leg (5)

The lower leg is innervated by several major nerves, each playing a crucial role in motor and sensory functions. The peroneal nerve and tibial nerve, branches of the sciatic nerve, are major contributors providing motor control and sensation to various muscles and areas of the leg *(Figure 3).* The peroneal nerve is responsible for motor control of the muscles in the anterior and lateral compartments, while the tibial nerve innervates the muscles in the posterior compartment. Additionally, the sural nerve provides sensory innervation to the lateral part, and the saphenous nerve supplies the medial region of the lower leg (3).

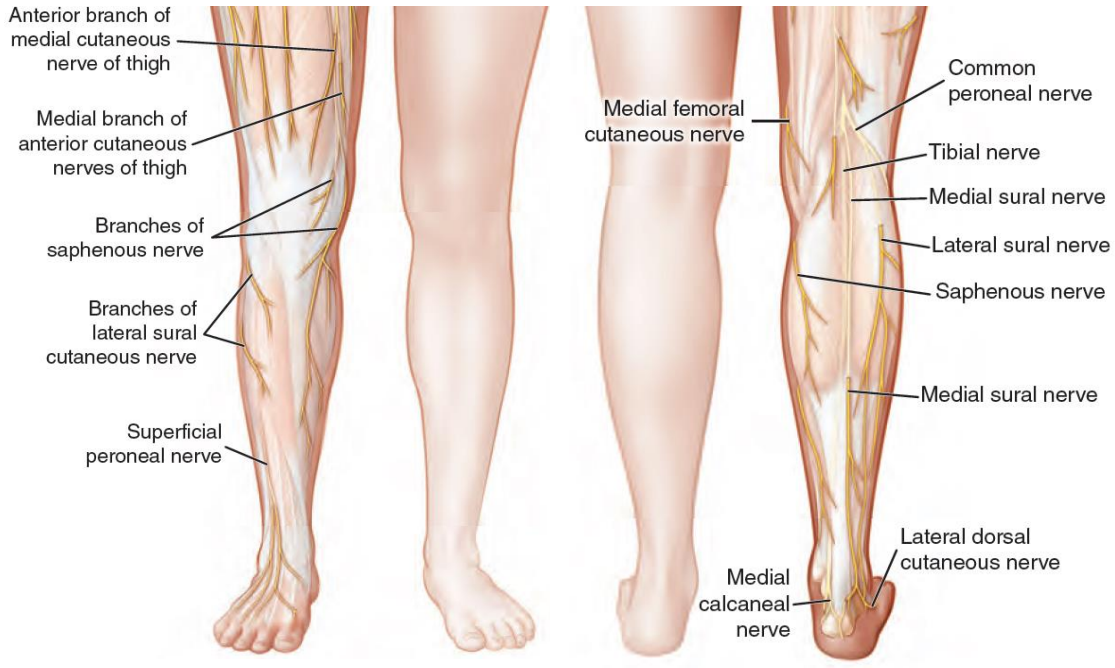

Figure 3 – Anterior and posterior cutaneous innervation of the lower leg (3)

3.2. EPIDEMIOLOGY OF LOWER LEG INJURIES

The epidemiology of lower extremity reconstruction addresses a significant problem in trauma care. It has been found that 18,5% of trauma emergency visits involve the lower extremity. In cases of traffic accidents, it is observed that 49% of patients have lower limb injuries, with the tibia being the most affected bone. The need for lower limb reconstruction is mainly due to trauma, accounting for 70% of cases, followed by tumours and chronic injuries (6). In particular, loss of substance in the distal third of the leg is the most common (37,5%), followed by injuries to the middle and upper third, respectively (7). The profile of patients requiring surgery is **predominantly male (70%) and young**, with an average age of 34 years.

Thus, these data show **that lower limb trauma is a common pathology** that causes a significant **morbidity** in the population, especially in young people. However, only a small proportion of injuries are complex enough to require free flap reconstruction.

3.3. DEFINITION AND ETIOLOGY OF LOWER LEG INJURIES

The leg has unique characteristics that make it susceptible to **extensive tissue injury and complex fracture patterns**. This is due to, for example, the fact that the front and middle section of the tibia is covered mainly by skin and subcutaneous fat, creating a relatively fragile anatomical structure that often leads to cases of exposed bone (8). Moreover, the anatomical characteristics of the lower third of the leg, such as the subcutaneous bone surrounded by tendons without muscles, and the vessels organized in separate compartments with limited intercommunication, or difficult venous return cause **more vulnerability to injury** and need from more complex reconstructions (4).

In this context, the principal etiological factors contributing to soft tissue loss in the lower leg include (3,9,10):

- Trauma
- Posttraumatic sequelae
- Chronic osteomyelitis
- Reconstruction after tumor ablation
- Dysvascular and diabetic foot

Thus, some population groups may be particularly vulnerable to lower extremity soft tissue injuries, such as athletes, construction workers, older people at risk of falls, and those with medical conditions that affect circulation or sensation.

3.3.1 CLASSIFICATION AND MANAGEMENT OF THE TRAUMATIC INJURIES

Lower extremity trauma often results in an open tibial fracture, constituting approximately 80% of all open fractures. The Gustilo-Anderson classification (*Table 1*) is commonly used to classify open fractures due to its simplicity and its significant implications for prognosis and therapy. There is a consensus that grade III tibial fractures have a higher risk of nonunion, infection, amputation and extended hospital stays, particularly if the wound cannot be successfully covered (3). Consequently, open tibia fractures are evaluated by plastic surgeons when the **Gustilo grade reaches IIIB or IIIC** (8).

However, caution is advised in interpreting treatment recommendations based on this classification due to its limitations, particularly concerning interobserver variability or interpretation. For example, some surgeons may consider it necessary to repair a second vessel in a one-vessel leg, while others may consider a single vessel sufficient for adequate blood supply to the foot, potentially altering the classification from IIIC to IIIB. Additionally, the classification makes no note of nerve injury, which are crucial in assessing prognosis (11).

Table 1 – Gustilo - Anderson Classification of Open Fractures of the Tibia (8)

Type	Description
I	Open fracture with a wound <1 cm
II	Open fracture with a wound >1 cm without extensive soft-tissue damage
III	Open fracture with extensive soft-tissue damage
IIIA	III with adequate soft tissue coverage
IIIB	III with soft-tissue loss with periosteal stripping and bone exposure
IIIC	III with arterial injury requiring repair

Although the principles of management are similar for all etiologies (described in section 3.4), there are some initial assessments specific to trauma.

Complex extremity trauma requires the combined expertise of the trauma, vascular and plastic surgeons. Before treating the fracture, it is vital to follow the guidelines for advanced trauma and life support, with priority given to the ABCs: Airway, Breathing and Circulation. If the patient has other life-threatening injuries, the management of the extremity injury should be limited to the stabilisation of the extremity and the control of bleeding (8).

Assuming that the patient's other injuries have been treated, a more careful examination must be made to determine if the limb is salvageable:

- **Vascular evaluation**: Examination of pulses, colour, temperature, and turgor of the foot. Signs of vascular injury, such as active haemorrhage, expanding or pulsatile hematoma, thrill/bruit over wound, absent distal pulses, or distal ischemic manifestations (1), require early intervention with either angiography or surgical

exploration. When a vascular injury is identified, the goal is revascularization **within 6 hours** (3).

- **Bone evaluation**: Once arterial flow has been restored, either by temporary shunting or definitive vascular repair, skeletal fixation may proceed. Bone evaluation is initially by visual inspection, with specific radiographs of any long bone suspected of injury (3).

- **Nerve evaluation**: A complete loss of neurological function may be a relative contraindication to limb salvage, as nerve repair in the lower extremity is associated with poor functional outcomes (8).

- **Soft-tissue evaluation**: The first goal of soft tissue evaluation is to debride the contaminated wound to healthy tissue and define the limits of the wound. It is important because it determines the type of reconstruction to be chosen and the need for prophylactic broad-spectrum antibiotics and tetanus vaccination (1) .

However, although reconstruction may be technically feasible, **amputation** of a mangled limb in a clinically unstable patient may be more prudent than extensive reconstruction (8). In fact, several studies show certain advantages of amputation over reconstruction in severe complex injuries, such as lower rates of rehospitalisation, shorter hospital stays, fewer operations and additional surgeries, and fewer cases of infection and osteomyelitis (12). Therefore, primary amputation should be considered in patients with **prolonged ischemia time** (6 hours or more), a large crush injury with soft tissue compromise, significant wound contamination or severe systemic disease.

Although there are no clear criteria, some algorithms have been developed in order to guide with the decision between salvage and amputation. This is the case of MESS (Mangled Extremity Severity Score *(Annex 1)*, which takes into account the skeletal and soft-tissue damage, the limb ischemia, the presence of shock, and the age of the patient (1,12). A score of 7 or more is considered the cut-off point for amputation.

3.4. GENERAL MANAGEMENT OF LOWER LEG INJURIES

The management of injuries with extensive tissue loss requires a **multidisciplinary team approach**. This collaborative effort involves the expertise of trauma, orthopedic, vascular surgeons, internists, radiologists and plastic surgeons (3). Once bone stability and vascular integrity have been established, general wound management consists of:

- **Debridement:** Early and aggressive debridement of necrotic tissue is essential for successful reconstruction. This allows a contaminated wound to be transformed into a clean one, reducing the risk of infection. It also helps to assess the extent of the injury and plan the reconstruction required (3,13).

- **Vacuum-assisted closure**: Vacuum-assisted closure is a form of negative pressure wound therapy used as a bridge until a definitive coverage can be performed. It is used to promote a healthy wound environment by increasing blood flow and reducing bacterial count (1,3).

- **Imaging**: A preoperative angiography is mandatory to identify arterial injuries and existing vascular conditions. This aids in deciding the most suitable treatment option, taking into account that the success of the flap depends on selecting appropriate recipient vessels away from the zone of injury (9,13).

3.5. RECONSTRUCTION TECHNIQUES

3.5.1 RECONSTRUCTION ORDER SCALE

Once the wound has been assessed as having a good vascular supply, stable skeletal structures and a relatively clean wound, soft tissue coverage is then considered.

Historically, the concept of **reconstructive ladder** has been used in plastic surgery to stratify reconstruction techniques (1). This ladder proposes choosing the simplest and least technically demanding procedure, starting with skin grafts and advancing to local, regional, or free flaps *(Figure 4*). However, although the simplest methods may achieve wound closure, they do not ensure optimal aesthetic and functional outcomes. This is particularly true in the lower

extremity, where the consequences of inadequate coverage can lead to complications such as additional soft tissue loss, osteomyelitis, loss of function, increased medical costs and even amputation.

Thus, in order to provide the best possible results, the **reconstructive elevator** model was created, which allows the surgeon to jump directly to the level of reconstructive complexity with a highest chance for success (14). This formulation emphasizes the importance of selecting the **most appropriate level of reconstruction** instead of choosing the least complex (15).

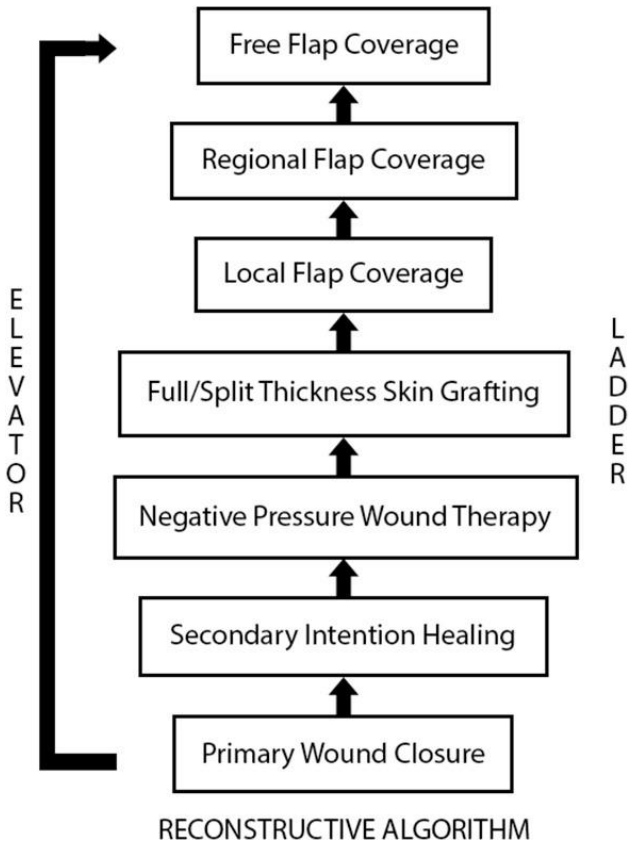

Figure 4 – Reconstructive ladder vs elevator for lower leg injury (14)

3.5.2 DEFINITION AND CLASSIFICATION OF FLAPS

In the highest steps of the classification of reconstruction techniques, flaps appear as the most complex reconstructive option. A flap is a **vascularized piece of tissue transferred from a donor site to another location**, either nearby or distant, to facilitate reconstruction (16).

Flaps can be classified in different ways:

- Blood supply *(Figure 5)*
  - **Random:** Irrigation based on small, unnamed blood vessels located in the dermal-subdermal plexus, which comes from the perforating artery that falls randomly at the anatomical base of the flap. This type of flap is limited by its length to width ratios.

  - **Axial:** Direct irrigation from septocutaneous or musculocutaneous artery. They can be categorized as direct when they reach the deep fascia without traversing other structures, or indirect when the vessels pass through deep tissues, leading to the formation of **muscle-cutaneous** flaps and **fasciocutaneous** flaps (16).

    For an axial flap to be viable, it must contain at least one **angiosome**. An angiosome is defined as a three-dimensional vascular territory supplied by an identified perforating artery that, identified by echo-Doppler, allows the flap to be designed (17).

  - **Perforator:** Flap perfused by an isolated artery and vein that pierces deep tissues (muscle or fascia), but without harvesting them. This approach is less invasive and more complex, as it involves preserving major vessels and muscles through intramuscular vessel dissection (18,19).

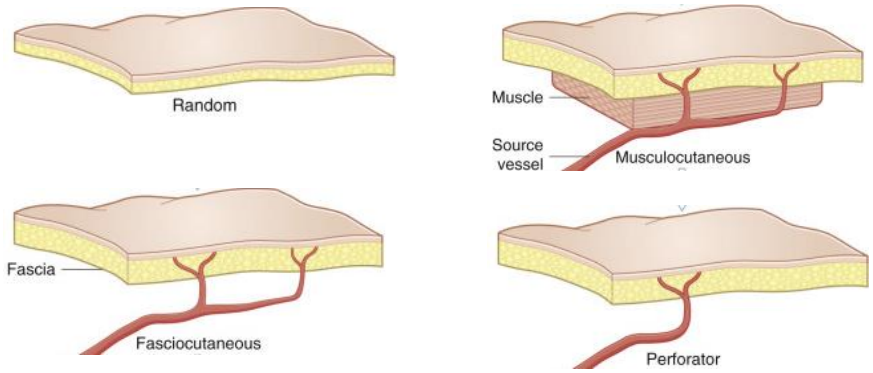

Figure 5 - Types of flaps according to their bood supply (20)

- Location (16)
  - **Local:** donor site is next to the defect.
  - **Regional:** flap corresponds to the same region of the body as the defect but does not share the defect margin.
  - **Distant:** flap transfer to a different anatomical region. These can be either pedicled or free.

- Attachment
  - **Pedicled**: transferred while still attached to their original blood supply.
  - **Free:** the tissue is cut away from the blood supply, requiring a re-attachment using microsurgical techniques.

- Tissue composition (16)
  - **Simple:** consisting of a single type of tissue, such as skin, fascia and muscle flaps.
  - **Composed:** with 2 or more tissues such as musculocutaneous, fasciocutaneous and osteomyocutaneous *(Table 2)*.

Table 2 - Types of flaps according to their tissue composition (16)

	Skin	Fasciocutaneous	Musculocutaneous	Osteomyocutaneous
Skin	⊕	⊕	⊕	⊕
Fat	⊕	⊕	⊕	⊕
Superficial Fascia	⊕	⊕	⊕	⊕
Deep Fascia		⊕	⊕	⊕
Muscle			⊕	⊕
Bone				⊕

3.6. FREE FLAP

3.6.1 DEFINITION AND INDICATIONS OF THE FREE FLAP

As mentioned above, free flaps are those tissue transfers that require an interruption of circulation to the donor site and re-anastomosis to the recipient site using microsurgical techniques. Microvascular free tissue transfer has revolutionised the treatment of soft tissue reconstruction of the complex lower extremity wound, providing a reliable and often better option that **meets both functional and aesthetic goals** (3,9).

Microvascular free flaps are preferred over local or pedicled flaps for complex lesion repair (9). They offer several advantages, including the avoidance of additional trauma to an already compromised region, shortened recovery time, greater flexibility in flap design and increased availability of donor tissue (3,9,13).

Therefore, free flaps are indicated in the following situations (13,21):

- **Exposed vital structures** like bone, tendons, vessels and nerves and prostheses
- **Large or extensive** surface areas
- **Highly complex** injuries
- Coverage of regions with **inadequate blood supply**

When choosing a flap for leg defects, the traditional rule of thirds suggests using local or regional flaps for small proximal and middle third defects, and free flaps for distal third defects (9). However, it is important to note that **almost every defect in the proximal, middle, or distal third of the leg that exposes bone and/or neurovascular structures or affects a large surface area requires reconstruction with a free flap** (3).

Despite increased technical demands and extended duration of the surgery, free flap reconstruction frequently leads to a **reduced number of postoperative complications** because of a better vascularization (13), with **success rates reaching up to 95%** (16). This becomes crucial when early postoperative mobilization or adjuvant therapy is necessary.

3.6.2 TYPES OF FREE FLAPS AND SELECTION

As microsurgery progresses, the options of free flaps available to reconstructive surgeons have increased exponentially, with over 100 potential donor sites reported in the literature (13).

Each flap has different characteristics, so it is necessary to carefully select the most appropriate flap for each individual (*see the algorithmic approach in Figure 9*). In general, due to the specific features of the lower leg, the most commonly used in clinical practice are those with a substantial and reliable cutaneous territory and a long pedicle of large calibre, allowing anastomosis beyond areas affected by trauma or radiotherapy. This, in turn, reduces the risk of vessel spasm and thrombosis at the anastomosis site (13). The main considerations to be taken into account in the lower leg reconstruction are the following (3,13):

- Defect size
- Pedicle length
- Defect location
- Available recipient vessels
- Volume of the deficient tissue
- Donor site morbidity
- Types of deficient tissue
- Colour and texture of the tissue surrounding the defect
- Wound status

Despite the number of flaps available, lower extremity reconstruction commonly uses only a few select flaps. The gracilis and latissimus dorsi are examples of musculocutaneous flaps, while the ALT is a fasciocutaneous flap. They are described below:

LATISSIMUS DORSI FLAP (9,13,22)

The latissimus dorsi is the largest muscle available, and is notable for its versatility and long pedicle *(Figure 6).* The muscle obtains its blood supply from the thoracodorsal artery, which branches from the subscapular artery in the axilla, as well as from perforators from the branches of the posterior intercostal arteries.

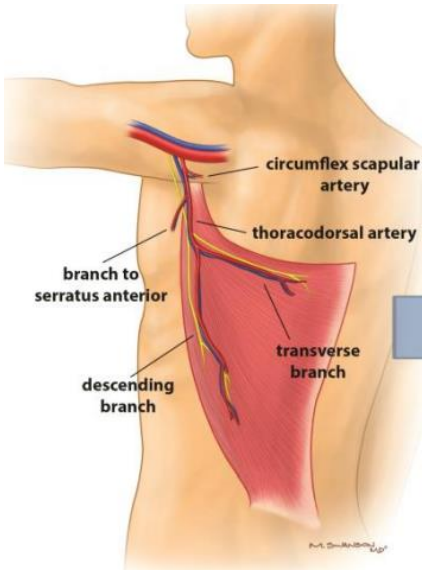

Figure 6 – The latissimus dorsi flap (23)

- ADVANTATGES:
  - Long vascular pedicle
  - Large muscle size
  - High flap viability due to its robust vasculature
  - Remarkable versatility: can be integrated with other flaps, customised, and precisely adjusted to accommodate virtually any size and shape
  - Quick, easy and low risk dissection due to its reliable vascular anatomy
  - Minimal functional deficit in the donor site

- DISAVANTATGES:
  - Inadequate for more delicate reconstructions due to its considerable volume
  - Common seroma formation in the donor site
  - Long-term chronic shoulder/back pain

- INDICATIONS:
  - Reconstruction of **large defects**
  - **Weight bearing surfaces** due to its combination of durability and high survivability
  - **Chronic infections** due to its hardy vascular supply

GRACILIS (1,9,13,22)

The gracilis flap, a thin and flat muscle situated on the medial thigh, provides surgeons with an easily accessible musculocutaneous donor supported by a robust pedicle *(Figure 7)*. Its vascular supply is primarily derived from branches of the medial femoral circumflex artery or deep femoral artery, supplemented by secondary sources from the superficial femoral artery.

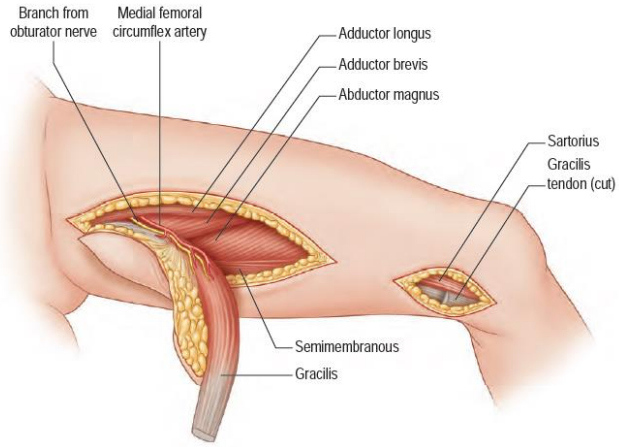

Figure 7 – The gracilis flap (1)

- ADVANTATGES:

  - Reliable vascular pedicle
  - Minimal donor site morbidity
  - The donor-site scar is concealed in the inner upper thigh, a well-accepted location for patients
  - Preference for the gracilis over the latissimus dorsi is driven by the potential functional limitations of the latissimus, which can hinder the use of crutches. This is especially pertinent for patients with lower limb defects.

- DISAVANTATGES:

  - Short pedicle
  - Surface limited in width
  - The distal third of the flaps is unreliable due to the decrease in vascular supply towards the peripheral margins of the skin.

- INDICATIONS:
  - Reconstruction of **moderate-large** sized wounds
  - Reconstruction of **smaller defects if trimmed**
  - **Osteomyelitis** due to its vascular stability

ANTEROLATERAL THIGH FLAP (1,9,13)

The anterolateral thigh (ALT) flap is a is a perforated flap that obtains its vascularisation through septocutaneous or musculocutaneous perforators coming from the descending branch of the lateral circumflex femoral artery, located between the rectus femoris and vastus lateralis muscles. The versatility and location of ALT flap make it a mainstay for lower extremity reconstruction.

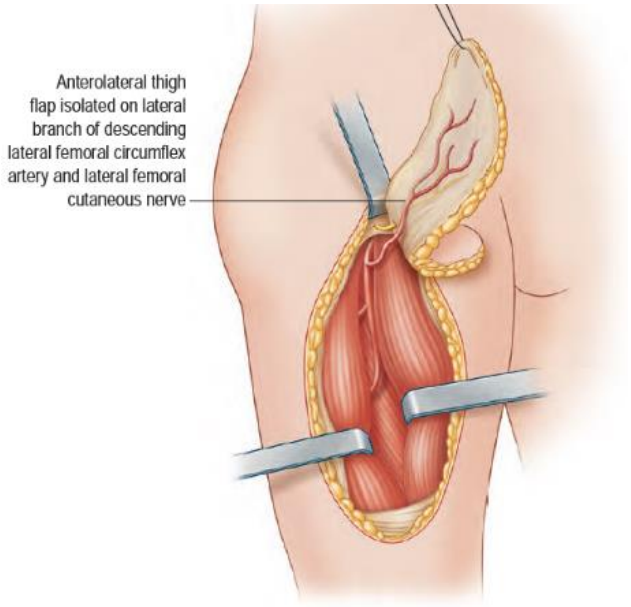

Figure 8 – The anterolateral thigh flap (1)

- ADVANTATGES:
  - Remarkable versatility: commonly used as a fasciocutaneous flap, it can also be used as a combined flap when combined with skin, fascia, muscle or any these in combination
  - Possibility to adjust the flap thickness
  - Minimal donor site morbidity
  - Large and reliable adipocutaneous territory
  - Long and thick pedicle

- DISAVANTATGES:

  - Lack of reasonable perforators or vessels if an anatomical variability is present

- INDICATIONS:

  - The ALT flap can be used in **most clinical situations** (chronic osteomyelitis, tumor resection or foot and ankle defects...), especially when a **skin flap** is needed.

The wound management process and choice of coverage is summarised in below:

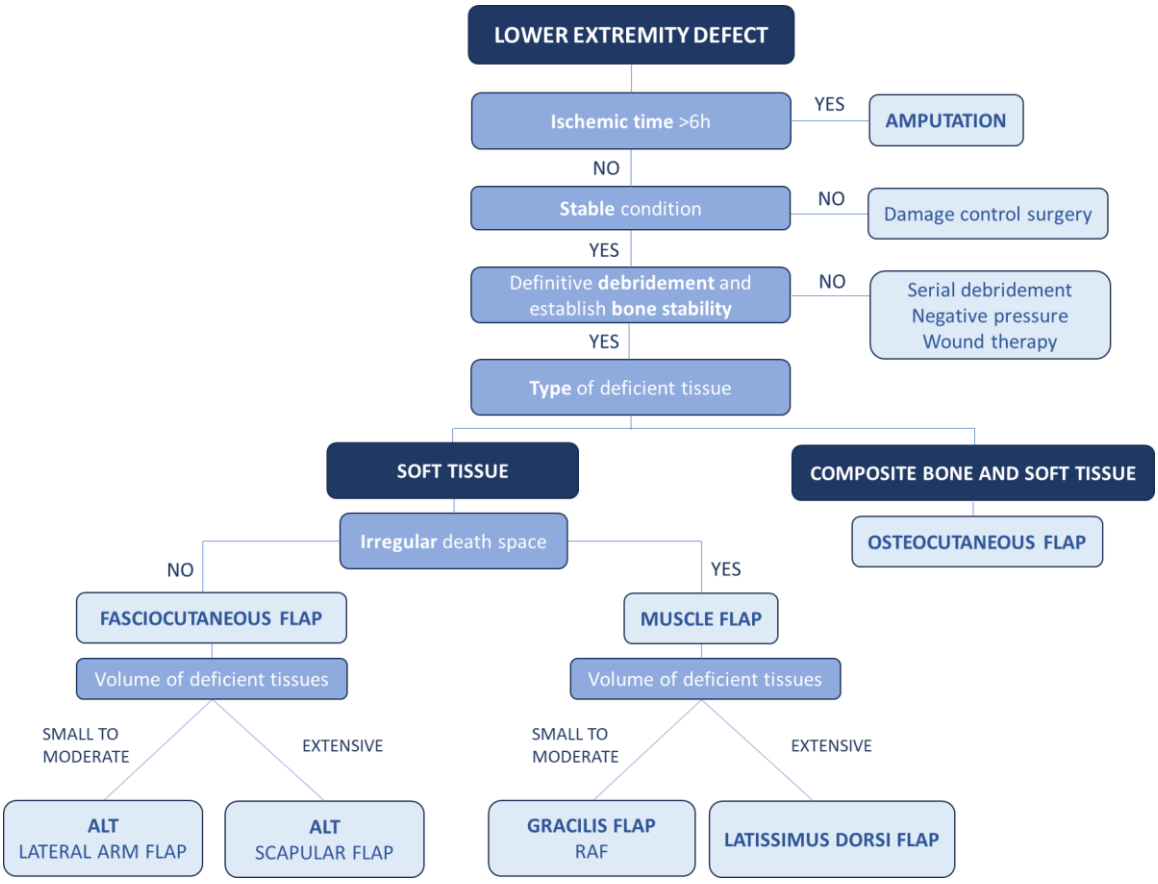

Figure 9 - Algorithmic approach for selecting free tissue transfer in lower leg. Adapted from "Reconstructive Surgery of Lower Extremity" (3) and "Plastic Surgery" (1). Keep in consideration that the reconstructions must be tailored to the specific needs of each patient. (ALT, anterolateral thigh; RAF, rectus abdominis).

3.6.3 FLAP COMPLICATIONS AND MONITORING

Lower leg reconstruction using free tissue transfer is a safe and reliable technique with a success rate of up to 95% (16). However, the significantly higher complication rate compared to free tissue transfer in other anatomical regions requires an **increased vigilance in the postoperative care** (3).

In **more than 80% of cases, complications occur within the first 72 hours** and especially within the first 24 hours (8,13,24). As mentioned earlier, close monitoring for potential problems at the outset is essential to identify them early, allowing the salvage of the 85% of flaps involved (1).

Flap loss is the most feared complication. It is usually immediate and rapid, and requires re-entry to the operating room to check/redo the anastomosis. The main cause is **arterial or venous thrombosis** (25). Prevention involves avoiding thrombogenic factors such as endothelial injury, disruption of laminar blood flow and alteration of blood viscosity (Virchow's triad) (16). For this reason, antithrombotic agents such as Dextran are often administered (13).

Other complications that may occur with less frequency and severity include: **partial flap loss**, **haematoma formation**, **infection** and **wound dehiscence**.

Partial flap loss is considered as a major complication if a reintervention is need or as a minor complication if can be addressed by conservative treatment. Wound dehiscence, wound infection, and hematoma are defined as minor complications because may be salvaged by conservative strategies (26).

Although flap monitoring can be performed using various techniques such as Doppler ultrasound, arterial or venous catheters or spectroscopy, **clinical evaluation** has been shown to be sufficient (24,27). This none invasive monitoring includes visual inspection of **colour, capillary refill, venous congestion, turgor, and temperature**.

However, it's important to note that there are limitations to physical examination. For example, skin colour is subjective and can be influenced by factors such as pigmentation and lighting conditions. Variations in skin colour between donor and recipient sites can also complicate the interpretation of results. In addition, individuals with darker skin may have difficulty assessing capillary refill (28).

Moreover, it's crucial to recognise that the impact on a patient's wellbeing goes beyond surgical complications. Given the extended hospital stays that these patients undergo, a

number of complications can arise. **Prolonged immobilisation** has been associated with multiple effects on almost every organ system (29), with pressure ulcers, pneumonia, deep vein thrombosis and urinary tract infections being the most common. Ultimately, this situation has been associated with **increased morbidity, mortality and hospital costs** (30).

3.7 DANGLING

3.7.1. DANGLING PHYSIOLOGY

In a healthy lower limb, **gravity dependence** leads to increased capillary pressure, increased interstitial edema and it can lead to venous congestion (31).

Physiologically, when the venous pressure in a limb rises to 25 mmHg, cutaneous, subcutaneous and muscle vascular resistances increase locally, resulting in a 40% reduction in blood flow (32,33). There are many adaptive mechanisms to limit edema formation in the lower limbs, including sympathetic innervation, muscular pumps, collateral flow or the venoarteriolar response (VAR). However, most of these mechanisms are lost during free flap transfer and only the VAR mechanism has been shown to be preserved (24,31,33). VAR, defined as a local response activated by stretch receptors in small veins, causes vasoconstriction of proximal arterioles when venous distension is detected, resulting in a reduction in blood flow (32).

During orthostasis, VAR has been shown to be responsible for up to 45% of the increase in vascular tone (32). However, this is not sufficient to prevent excessive congestion and edema formation (31). **Edema formation** in the post-operative period adversely affects the blood supply to the flap tissue by increasing capillary and interstitial pressure, resulting in a decrease in venous drainage, which is associated with an increase in pCO2 and decreased flap viability *(Figure 10)* (24,33).

In order to prevent complications, some surgeons implement **protocols for gradual dangling** in the post-operative period. This involves patients hanging the reconstructed lower leg from the side of the bed, gradually exposing the free flap to increased venous pressure generated by gravitational forces (26). The aim is to acclimatise flaps to the variations in arterial pressure, venous congestion and edema that occur when the limb is dependent. In this way, dangling

results in physiological adaptation, **gradually decreasing the severity of desaturation and recovery time** (34).

Furthermore, dangling is thought to trigger or accelerate changes by producing a **hypoxic drive to angiogenesis** (35). Hypoxia is a potent driver of angiogenesis, with hypoxia-inducible factor (HIF) driving vascular endothelial growth factor (VEGF) (34).

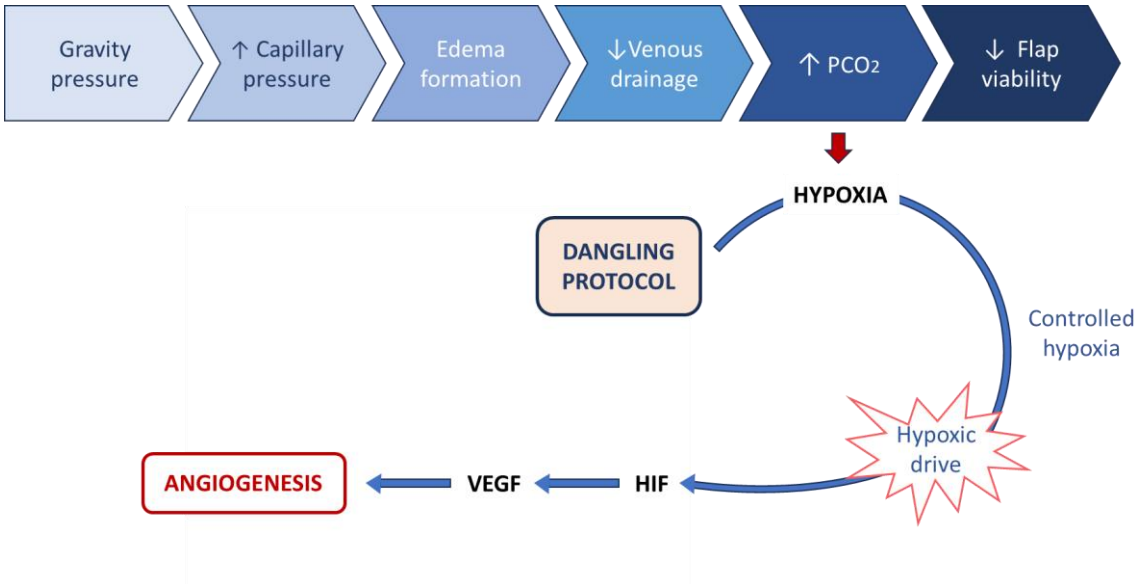

Figure 10 – Presentation of the physiology of the effect of gravity on the lower leg and the effects of the dangling protocol for the induction of angiogenesis. HIF: Hypoxia-induced factor, PCO_2: partial pressure of carbon dioxide, VEGF: vascular endothelial growth factor

Elastic wrapping of the dependent limb might be able to mitigate edema formation by reducing the potential intravascular venous and interstitial space in the flap and limb (35). This has the effect of controlling the deterioration of wound healing and attenuating the drop in tissue oxygenation during dangling (36). This, together with a possible increase in venous reflux caused by the wrapping (37), may explain the faster recovery in tissue oxygenation time seen in studies comparing the wrapped flap during dangling with the unwrapped limb (36,37).

As a result of implementing this **dangling and wrapping protocol**, we expect not only to achieve a physiological adaptation of the flap to its new environment, but also to accelerate the entire process.

3.7.2. BACKGROUND OF THE MOBILISATION START TIME

Although flap surgery has been extensively studied, post-operative care, such as mobilisation protocols, has received less attention (31,36). These studies are mostly uncontrolled and have low level of evidence, making it impossible to make evidence-based recommendations about when to start mobilisation (31,35,37). In order to reach a consensus, it is necessary to carry out studies of a higher quality. In fact, in current clinical practice, we find **wide variation in protocols between surgeons and centres, mostly based on anecdotal experience and opinion** (3,31,35). For example, the protocol used in the HUJT establishes the beginning of mobilisation on the 10th day, while the one used in Vall d'Hebron Hospital establishes the beginning on the 14th day.

The work of Rohde (2009) is the first, and probably the most famous, study to look at the optimal time to begin dangling. This study concludes that aggressive mobilisation can compromise the flap due to the effect of capillary pressure and venous congestion worsened by gravity, **suggesting to start the mobilisation in the 14th day after surgery** (38).

While future randomised controlled trials are needed, recent studies as Kolbenschlag (2015), Henton (2015), Trull (2021) or Lee (2021) contradict Rohde (2009), suggesting that an **early initiation of dangling protocols could be a safe and effective** component of postoperative management in most patients (31,34,36,39). Furthermore, early dangling appears to be safe across various free flap locations, sizes, and indications (31).

McGhee's systematic review even hypothesized that mobilisation **could be safely started on POD 2**. Although no study has been conducted to verify this, it is based on the fact that the angiogenesis process has already started on day 2, so it is thought to be responsive to a hypoxic stimulus (35).

Some studies also point in the same direction, in this case from a microscopic perspective. Kolbenschlag et al. (37) studied oxygenation and hemoglobin concentration using infrared spectroscopy in a three times a day for 5 minutes dangling protocol, starting on POD6. They found that, immediately after the beginning of dependency, there was an **initial increase in StO2 in the flap** (*Figure 11*), possibly indicating a transient rise in well-oxygenated blood before venous pooling occurred. After reaching a peak, approximately after 1 minute, **StO2 started to decrease continuously**. This subsequent decrease may be representing the presence of venous congestion since, as mentioned before, an increase of venous pressure leads to the accumulation of interstitial fluid, limiting the entry of oxygenated blood due to

proximal vasoconstriction (33). Following re-elevation of the leg, StO2 continued to decrease, possibly due to the ongoing compensation mechanism for venous congestion and until the desaturated blood is drained from the flap (36). The lowest StO2 was reached approximately 1 minute after re-elevation. It then began to rise and gradually returned to baseline values.

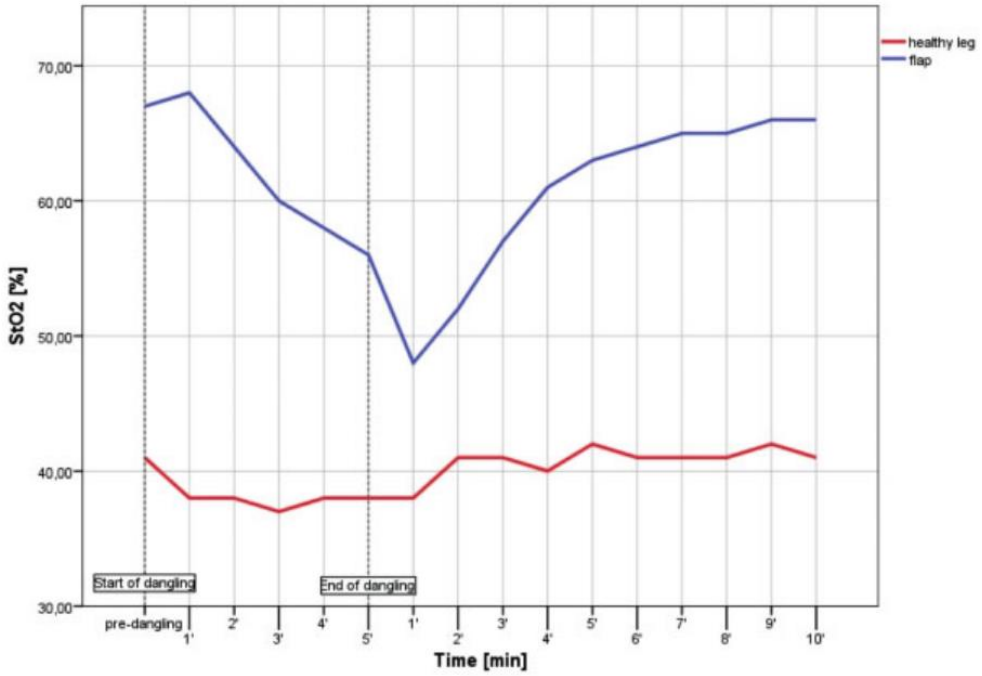

Figure 11 – The relationship between the oxygenation values (StO2) in the flap and in the contralateral (healthy) leg was observed during dangling on POD6. It's remarkable that the changes in the healthy leg were significantly less pronounced, both during dependency and during re-elevation. Extracted from Kolbenschlag et *al (37). POD: Post-operative day, StO2: arterial oxygen saturation.*

The consistent pattern continues throughout the study days as shown in *Figure 12*. However, some interesting observations were made. The StO2 value before the start of dangling showed an increase each day. It's worth noting the delayed appearance of the lower StO2 peak and its less pronounced decline. In addition, the decrease in StO2 after re-elevation gradually diminished. Finally, the time taken to return to baseline StO2 levels decreased over the days (37). In short, the flap matures as the training progresses, resulting **in improved baseline StO2 values and faster recovery times** (36).

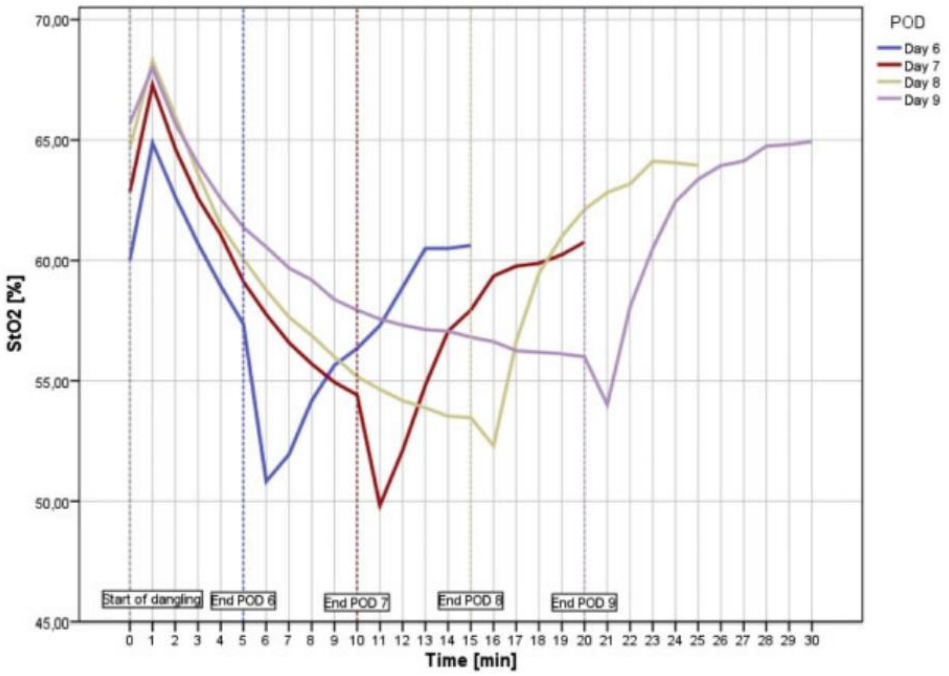

Figure 12 – Changes in the values of oxygenation (StO2) during the course of the dangling started on POD6. Extracted from Kolbenschlag et al (37). POD: Post-operative day, StO2: arterial oxygen saturation

Kolbenschlag et al. (37) also analysed the pattern of hemoglobin concentration *(Figure 13*). Pre-dangling hemoglobin concentration increased over the days, and the post-dangling accumulation recovery time decreased. However, these changes were of shorter duration than in O2 saturation.

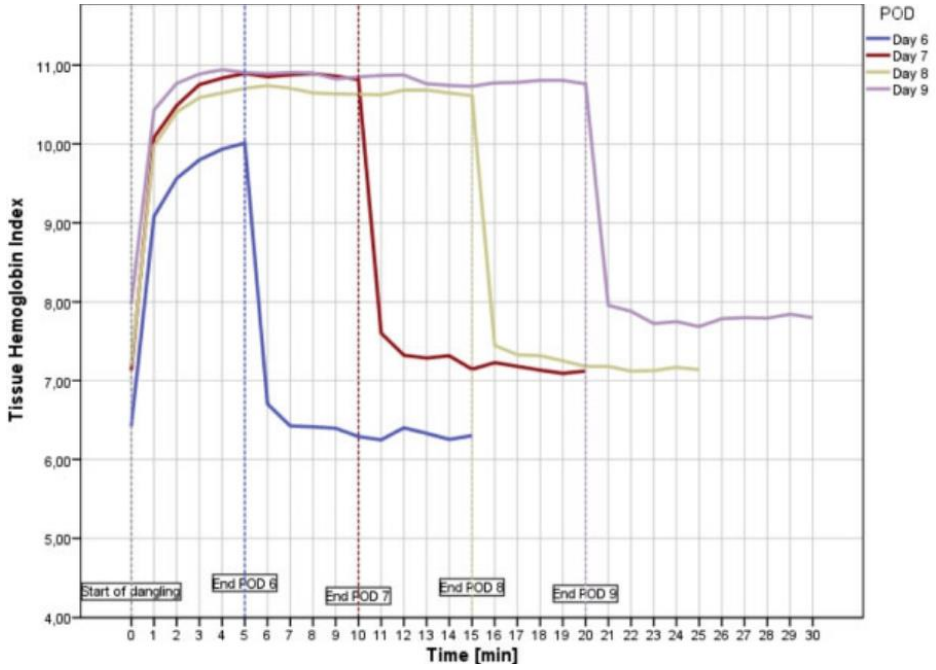

Figure 13 – Variations in tissue hemoglobin index values throughout the dangling process of dangling started on POD6. Extracted from Kolbenschlag et *al (37). POD: Post-operative day, StO2: arterial oxygen saturation.*

Another example is the Ridgway et al study (33). This research also investigates StO2 in response to dangling, but, in this case, it allows us to compare the leg with and without wrapping and provides a longer-term perspective on the adaptation process. In *Figure 14*, the graph illustrates the difference between wrapped and unwrapped limbs, both from the flap and the healthy leg, in a dangling protocol initiated on day 10. **Wrapped limbs show a smaller decrease in StO2 levels**. As mentioned earlier, this is because the use of wrapping prevents edema formation, allowing a more controlled protocol with fewer complications related to it, such as total or partial flap loss.

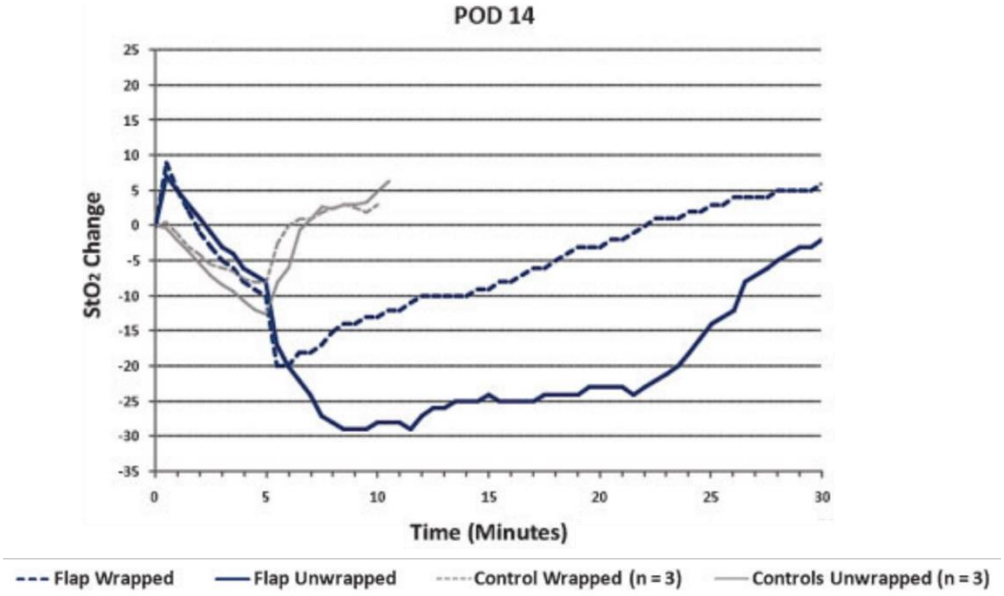

Figure 14 – Comparing the tissue oxygenation (StO2) curve during dependency between the unwrapped and wrapped lower extremities and the wrapped and unwrapped healthy controls. Extracted from Ridgway et al (33). POD: Post-operative day, StO2: arterial oxygen saturation.

Finally, an additional graph (*Figure 15*) provides an insight into the long-term adaptation of the flap. As can be seen, **the characteristic pattern gradually flattens out**, indicating a tendency towards a reduction in StO2 drop and shorter recovery times after dangling. At month 10, the StO2 curve begins to resemble the control curve in both wrapped and unwrapped conditions (33).

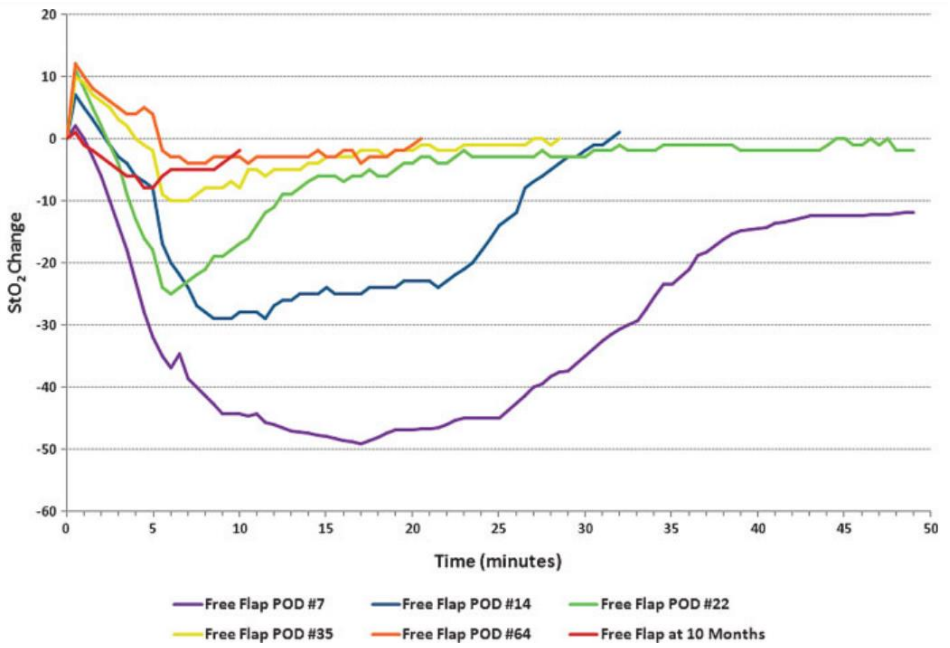

Figure 15 – Tissue oxygenation (StO2) curve during dependency comparing unwrapped flap on subsequent visits (POD 7, 14, 22, 35, and 64) and at 10 months postoperatively. Extracted from Ridgway et al (33). POD: Post-operative day, StO2: arterial oxygen saturation.

4. JUSTIFICATION

Large or complex soft tissue defects of the lower extremity remain a reconstructive challenge, usually requiring complex reconstructive techniques. The use of free tissue transfer for lower leg repair has become a common and safe procedure. However, despite extensive experience with free flap reconstruction of the lower leg, there is still considerable uncertainty regarding the postoperative management of these patients (31).

Typically, after a free flap reconstruction, patients undergo a dangling protocol. However, the timing of start of this post-operative mobilisation is still largely empirical, and protocols vary widely from surgeon to surgeon and institution to institution and are typically based on anecdotal experience and opinion (3). For example, at the Hospital Universitari Vall d'Hebron, leg mobilisation begins on postoperative day 14, while at the Hospital Universitari Josep Trueta, it begins on postoperative day 10.

The evidence available from the few studies that have considered this question has limitations in terms of control, representativeness and sample size, which make it difficult to draw definitive conclusions (37). Despite these limitations, the data collected suggest that early mobilisation may be as safe as a more conservative strategy. However, the same studies highlight the need to conduct studies with a higher level of evidence to support this statement (35,36).

For this reason, we propose to conduct a clinical trial with the largest number of participants to date, starting on postoperative day 3 (PO3). This decision is based on several considerations. Firstly, it is widely accepted that most complications occur within the first 72 hours and are unlikely to manifest later (1,8). Secondly, from a physiological perspective, we know that angiogenesis begins on day 2, suggesting that from this point the flap could benefit from angiogenic mediators generated in controlled hypoxia (37). Additionally, we also know that a reduction in hospital stay correlates with a reduction in complications and associated costs (35).

For these reasons, the main objective of this study is to demonstrate that earlier mobilisation can reduce the length of hospital stay (mean of 21,7 days) without increasing the incidence of complications, rehabilitation needs or total economic costs.

In particular, this study will allow us to generate new knowledge from a controlled clinical trial. Therefore, its completion could help to establish a consensus on the optimal time to start mobilisation, which could serve as a uniform guideline for daily clinical practice.

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

Early mobilisation (start dangling on post-operative day 3 [POD3]) in patients undergoing free flap lower leg surgery **reduces the length of hospital stay** compared to late mobilisation (start dangling on post-operative day 10 [POD10]).

5.2. SECONDARY HYPOTHESIS

1. In patients undergoing lower leg surgery, an early mobilisation (POD3) **does not increase free flap failure** (recorded at during hospital stay, 1 month, and 3 months post-operatively) compared to those who have a late start to mobilisation (POD10).

2. The **incidence of complications** (including arterial or venous thrombosis, hematoma, partial flap loss, wound dehiscence, or infection) **does not increase** in patients undergoing early mobilisation (POD3) compared to those undergoing late mobilisation (POD10).

3. Early mobilisation (POD3) in patients who have undergone lower leg reconstructive surgery **does not increase the need for rehabilitation**, as evaluated by the LEFS score at 1, 3, 6, 9 and 12 months post-operatively day, compared to those who underwent late mobilisation (POD10).

4. Early mobilisation (POD3) in patients who have undergone reconstructive surgery of the lower leg **reduces the direct economic costs** associated with hospital and outpatient treatment for all short- and long-term complications, including hospitalisation, re-intervention, complication management, and rehabilitation; compared to those who underwent late mobilisation (POD10).

6. OBJECTIVES

6.1. MAIN OBJECTIVE

To compare the **length of hospital stay** in patients who have undergone lower limb reconstruction between those who underwent early mobilisation (POD3) and those who underwent late mobilisation (POD10).

6.2. SECONDARY OBJECTIVES

1- To evaluate and compare the **percentage of free flap failure** in patients undergoing lower leg surgery during the intervention, one month and three months post-operatively using early mobilisation (POD3) and late mobilisation (POD10).

2- To identify and compare the **incidence of complications** (including arterial or venous thrombosis, hematoma, partial flap loss, wound dehiscence, or infection), between patients undergoing early mobilisation (POD3) and those undergoing late mobilisation (POD10).

3- To evaluate and compare the **need for rehabilitation** in patients who have undergone lower leg surgery at 1, 3, 6, 9 and 12 months post-operatively day, using the LEFS score for those who underwent early mobilisation (POD3) versus those who underwent late mobilisation (POD10).

4- To analyse and compare the **direct economic costs** related to hospital and outpatient treatment, encompassing short- and long-term complications, hospitalization, re-intervention, complication management, and rehabilitation in patients who underwent reconstructive surgery of the lower leg with early mobilisation (POD3) compared to those with late mobilisation (POD10).

7. MATERIAL AND METHODS

7.1. STUDY DESIGN

This is a **multicentre, prospective, randomized, open-label, parallel-group trial** that includes patients undergoing free flap lower leg reconstruction.

The principal outcome is to assess whether if an earlier mobilisation (intervention group starting on POD 3), can reduce the length of hospital stay compared to those who start a late mobilisation (control group starting on POD 10).

Once the patients who meet the inclusion criteria and do not present any exclusion criteria have signed the Informed Consent Document (*Annex 2*), they will be **randomly divided into two groups** (1:1 ratio). The assignment of the subjects will be done by a statistician using a computer-based system to do randomization.

The expected duration of the study and results is **5 years**, including 2 years for recruitment and intervention and 1 year for follow-up.

The trial will also follow the **intention-to-treat** principle. This means that all participants who were randomised will be analysed according to their original group allocation, regardless of the treatment they received. This principle increases both internal and external validity by maintaining the advantages of randomization. However, it is dependent on patient drop-out, which means that the higher the drop-out rate, the greater the threat to the validity.

7.2. STUDY SETTING

This protocol has been developed as a multicentre trial, and will be conducted in three Catalonian hospitals:

- Hospital Universitari Dr. Josep Trueta (HUJT)
- Hospital Universitari Vall d'Hebron (HUVH)
- Hospital Universitari de Bellvitge (HUB)

These hospitals are reference centres in Catalonia for reconstructive surgery. They all have the required human resources and equipment.

7.3. STUDY POPULATION

7.3.1. INCLUSION CRITERIA

Patients may be included in the study only if they meet all the following inclusion criteria at the time of patient selection:

- Age between 18 and 65 years
- Lower leg defect tributary of a free flap reconstruction
- Patients who have read the Patient Information Document *(Annex 3)* and have signed the Informed Consent Document *(Annex 2).*
- Follow-up at least 1 year

7.3.2. EXCLUSION CRITERIA

Patients excluded of the study will be those who meet one or more of these characteristics:

- Patients who had complications during the first 3 days after surgery
- Reconstruction with 2 or more flaps
- Patients who are getting a re-intervention due to a partial or total free flaps necrosis
- Patients who had previous surgery and/or radiotherapy on the surgical location
- Patient with coagulation disorders
- Patients who, for whatever reason, do not have the ability understand the study and, therefore, do not have the autonomy to decide whether or not to participate
- Uncooperative patient for rehabilitation

7.3.3. WITHDRAWAL OF PATIENTS

Participants are free to withdraw from the study at any time. A record of patients who leave the study should be maintained. Reasons for participant removal from the study may include:

- Non-attendance at follow-up sessions despite several attempts to contact them.
- The participant meets an exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.
- The participant has asked to withdraw consent for the study *(Annex 4).*
- Case of death

In the event of withdrawal or death, no extra patients will be added to the clinical trial, as a 10% of withdrawal is already included in the sample size calculation.

7.4. SAMPLING

7.4.1. SAMPLE SIZE

The sample size has been calculated with the help of the GRANDMO sample size and power calculator (version 8.0).

The mean of length hospital stay, calculated according to the mean of Jokuszies et al. (40) and Neubert et al. (24) studies, has been demonstrated in 21.7 days of length hospital stay. A minimum difference to be detected of 2 days has been established and a common standard deviation of 4 has been assumed. A drop-out rate of 10% has been anticipated. Thus, accepting an alpha risk of 0,05 and beta risk of 0.2 (i.e., statistical power of 0.8) in a two-sided test, 70 subjects are necessary in the control group and 70 in the intervention group **(140 in total)** to recognize as statistically significant a difference greater than or equal to 2 days.

7.4.2. SAMPLE SELECTION

A **non-probabilistic consecutive method** of recruitment will be used in this study. Patients who underwent lower leg reconstruction surgery with free flaps in any of the three affiliated hospitals and meet the inclusion criteria, without meeting the exclusion criteria, will be invited to participate in the study.

7.4.3. ESTIMATED RECRUITMENT TIME

The approximate number of patients per year who would be eligible for the trial, based on the data provided by the three hospitals, is:

- ➔ 20 patients from Hospital Universitari Dr. Josep Trueta
- ➔ 35 patients from Hospital Universitari Vall d'Hebron
- ➔ 30 patients from Hospital Universitari de Bellvitge

Therefore, to reach our sample size of 140 patients who meet the inclusion criteria, recruitment is estimated to take approximately **two years**.

7.4.4. MASKING TECHNIQUES

As mentioned early, this will be an open-label trial, as the assignments will be known by the investigation team and the patient. However, no member of the team will have the authority to decide which arm the patient will be enrolled in. With the aim to reduce any potential bias, the **statistician analysing** the results and the **physician following up** with the patient **will not be informed of the group of origin**.

7.5. VARIABLES AND MEASUREMENTS

7.5.1. INDEPENDENT VARIABLE

Independent variables of this study are the type of intervention being performed:

- **Group A – Control group**: The patient will be treated with the **HUJT's protocol**, starting mobilisation on the **10th day** (POD10).
- **Group B – Intervention group**: The patient will be treated with the **early mobilisation protocol**, starting mobilization on the **3rd day** (POD3).

7.5.2. DEPENDENT VARIABLES

Main dependent variable

- **Length of hospital stay:** Total time of stay in hospital, collected from patient's medical history, counting the days from the patient's surgery to his or her discharge from hospital / from Plastic Surgery department. This variable will be treated as a quantitative variable.

Secondary dependent variables

- **Flap success**: medically evaluated as a dichotomous qualitative variable as "yes" if the flap survives and "no" if the flap is lost. Follow-up will be done during the hospital stay, at month 1 and month 3 after the surgery *(Annex 5)*.

- **Post-intervention complications:** Each complication will be categorized as a dichotomic yes/no variable. It will be obtained from the patient's clinical chart and will be noted in the "Data Collection Sheet" *(Annex 5).* Main complications include arterial or venous thrombosis, hematoma, partial flap loss, wound dehiscence or infection (41). If other complications exist, they will be specified. It would be considered "post-intervention" until discharge.

- **Need of rehabilitation:** It will be evaluated dichotomously based on the LEFS (Lower Extremity Functional Scale) questionnaire at months 1, 3, 6, 9 and 12 after the intervention *(Annex 6)*. LEFS is a validated patient-reported measure designed to examine the functional status in the presence of lower extremity musculoskeletal problems. It consists of 20 items, with scores ranging from 0 (extreme difficulty/unable to perform activity) to 4 (no difficulty) (42).

  Scores between 0-20 (severe functional limitation) and 21-40 (moderate functional limitation) will have an indication for rehabilitation and will be indicated as "yes". On the other hand, scores between 41-60 (milt functional limitation) and 61-80 (minimal or non functional limitation) will not require rehabilitation and will be indicated as "no". However, considering that the patient's response may be influenced by the type of procedure performed, the opinion of the independent clinician conducting the follow-up is also necessary.

- **Direct economic costs:** The study will investigate the direct costs associated with hospital and outpatient treatment for all short- and long-term complications, including hospitalisation, re-intervention, complication management, and rehabilitation in both groups. This analysis will be evaluated a year from the intervention and will be treated as a continuous quantitative variable measured in euros.

  Costs for the different procedures were obtained from the HUJT's 2022 costs and are detailed in *Table 3*. It is important to note that the prices of these procedures may increase at the time of the study.

Table 3 - Economic costs of the management of the complications. The costs are based on HUJT's 2022 costs.

1 hour in the operating room	1.270,20 €
1 day in the reanimation area	1.355,30 €
1 day conventional hospitalization	520,93 €
1 hour of rehabilitation with physiotherapist	29,08 €

7.5.3. COVARIABLES

As this is a randomised trial, no baseline differences between patients are expected. Nevertheless, in order to identify possible confounding, we will collect the following data:

- **Age:** Patient age is associated with more medical complications after a free flap reconstructive surgery (43). Age will be expressed as a continuous quantitative variable and expressed as years at the moment of treatment. The answer will be extracted from the ID card or any other official document and collected into the "Data Collection Sheet" (*Annex 5*).

- **Sex**[1]**:** Categorized as a dichotomic male/female covariate. The answer will be extracted from the ID card or any other official document and collected into the "Data Collection Sheet" (*Annex 5*).

- **Smoking habit:** The negative effects of smoking on wound healing are well known, and several studies have evaluated the effects of cigarette smoking on the outcomes of flap reconstructions, noting increased incidences of flap and donor site complications (41).

  We will consider three groups between (i) non-smokers, (ii) smokers (considering those who smoke at the time of the treatment or on its 6 months prior) and (iii) ex-smokers (considering those who smoked during their life but haven't smoke during the

[1] The covariable "sex" will be understood as the chromosomal sex, even though we assume that gender identification can be different from the chromosomal sex.

past 6 months). The answer will be asked to the patient and collected into the "Data Collection Sheet" (*Annex 5*).

- **Alcohol consumption:** The intake of alcohol is associated with higher rates of flap failure, impairs wound healing and increases the incidence of infection (44).
  Categorized in three groups (45): (I) Non-consumer, (II) Moderate consumer (20-40g/day in women and 50-60g/day in men), and (III) High consumer (>40g/day in women and >60g/day in men). 10 grams of alcohol is approximately 1 pint of beer or 1 glass of wine or ½ glass of liquor. The answer will be asked to the patient and collected into the "Data Collection Sheet" (*Annex 5*).

- **BMI:** Individuals with high BMI frequently face wound complications as including skin wound infection, dehiscence, hematoma and seroma formation (46). BMI will be calculated using the following formula BMI = Weight/Height^2 and expressed in Kg/m^2. This covariable will be registered using the BMI classification (47), categorized in six weight statuses: (I) Underweight, (II) Normal, (III) Overweight, (IV) Obesity class I, (V) Obesity class II and (VI) Obesity class III.

- **Type of flap:** The type of free flap, which can be an ALT, gracilis or latissimus dorsi, will be taken as a qualitative polytomous variable and recorded in the "Data collection sheet" (*Annex 5*).

- **Wound locations:** The location of the wound, whether proximal, middle or distal third; will be treated as a qualitative polytomous variable and documented in the "Data Collection Sheet" (*Annex 5*).

- **Comorbidities:** Independent of the age, comorbidities and chronic diseases have found to correlate with postoperative outcomes and wound healing (43). We will analyse comorbidities using the Charlson Comorbidity Index (CCI), a weighted index that takes into account the number and the seriousness of comorbid disease (48). To use it we will collect the patient information from the personal history and categorize the illness with assigned weights (ranging from 1 to 6) based on the adjusted risk of mortality (*Annex 7*). The resulting number is the sum of all weights results in a comorbidity score, so it's a discrete quantitative variable. The higher the score, the greater the likelihood that the predicted outcome will result in dying or increased resource use. A

score of 0-1 indicates no comorbidity, 2 indicates low comorbidity, and 3 or more indicates high comorbidity.

- **Hospital:** Although hospitals with similar experience, resources and professionals have been selected, we will examine whether the outcome of the intervention in HUB, HUJT or HUVH can influence the results, considering it as a nominal qualitative polytomous variable.

- **Socioeconomic status:** It will include social classes from I to V, considering the patient's education level and occupation according to Domingo et al (49). It will be asked to the patient and collected in the Data Collection Sheet (*Annex 5*).

Table 4 - Summary of variables and covariables

	Variable	Type of data	Categories	Instrument of measure
Independent	**Beginning of the treatment**	Dichotomic nominal qualitative	- POD 3 - POD 10	
Main dependent variable	**Length of hospital stay**	Discrete quantitative	Numerical (days)	Computerised medical history
Secondary dependent variables	**Flap success**	Dichotomic nominal qualitative	-Yes -No	Data collection sheet
	Post-intervention complications	Dichotomic nominal qualitative	-Yes -No	Computerised medical history
	Need of rehabilitation	Dichotomic nominal qualitative	-Yes -No	Lower Extremity Functional Scale
	Direct economic costs	Continuous quantitative	Numerical (euros)	Computerised medical history
Covariables	**Age**	Discrete quantitative	Numerical (years) From 18 to 65	
	Sex [1]	Dichotomic qualitative	-Male sex -Female sex	
	Smoking habit	Polytomous qualitative	-Non-smoker -Ex-smoker	

		-Smoker	Computerised medical history or anamnesis, summarized in Data Collection Sheet
Alcohol consumption	Polytomous qualitative	-Non-consumer -Moderate consumer -High consumer	
BMI	Polytomous ordinal qualitative	IBM classification from I to VI	
Type of flap	Polytomous nominal qualitative	-Latissimus Dorsi -Gracilis -ALT	
Wound locations	Polytomous nominal qualitative	-Proximal third -Middle third -Distal third	
Comorbidities	Discrete quantitative	Numerical (0-7)	
Hospital	Polytomous nominal qualitative	-HUB -HUJT -HUVH	
Socioeconimic status	Polytomous ordinal qualitative	Social classes from I to V	

7.6. STUDY INTERVENTION

7.6.1. ENROLMENT AND RANDOMISATION PROCEDURES

All patients undergoing lower leg reconstruction with free flaps and admitted to any of the three participating hospitals, who meet the study's inclusion criteria and do not meet the exclusion criteria, will be eligible for enrolment in the clinical trial. Plastic surgeons will invite patients on postoperative day 1 or 2, providing them with the Patient Information Document (*Annex 3*) and asked to give written informed consent. Patients will be given at least 24 hours to decide whether to participate. The enrolment will be completely voluntary and only those signing the Informed Consent Document *(Annex 2)* will participate.

After the patient has comprehended the study and agreed to participate by signing the Informed Consent Document, they will be **randomly assigned in a 1:1 ratio** to one of the two groups using a computer-based system for randomisation:

- **Group A – Control group**: Patient will undergo a late mobilisation, beginning on **POD 10.**
- **Group B – Intervention group**: Patient will undergo an early mobilisation, beginning on **POD 3**.

7.6.2. INTERVENTION

Once the patient has been stabilised and evaluated, and all standard pre-operative protocols have been followed (General management section), an expert surgical team will perform the free flap reconstruction. Standardised postoperative care will be followed. Eligible patients will be informed about the study and offered the opportunity to participate during the first two days after the operation. They will be given at least 24 hours to read the Patient Information Document (*Annex 3*), ask any questions and, if they wish to participate, sign the Informed Consent Document (*Annex 2*).

All post-operative care will be performed equally, **with the only difference being the starting time of the dangling protocol**. The group randomly assigned to early mobilisation will start the protocol on day 3, while the control group will start on day 10.

The protocol for both groups involves **wrapping the affected leg and dangling** the lower extremity. This will be done with the patient seated in an upright position at the edge of the bed with the knee joint flexed at a 90-degree angle, without any restriction of movement and without supporting the heel. It is important to remember that mobilization can be influenced by the bone-stabilizing elements used by the trauma team, so the clinician must adapt the dangling movement to the patient's reality. The duration of the suspension will be the following:

Table 5 - Duration and frequency of dangling

Nº of dangling training days	Duration
1	5 min / 3 times per day
2	10 min / 3 times per day
3	20 min / 3 times per day
4	30 min / 3 times per day
5	45 min / 3 times per day
6	60 min / 3 times per day

A physician will supervise each dangling and perform a **clinical evaluation before and after each dangling**, including observation of colour, capillary refill, venous congestion, flap turgor and temperature. Trained nursing staff will also closely **monitor these parameters every 4 hours** throughout the day in order to maintain precise control of the flap and to identify any complications at an early stage. As this may be subjective, doctors and nurses will have undergone training to standardise criteria. **Any observed complications will be documented** on the Data Collection Sheet (*Annex 5*).

Once the patient has satisfactorily completed the dangling protocol and the patient is autonomous, the patient can be discharged from the Plastic Surgery department if the doctor considers it appropriate.

7.6.3. FOLLOW-UP

Follow-up visits will be made at 1 month, 3 months, 6 months, 9 months and 1 year after the day of surgery. At the first two visits, another doctor, unaware of the assigned procedure, will make a dichotomous assessment of flap survival and provide the patient with the LEFS questionnaire to determine the need for rehabilitation based on the results combined with his or her own criteria. At the subsequent 6-month, 9-month, and 1-year follow-up visits, only the need for additional rehabilitation will be assessed using the LEFS questionnaire and medical criteria. This information will be recorded on the patient Data Collection Sheet (*Annex 5*).

7.7. DATA COLLECTION

The information required for this work will be obtained from the computerised clinical history, anamnesis, physical examination and scheduled clinical visits. The collected data will be recorded in a Data Collection Sheet (DCS - *Annex 5*) at different stages of the study, as summarized in *Table 6*.

As soon as the participant has given his or her consent to take part in the trial, the attending physician will collect the personal information (age, sex, comorbidities, smoking habits, alcohol consumption, BMI, and socioeconomic status) from the patient's medical history and anamnesis. **Throughout the dangling process** and the remainder of the hospital stay, the responsible doctor and the nursing team, will document any complications in the DCS. **At discharge**, the number of days of hospitalization will be calculated and recorded in the patient's DCS for further analysis. **Subsequent visits** will focus on collecting information about the success of the flap and the need for rehabilitation based on the LEFS, as explained in the 'Follow-up' section.

After 1 year from the surgery, the costs of hospitalisation, rehabilitation, associated complications, and re-interventions will be summed up for comparison between the two groups. Prices are obtained from costs in 2022, as provided in *Table 3* from Economic Cost section.

The collected information from the other hospital coordinators will be verified by the general coordinator to ensure accuracy. Once all the DCSs have been filled in, a **computer scientist** will create a database to collect all the data for its subsequent analysis. The computer scientist will also anonymise all the data using an identification code to maintain patient anonymity and to ensure that the statistician remains blinded. Subsequently, the **statistician** will conduct the analysis of the survey data.

Table 6 - Summary of data collection

	Before intervention **1 o 2 days POD**	**During hospital stay**	**Discharge**	1st visit **1 month POD**	2nd visit **3 months POD**	3th visit **6 months POD**	4th visit **9 months POD**	5th visit **1 year POD**	**1 year POD**
Personal information	**X**								
Complications		**X**							

Flap success		X		X	X				
Length of hospital stay			X						
LEFS				X	X	X	X	X	
Economic costs									X

7.8. FLOW DIAGRAM

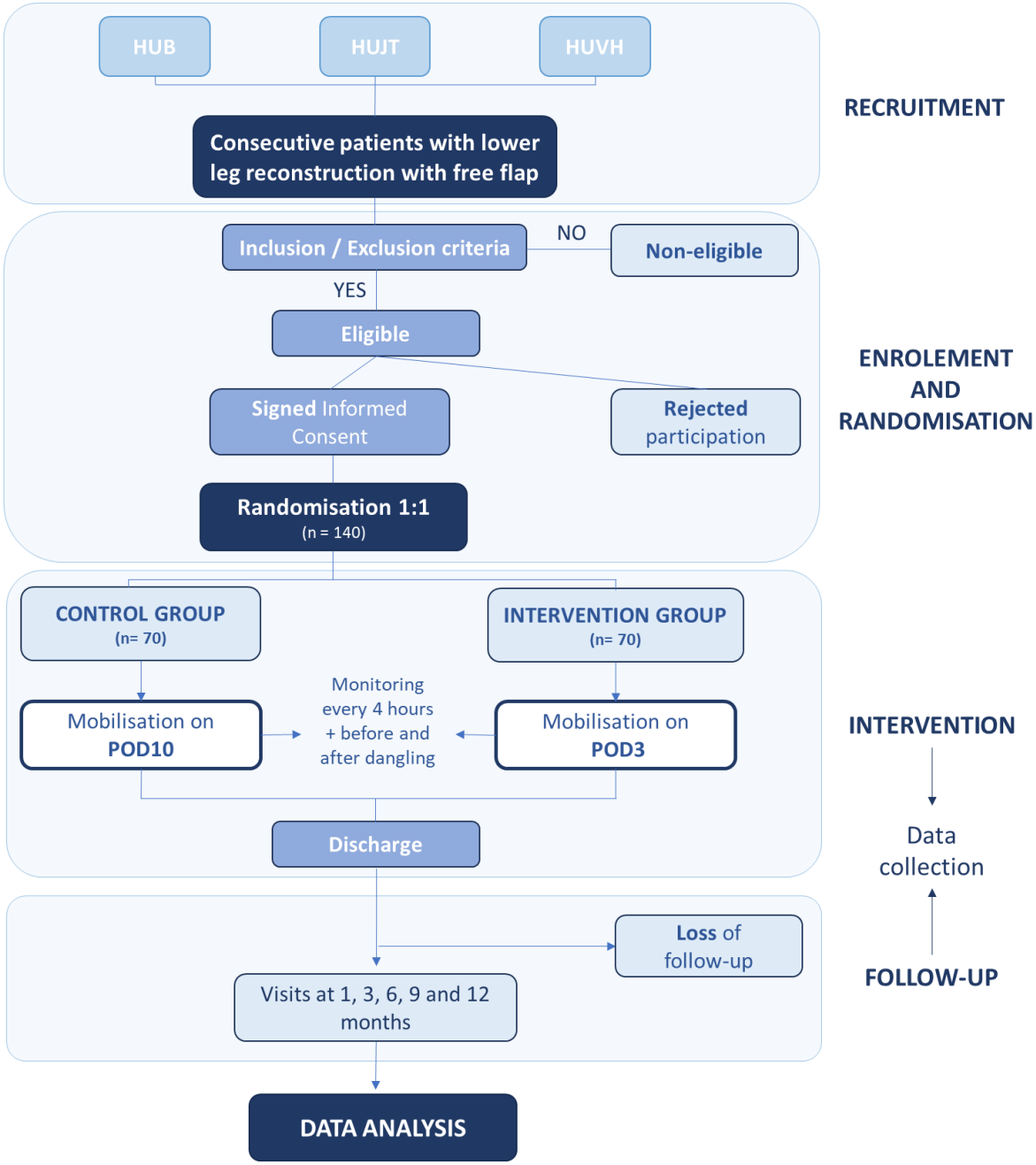

Figure 16 – Flow diagram of the study.
HUJT (Hospital Universitari Josep Trueta), HUB (Hospital Universitari de Bellvitge), HUVH (Hospital Universitari Vall d'Hebron), POD (Post-Operative Days)

8. STATISTICAL ANALYSIS

The statistical analysis will be performed by a blinded statistician, using the *Statistical Package for the Social Sciences (SPSS)* software (version 29.0.1). A confidence interval of 95% will be assumed and the differences will be statistically significant with an error probability of less than 5% ($p<0.05$).

8.1. DESCRIPTIVE ANALYSIS

In this analysis, variables and covariables will be defined as quantitative or qualitative (*see Variables; Table 4*).

For the **quantitative variables**, the **mean** and **standard deviation** (for variables with a symmetrical distribution, for example age) and **medians and interquartile ranges** (for variables with an asymmetrical distribution, for example, length of stay and probably direct cost) will be used. Finally, **qualitative** variables and covariables, will be described with proportions.

These descriptives for the dependent variables will be stratified by the two groups of intervention, and additional stratification will be done by the covariates. Age will be categorized in quartiles.

For length of stay we will additionally estimate and draw **Kaplan-Meier curves** for the intervention and control group.

8.2. BIVARIATE INFERENCE

The difference of medians between the type of intervention and the quantitative variables, such as the length of hospital stay or economic costs, will be tested using a **Mann-Whitney's U test**, because their distribution is not symmetrical.

The difference of proportions between effect of the intervention on the other dependent variables (all of them qualitative: flap success, post-intervention complications and need of rehabilitation) will be test using a **Chi Square test** or, if the expected number of subjects in any cell is less than 5, the **Fisher's exact test** will be used.

The difference between the Kaplan-Meier curves will be assessed using the **log-rank test**.

8.3. MULTIVARIATE ANALYSIS

As mentioned before, a randomized trial anticipates no initial differences among patients. However, to detect potential confounding factors, a multivariate analysis will be conducted.

To assess the effect of the intervention on economic costs a **linear regression** model (in case that the distribution of the costs will be symmetrical) or a **Poisson regression** (in case that the distribution of the costs will not be symmetrical) will be used, in all cases controlling for covariates.

Multivariate logistic regressions will be used for the association between the intervention and qualitative variables (flap success, post-intervention complications and need of rehabilitation), again controlling for covariates.

To evaluate the intervention on the length of hospital stay, a **Cox regression** adjusting for covariates will be estimated.

9. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with human rights and the *"Ethical Principles for Medical Research Involving Human Subjects"* as stated in the World Medical Association's **Declaration of Helsinki** (1964, last revised in 2013). We will also follow the ethical principles of **Beauchamp and Childress**, ensuring that the four fundamental principles are respected:

- **AUTONOMY**

  Enrolment in the study will be entirely voluntary, as the principle of autonomy recognizes individuals' rights to make choices regarding their own health. All eligible people who consider taking part in this study will receive an easy-to-understand "**Patient Information Document**" (*Annex 3*) explaining the study. If they decide to participate, we will ask for their written consent using the "**Informed Consent Document**" (*Annex 2*). Participants are free to refuse or withdraw from the study at any time without negative consequences, and this decision will be documented on the "**Withdraw Consent Document**" (*Annex 4*).

  The principle of autonomy also guarantees **confidentiality and data protection**. Consequently, this study complies with the Spanish's law "***Ley Orgánica 3/2018,***

de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales" and European law "***Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016*** *on the protection of natural persons with regard to the processing of personal data and on the free movement of such data*".

This way, the collected data will be anonymized, accessible only to the research team and utilized exclusively for research purposes.

- **BENEFICENCE**

  The principle of beneficence is respected because we expect our intervention to reduce the length of the patient's stay in hospital, which will have a **positive impact** on the patient and the healthcare system.

  In addition, the study is justified (see justification section) and the design is appropriate (see study design section).

- **NON-MALEFICENCE**

  It is expected that the principle of non-maleficence will be respected, as the **available literature suggests that early initiation of the dangling process is safe**. However, a close monitoring will be implemented to ensure this. In addition, patients who meet the exclusion criteria will be excluded from the project as they are not expected to benefit from the study procedure.

- **JUSTICE**

  We will ensure the principle of justice by considering all patients who meet inclusion and exclusion criteria and have signed the consent form **equally for participation** in the study, avoiding any positive or negative discrimination.

  Furthermore, all patients in this trial will be covered by clinical trial **insurance** to protect them against any unexpected problems during the research.

This protocol has also been developed in accordance with the Spanish legislation "**Ley 14/2007**, de 3 de julio, de Investigación Biomédica".

This clinical trial will be registered with the *Registro Español de Estudios Clínicos* before it begins and its results will be openly published, whether they are **favourable or not**. The investigators involved in this study will also confirm that they have **no personal conflicts** of interest related to any aspect of this research.

This protocol will be evaluated by the **Clinical Research Ethics Committee (CEIC)** of each hospital participating in the study. In case the CEIC presents objections and/or makes recommendations, the protocol will be adjusted to ensure all ethical standards are met and approved.

10. WORK PLAN AND CHRONOGRAM

10.1. RESEARCH TEAM MEMBERS

The research team will be composed of:

- **Main investigator (MI):** is the person leading the study, assembling the team, elaborating the protocol and ensuring that all goes as planned.

- **General coordinator (GC)**: is the person who maintains contact with all other hospital coordinators, oversees the data collection process in the study and presents the collected information to the computer scientist.

- **Hospital coordinator (HC):** a person from each hospital who will be in charge of recruiting patients, collecting data and ensuring the proper execution of procedures within their respective centre.

- **Health care personnel (HCP)**: includes the surgeons, nursing staff and nursery assistants from the Plastic Surgery department from each hospital who are in charge of patient care, data collection and performance of the interventions.

- **Other staff:** a member of the economic department (ED) of each hospital, training personnel (TP) and physiotherapists.

10.2. INDEPENDENT RESEARCH MEMBERS

The study will need to hire different professionals for its development:

- **Computer scientist (CS):** is the person who will create a specific database for this study.

- **Statistician (ST):** an independent statistician will be responsible for carrying out the statistical analysis of the study.

10.3. STUDY STAGES

The estimated duration of the study will be **5 years,** plus 2 months of 2023. It will include 6 main stages in the following order:

STAGE 0: STUDY DESIGN

- **Bibliographic research** (November 2023 – January 2024): A bibliographic research has been conducted to provide background and context for the study.
- **Protocol elaboration** (November 2023 – January 2024): Protocol has been elaborated, including the objectives, hypothesis, variables and methodology.
- **Participating hospitals contact** (February 2024): The selected hospitals will be contacted and invited to participate in the study.

Personnel involved: Main investigator

STAGE 1: ETHICAL APPROVAL

- **Ethical evaluation and approval** (February 2024 – April 2024): The protocol will undergo review and approval by the CEIC of HUJT, followed by ethical approval from the CEICs of all participating centres. Any contributions from the respective CEICs will be used to adjust the protocol.

Personnel involved: Main investigator

STAGE 2: RESEARCH MEMBERS COORDINATION

- **Research team meeting** (May 2024): The main investigator will meet with the research teams from each participating hospital. The meeting will involve selecting a hospital coordinator, defining the project, explaining and assigning tasks, and visualizing the project timeline. All participants will be asked to sign a statement confirming their agreement to the protocol and to the legal and ethical aspects of it.
- **Formation sessions** (May 2024): In order to reduce potential bias in the identification of complications among doctors, we will provide training to standardise the criteria for identifying complications. In addition, we will provide training to nurses to recognise the warning signs of complications. Furthermore, training for doctors and nurses will be carried out to standardise the surgical procedure and related medical care.

Personnel involved: main investigator, hospital coordinator, health care personnel and training personnel.

STAGE 3: RECRUITMENT AND DATA COLLECTION

These tasks will be performed simultaneously in every hospital the study is working.

- **Sample recruitment** (June 2024 – June 2027): Sample selection will be based on a consecutive non-probabilistic recruitment process. Only patients who meet the inclusion criteria, do not meet the exclusion criteria, and provide signed informed consent will be included in the trial. They will then be randomly assigned to one of the intervention groups.
- **Intervention** (June 2024 – June 2027): Depending on the randomly assigned group, the patient will undergo early mobilisation (POD3) or late mobilisation (POD10). During this procedure, the flap will be monitored every 4 hours by the nurses and doctors and any complications will be noted. The length of hospital stay will also be recorded.
- **Follow-up** (July 2024 –June 2028): Follow-up visits will take place during the following year and economic costs will be recorded at the end of the year. At the first visit, at one and three months, the success of the flap will be assessed and the patient will perform the LEFS scale. At the sixth, ninth and twelfth month visits, the need for rehabilitation will be assessed using the LEFS.

- **Data collection** (June 2024 – June 2028): All the information collected in the DCSs by the respective doctors during the study will be collected by the hospital coordinator and sent to the general coordinator. The general coordinator will collect and verify all the information.

Personnel involved: health care personnel, hospital coordinator and general coordinator

STAGE 4: DATA ANALYSIS AND INTERPRETATION

- **Creation of database** (July 2028): a computer scientist will create a database and will anonymise all the data using an identification code.
- **Statistical analysis** (August - September 2028): A blinded statistician will analyse all the data collected by a descriptive, bivariate and multivariate analyses and will then interpret the data obtained.
- **Results and conclusions** (October 2028): The final statistical analysis will be interpreted with the entire research team for discussion and drawing conclusions.

Personnel involved: Computer scientists, statistician, main investigator and general and hospital coordinator.

STAGE 5: FINAL ARTICLE ELABORATION AND PUBLICATION

- **Article redaction and publication** (October - December 2028): The MI will write the final article. It will be edited and supervised by English correctors and published afterwards.
- **Dissemination** (October – December 2028): The article will be published in scientific journals and the findings will be disseminated at national and international Plastic Surgery congresses.

Personnel involved: Main investigator

10.4. CHRONOGRAM

Table 5 - Chronogram

Stage and activity	Staff	Period																													
		2023		2024							2025	2026	2027							2028											
		N	D	J	F	M	A	M	J	July - Dec	Jan - Dec	Jan - Dec	Jan - June	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
STAGE 0: STUDY DESIGN																															
Bibliographic research																															
Protocol elaboration	MI																														
Participating hospitals contact																															
STAGE 1: ETHICAL APPROVAL																															
Ethical evaluation and approval	CEIC																														
STAGE 2: RESEARCH MEMBERS COORDINATION																															
Research team meeting	MI, HC, HCP																														
Formation sessions	TP, HCP																														
STAGE 3: RECRUITMENT AND DATA COLLECTION																															
Sample recruitment	HCP																														
Intervention	HCP																														
Follow-up	HCP																														
Data collection	HC, GC, ED																														
DATA ANALYSIS AND INTERPRETATION																															
Creation of database	CS																														
Statistical analysis	ST																														
Results and conclusions	MI, GC, HC																														
STAGE 5: FINAL ARTICLE ELABORATION AND PUBLICATION																															
Article redaction and publication	MI																														
Dissemination																															

11. BUDGET

The estimated budget for this study is **28.063€**. The following costs have been taken into account:

11.1. NOT-INCLUDED COSTS

11.1.1. PERSONNEL

The main research team (MI, GC, HCP and ED) will be made up of staff from the three hospitals involved in the study, so there won't be any additional costs and will not receive any extra payment for doing so. This will ensure that there are no financial incentives to take part in the study.

11.1.2. MATERIALS

The selected hospitals already have the materials needed for the post-operative care of the patients, so it will not be necessary to include them in our budget.

Follow-up visits will be carried out as they are already standardised, so they will not be an expense for the study. The rest of the costs that could result from the intervention (re-intervention, rehabilitation sessions, management of complications...) will be covered by the National Health System and will be included in the variable economic costs for the subsequent study.

11.2. INCLUDED COSTS

11.2.1. PERSONNEL

- **Computer scientist**: a computer scientist will be hired to create database. The work is estimated to take 30 hours at a cost of 40€/hour, so the estimated cost is 1.200€.

- **Statistical analyst:** an independent statistical analyst will be hired. This will require an estimated 100 hours of work, at a rate of 40€/hour, and is expected to cost 3.200€.

11.2.2. TRAINING SESSIONS

- **Training sessions for doctors:** doctors will be trained in order to standardise the criteria for defining complications and the time of discharge. The total cost of the training for the three centres is estimated at 1.200€ for 10 hours at 40€ per hour.

- **Training sessions for nursing staff:** nursing staff will be trained in the recognition of warning signs in each centre. The training will be 5 hours at a cost of 40€/hour. The total cost for the three centres is estimated at 600€.

- **Training sessions for the health care staff**: Another training will be given to medical and nursing staff to unify the strategy for the surgical process and adjuvant treatments. This training will last 5 hours at a cost of 40€/hour, for a total of 600€ for the three centres.

11.2.3. LIABILITY INSURANCE

- **Liability insurance**: As our study is a clinical trial, insurance will be required. The cost of insurance is estimated at 100 euros per patient, with a total price of 14,000 euros.

11.2.4. MATERIALS

- **Printing costs**: It is estimated that 11 sheets will be printed for each patient during the study: Patient Information Document (4 pages), Informed Consent Document (1 page) and 5 LEFS scales (1 page). Considering that the printing cost per page is 0.05€/page and that 140 patients will be needed, the printing cost is estimated at 77€.

11.2.5. ADMINISTRATIVE TAXES

- **Hospital administrative fees:** As our work is a non-commercial clinical trial, we are eligible for an exemption from the hospital's administrative fees, so there is no cost added to the budget.

11.2.6. TRAVEL AND COORDINATION EXPENSES

- **Travel expenses:** For the initial and subsequent discussion meetings, the HCs from other hospitals will need to travel to Girona. We estimate a total cost of 100€ per person for travel, allowances, and meals, amounting to a total of 400€. The annual control meetings will be held telematically, so no costs will be added.

11.2.7. PUBLICATION

- **English correction**: A budget of 300€ is calculated for the linguistic revision of the article.

- **Publication fees:** We will publish the results of this clinical trial in an international open access medical journal, we estimate the cost of publication at 1.800€.

11.2.8. DISSEMINATION

- **National congress:** The article will be presented at the SECPRE (*Sociedad Española de Cirugía Plástica Reparadora y Estética*) Congress, which has a registration fee of 600€ euros. 300€ euros will be charged per participant for travel, food and accommodation. The total cost for the two participants will be 1.800€.

- **International congress:** The paper will be presented internationally at the ECPS (European Course in Plastic Surgery) at a cost of 550€ per participant. 500€ per participant will be charged for travel, accommodation and meals.

Table 6 - Budget of the study

	UNIT COST	HOURS OR UNITS	TOTAL
PERSONNEL			
Computer scientist	40€/hour	30 hours	1.200€
Statistical analysis	40€/hour	100 hours	4.000€
			Subtotal: 5.200€
TRAINING SESSIONS			
Doctors training	40€/hour	10 hours x 3 centres	1.200€
Nursing staff training	40€/hour	5 hours x 3 centres	600€
HCP training	40€/hour	5 hours x 3 centres	600€
			Subtotal: 2.400€
INSURANCE POLICY			
Liability insurance	100€/patient	140 patients	14.000€
			Subtotal: 14.000€
MATERIALS			
Printing costs	0,05€/page	11 pages x 140 patients	77€
			Subtotal: 77€
ADMINISTRATIVE TAXES			
Hospital administrative fees	0€	1	0€
			Subtotal: 0€
TRAVEL AND COORDINATION EXPENSES			
Travel expenses	100€/person and meeting	2 HC	400€
			Subtotal: 400€
PUBLICATION			
English correction	300€/article	1	300€
Publication fees	1800€	1	1.800€
			Subtotal: 2.100€
DISSEMINATION			
SECPRE Congress	900€/attendant	2	1.800€
ECPS Congress	1050€/attendant	2	2.100€
			Subtotal: 3.900€
			TOTAL: 28.077€

12. LIMITATIONS AND STRENGTHS

When revising our protocol, there are some limitations that should be taken into account because they may affect our research. The main limitations are explained below:

DETECTION BIAS

In this trial, it is impossible to hide the intervention from the patient and the doctor, so it is classified as an **open-label trial**. This type of study is susceptible to detection bias because masking techniques cannot be used. To minimize bias, the **statistician analysing the data will be blinded**. Additionally, to eliminate potential subjectivity from patients filling out the LEFS scale based on the performed protocol, the requirement for rehabilitation will be evaluated using the numerical result and the doctor's criteria. The doctor performing the **follow-up visits will not know which protocol** the patient has followed.

SELECTION BIAS

Another limitation related to the design of our study is the recruitment method. The consecutive recruitment is a **non-probabilistic recruitment** and may not obtain the best representative sample of the population, and therefore selection bias may occur. To minimise this bias, **randomisation** of the intervention will be performed to distribute patients between equal and comparable groups. In addition, very few exclusion criteria have been defined.

MEASURAMENT BIAS

In this multicentre study, we may encounter **inter and intravariability** not only between hospitals but also between professionals from the same hospital.

It is possible that the **data collected may vary** among different investigators. To minimize subjectivity and measurement bias, we have developed a "**Data Collection Sheet**" (*Annex 5*) and will employ **validated scales** such as LEFS (*Annex 6*).

Other variables, such as the presence or absence of complications based on physical examination, are also particularly susceptible to subjectivity. To address this, all participating physicians will undergo **training to standardize criteria** for identifying complications and

deciding when to discharge patients. In addition, nursing staff, responsible for patient monitoring, will be trained to early identify warning signs.

Given the involvement of three different hospitals, training will be extended to ensure uniformity in the surgical process and patient care. Despite selecting hospitals with **similar capacities and resources** to attain consistent results, we will **control for the hospital factor** in the multivariate models.

WITHDRAWAL

Due to the prospective nature of the clinical trial, there is a potential risk of withdrawals during the **follow-up period**. To account for this risk, a **10% dropout rate** was considered when determining the sample size, resulting in an increased overall sample size to cover it.
Additionally, in cases where patients are absent for their follow-up visits, the research team will conduct **telephone calls** to encourage them to continue participating in the study.
Moreover, randomization and **intention-to-treat (ITT)** analysis serve to prevent the impact of withdrawals from overestimating outcomes. ITT assumes that in real clinical practice, withdrawals and other non-compliances will also exist, providing a more realistic reflection of the intervention's effectiveness.

CONFOUNDING VARIABLES

A covariate is a variable that may affect the relationship between the independent and dependent variables in a study. It has the potential to introduce confounding, which could lead to distorted associations between variables. To mitigate the impact of any possible covariates on our conclusions, we will perform a **multivariate analysis**.

EXTERNAL VALIDITY

An inherent limitation of clinical trials is their reduced external validity. However, the inclusion of participants from two different regions in this **multicentre trial** and the **randomisation** aim to reduce this limitation to some extent.

However, this study also has some strengths:

STRONG EVIDENCE

This is a **randomized clinical trial**, which is considered the strongest scientific evidence among the primary studies.

REPRESENTATIVENESS

The multicentre nature of the clinical trial allows a more **diverse range of patient characteristics** compared to a single institution, which enriches the sample and strengthens external validity.

LONG TERM BENEFIT

The implementation of this study involves certain costs; however, if the hypotheses prove correct and are implemented, it will result in a **reduction of economic costs** in the daily practice of the National Health Care System.

13. CLINICAL AND HEALTHCARE IMPACT

While lower extremity free flap microsurgery has been extensively studied and complication rates are minimal, there is limited knowledge about postoperative management. In clinical practice, dangling training is used to gradually adapt the flap to gravity, but the starting point is unclear: in most cases there is no specific protocol, and management is based on the experience and judgement of the medical team. Existing studies are limited in patients and representativeness, highlighting the need for a standardized clinical trial.

This clinical trial aims to assess whether early dangling training reduces the length of hospital stay without increasing the incidence of complications or the need for rehabilitation compared to late mobilization.

Confirming the hypothesis would advance **medical evidence on postoperative mobilisation** in lower extremity reconstructive surgery, and provide the opportunity to establish a **standardised protocol for general clinical use**. Its implementation would significantly **benefit patients** by shortening hospital stays, reducing the physical and psychological impact of prolonged immobilisation, and reducing the likelihood of complications related to hospitalisation. Additionally, if early mobilization does not increase complications and the need for rehabilitation, the **direct economic costs associated with hospitalization of the Health Care System will also be reduced**.

14. FEASIBILITY

This study is expected to be feasible since no big obstacles have been identified.

The three hospitals participating in this trial are centres with experienced Plastic and Reconstructive Surgery Units that **routinely treat this type of surgery and patients**. This means that the hospitals have the **necessary space** (operating rooms, intensive care beds and hospital beds, as well as external consultation areas for post-operative care), **equipment and technology** to carry out the study. The hospital also boasts **expert multidisciplinary team** capable of conducting the study.

As the National Health Care System will cover all necessary expenses, including the salaries of the existing medical and administrative staff, only a computer scientist and an analyst will need to be recruited. The electronic equipment for data collection and statistical analysis will also be provided by the same hospital. For this reason, the estimated **budget is considered affordable**.

Although the hospital would be able to assume the cost and responsibility for any complication that could result from patients' participation in the study, a **liability insurance** will be acquired to cover any possible adverse effects.

The sample recruitment and intervention period are estimated to be two years and the follow-up period is estimated to be one year, which is considered to be a **feasible duration**.

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16. ANNEXES

ANNEX 1 – MANGLED EXTREMITY SEVERITY SCORE

Variable		Points
A	**Skeletal/soft-tissue injury**	
	Low-energy (stab, simple fracture, civilian gunshot wound)	1
	Medium-energy (open/multiple fractures, dislocation)	2
	High-energy (close-range shotgun, military gunshot wound, crush)	3
	Very-high-energy (above + gross contamination)	4
B	**Limb ischemia***	
	Pulse reduced or absent; perfusion normal	1
	Pulseless, paresthesias, diminished capillary refill	2
	Cool, paralyzed, insensate, numb	3
C	**Shock**	
	Systolic blood pressure always >90 mmHg	1
	Transient hypotension	2
	Persistent hypotension	3
D	**Age**	
	<30 years	1
	30–50 years	2
	>50 years	3
	Maximum score possible	16
	Threshold score for amputation	7
*Score doubled for ischemia time >6 hours.		

ANNEX 2 – INFORMED CONSENT DOCUMENT

DOCUMENT DE CONSENTIMENT INFORMAT DEL PACIENT

NOM DE L'ESTUDI: "Optimizing Recovery: Investigating the Role of Early Postoperative Mobilisation in Free Flaps Surgery for Lower Leg Reconstruction"

Jo, _____, amb document d'identificació personal (DNI/NIE)_____, declaro que:

- He estat correctament informada pel Dr./Dra._____
- He llegit i entès tota la informació que apareix a la fulla d'informació per al pacient. He rebut una còpia del Full d'Informació i del Consentiment Informat.
- He pogut fer preguntes sobre l'estudi i aquests s'han resolt de manera satisfactòria.
- Estic satisfet/a amb la quantitat d'informació que se m'ha proporcionat.
- Entenc els potencials riscs i beneficis derivats de participar en aquest estudi.
- No he ocultat informació essencial sobre el meu cas, els meus hàbits o règim de vida, que poguessin ser rellevants als metges que m'atenen.
- Entenc i accepto que les meves dades es recolliran a partir dels meus registres mèdics pels investigadors de l'estudi, i aquestes seran tractades de forma confidencial i respectant la meva intimitat.
- Comprenc que la meva participació és voluntària i no remunerada.
- Entenc que em puc retirar de l'estudi en qualsevol moment, sense haver de donar explicacions i sense que afecti en la meva assistència sanitària futura.
- Comprenc que puc demanar que s'eliminin les meves dades recopilades.

En conseqüència,

- Dono lliurement la meva conformitat a participar en l'estudi.

☐ Sí ☐ No

- Permeto que totes les dades de la intervenció, així com altres dades recopilades durant l'estudi, puguin ser utilitzades en investigacions futures.

☐ Sí ☐ No

- Accepto que els investigadors del projecte puguin posar-se en contacte amb mi en un futur si es considera oportú.

☐ Sí ☐ No

Firma del pacient: **Firma de l'investigador/a:**

A _____, ____ de _____ de l'any _____

ANNEX 3 – PATIENT INFORMATION DOCUMENT

DOCUMENT D'INFORMACIÓ DEL PACIENT

NOM DE L'ESTUDI: "Optimizing Recovery: Investigating the Role of Early Postoperative Mobilisation in Free Flaps Surgery for Lower Leg Reconstruction"

CENTRE ASSITENCIAL: ☐ Hospital Universitari de Bellvitge

☐ Hospital Universitari Josep Trueta

☐ Hospital Universitari Vall d'Hebron

Benvolgut/da,

Ens dirigim a vostè per proposar-li participar en un estudi d'investigació dut a terme pels Serveis de Cirurgia Plàstica i Reparadora de diferents hospitals de referència a Catalunya. Aquest estudi ha sigut aprovat pel Comitè d'Ètica i Investigació Clínica dels tres hospitals participants d'acord amb la legislació vigent, i seguint els principis enunciats en la declaració de Hèlsinki.

La nostra intenció és que vostè comprengui la raó per la qual es realitza aquest estudi i rebi la informació correcta i suficient perquè pugui decidir voluntàriament si desitja participar-hi o no. Per això, li demanem que es prengui el temps necessari per llegir amb atenció aquest resum informatiu sobre el nostre estudi. No és necessari que prengui una decisió avui sobre la seva participació. Si té qualsevol dubte no dubti en fer-ho saber al nostre equip, que li proporcionarà tota la informació necessària.

PARTICIPACIÓ VOLUNTÀRIA

Ha de saber que la seva participació en aquest estudi és estrictament voluntària i que la seva acceptació o renúncia no produirà cap alteració en la relació amb el seu metge ni afectarà a la seva atenció sanitària. També ha de saber que vostè podrà canviar la seva decisió en qualsevol moment i revocar el seu consentiment sense necessitat de justificar-se i sense que es produeixi cap alteració en la seva assistència sanitària.

PER QUÈ ÉS NECESSITA AQUEST ESTUDI I QUINS SÓN ELS SEUS OBJECTIUS?

La cirurgia de reconstrucció de l'extremitat inferior amb penjoll lliure és un procediment complex que sovint requereix períodes prolongats d'immobilització i, com a resultat, llargues

estades a l'hospital. Durant la fase de recuperació després de la cirurgia, es realitzen habitualment petits entrenaments, de durada creixent, que consisteixen a penjar la cama des de l'extrem del llit per aconseguir una adaptació gradual del penjoll al seu nou entorn.

El moment d'inici d'aquesta mobilització no està clara. D'aquesta manera, ens trobem que cada hospital estableix un moment d'inici de la mobilització diferent, segons l'experiència i criteri del seu equip mèdic.

Per aquest motiu, aquest estudi pretén buscar evidència científica que permeti establir el moment d'inici idoni per començar la mobilització i que, per tant, serveixi com guia en la pràctica assistencial diària per a tots els centres.

En l'estudi plantegem estudiar dos grups. El primer grup, anomenat "grup control", seguirà el protocol que s'utilitza en l'Hospital Universitari Josep Trueta, que consisteix a iniciar la mobilització en el desè dia després de la cirurgia. El segon grup, anomenat "grup d'intervenció", començarà la mobilització de la cama en el tercer dia després de la cirurgia.

Aquesta intervenció que proposem està recolzada per estudis recents que apunten que una mobilització més agressiva no afecta la seguretat del penjoll ni del pacient. Aquests estudis recents canvien el paradigma del que s'havia cregut fins fa uns anys i obren la porta a un inici més precoç de la mobilització.

Més concretament, entre aquests dos grups volem observar si avançant el moment d'inici de la mobilització s'aconsegueix una disminució de la duració de l'estada hospitalària. També volem demostrar que la mobilització precoç no augmentarà l'aparició de complicacions ni augmentarà la necessitat de rehabilitació. A més, volem analitzar si fent-ho d'aquesta manera aconseguim reduir les despeses hospitalàries directes totals.

METODOLOGIA I INTERVENCIÓ

En aquest estudi participaran 140 pacients, procedents de 3 centres (Hospital Universitari de Bellvitge, Hospital Universitari Josep Trueta i Hospital Universitari Vall d'Hebron). A cada participant se li assignarà un codi numèric i es distribuirà de manera aleatòria entre els dos grups d'estudi:

· Grup control, amb inici de la mobilització als 10 dies després de l'operació.

· Grup d'intervenció, amb inici de la mobilització als 3 dies després de l'operació.

A part del dia d'inici de la mobilització, la resta de paràmetres, com són les cures mèdiques i el seguiment mèdic, es realitzaran exactament igual pels dos grups. Per tal que qualsevol complicació es detecti de manera precoç, el personal d'infermeria farà un seguiment del penjoll cada 4 hores i avisarà de qualsevol possible anomalia. A més, abans i després de cada mobilització, el seu/la seva metge/metgessa responsable també revisarà l'estat del seu penjoll.

Un cop se li hagi donat l'alta, se'l citarà, de mateixa manera pels dos grups, al primer, tercer, sisè, novè i dotzè mes per fer el corresponent seguiment. En aquestes visites el seu/la seva metge/metgessa responsable revisarà l'estat del penjoll i li demanarà omplir un qüestionari per avaluar la funcionalitat de la seva cama.

BENEFICIS I RISCS DE L'ESTUDI

Participant en aquest estudi ajudarà a aportar coneixement científic sobre el tema, contribuint a crear un protocol estàndard per tots els centres. A més, pels pacients que participin en la mobilització precoç, esperem que presentin una estada hospitalària més curta.

Pel que fa als riscos, no es preveu que augmentin el nombre de complicacions del grup d'intervenció respecte al grup control. Així doncs, les complicacions seran les pròpies que se'n poden derivar de la cirurgia: trombosis, infecció, necrosi, separació de la cicatriu… No obstant, es realitzarà un control estret.

ALTERNATIVES AL PROCEDIMENT

Si el pacient decideix no participar en l'assaig clínic, començarà la mobilització en el moment que el seu centre ho faci habitualment. En referència al seguiment, el pacient que decideixi no participar a l'estudi rebrà també la mateixa atenció que aquell que si hi participi, amb les visites de seguiment adequades, així com amb el tractament adjuvant que precisi.

CONFIDENCIALITAT

Des del principi de la seva participació en aquest estudi, totes les dades personals que es recullin seran gestionades i emmagatzemades amb total confidencialitat, ajustant-se a la legislació actual de la Llei Orgànica 3/2018, de 5 de desembre, de Protecció de dades personals i garantia dels drets digitals. Aquesta informació serà identificada amb un número i només s'utilitzarà amb fins d'investigació.

L'accés a la informació només serà disponible per a investigadors i altres autoritats sanitàries. El pacient té el dret de poder consultar la informació recopilada sobre ell i corregir-la en cas d'error. Garantim que cap informació personal serà publicada.

DIFUSIÓ DELS RESULTATS

Quan hagi finalitzat l'estudi i s'hagin extret conclusions, la intenció és publicar aquests resultats obtinguts en revistes científiques. D'aquesta manera, altres centres assistencials i pacients en la mateixa situació podran beneficiar-se'n. Tal i com s'ha comentat anteriorment, en aquestes publicacions no constarà cap dada personal.

COMPENSACIÓ ECONÒMICA

Els investigadors que participen en l'estudi no reben cap tipus de benefici econòmic.

La participació a l'estudi és voluntària i per tant, no serà remunerada. Tampoc li comportarà cap cost econòmic addicional a la pràctica clínica habitual.

RESPONSABILITAT I ASSEGURANÇA

Els promotors d'aquest estudi tenen contractada una pòlissa d'assegurança per a la seva realització, tal i com s'estableix en la legislació. En cas de perjudici o detriment de la seva salut com a conseqüència de la seva participació en aquest estudi, se li proporcionarà la indemnització corresponent.

CONTACTE

En cas de qualsevol dubte abans, durant o després de la realització d'aquest estudi, podrà posar-se en contacte sempre que ho necessiti amb: _____.

ANNEX 4 – WITHDRAWAL CONSENT DOCUMENT

REVOCACIÓ DEL CONSENTIMENT

Jo, (noms i cognoms) _____ amb DNI _____, revoco el consentiment informat prèviament firmat de participar en l'estudi "Optimizing Recovery: Investigating the Role of Early Postoperative Mobilisation in Free Flaps Surgery for Lower Leg Reconstruction"

Firma del pacient: **Firma de l'investigador/a:**

A _____, ____ de _____ de l'any _____

ANNEX 5 – DATA COLLECTION SHEET

FULL DE RECOLLIDA DE DADES DEL PACIENT

NOM DE L'ESTUDI: "Optimizing Recovery: Investigating the Role of Early Postoperative Mobilisation in Free Flaps Surgery for Lower Leg Reconstruction"

CODI DEL PACIENT:

DADES PERSONALS

- **Hospital**: ☐ Hospital Universitari de Bellvitge
  ☐ Hospital Universitari Josep Trueta
  ☐ Hospital Universitari Vall d'Hebron

- **Data de naixement** (dia/mes/any): _____/_____/_____

- **Sexe**: ☐ Dona ☐ Home

- **Comorbiditats**:

  Resultat Índex de Charlson: _____

- **Índex de Massa Corporal**:

  ☐ Baix pes: IMC < 18.5
  ☐ Peso normal: IMC 18.5 – 24.9
  ☐ Sobrepès: IMC 25-29.9
  ☐ Obesitat classe I: IMC 30-34.9
  ☐ Obesitat classe II: IMC 35-39.9
  ☐ Obesitat classe III: IMC ≥40

- **Consum d'alcohol*:**

  ☐ No consum
  ☐ Consum moderat (20-40g/dia en dones i 50-60g/dia en homes)
  ☐ Alt consum (>40g/dia end ones i >60g/dia en homes)

  * 10 grams d'alcohol són aproximadament 1 cervesa o 1 got de vi o 1 copa de cava o ½ de licor

- **Hàbit tabàcic:**

  ☐ No fumador

  ☐ Ex-fumador: no ha fumat en els últims 6 mesos i si que ho havia fet prèviament

  ☐ Fumador: fumador en actiu o en els últims 6 mesos

- **Estatus socioeconòmic:**

  ☐ Classe I: Directiu d'Administració i de les empreses (excepte els inclosos en la Classe II). Alts funcionaris. Professionals liberals. Tècnics superiors.

  ☐ Classe II: Directius i propietaris-gerents de comerços i del serveis personals. Altres tècnics (no superiors). Artistes i esportistes.

  ☐ Classe III: Càrrecs intermedis. Administratius i funcionaris. Personal dels serveis de protecció.

  ☐ Classe IV: Treballadors manuals qualificats o semiqualificats de la indústria, comerç i serveis. Treballadors del sector primari.

  ☐ Classe V: Treballadors no qualificats.

- **Tipus de penjoll:**

  ☐ ATL

  ☐ Gracilis

  ☐ Latissimus Dorsi

- **Localització del defecte:**

  ☐ Terç proximal

  ☐ Terç mig

  ☐ Terç distal

DURANT L'INTERVENCIÓ I L'ESTADA HOPITALÀRIA

- **Supervivència del penjoll**: ☐ Sí ☐ No
- **Complicacions post-intervenció:**

☐ Trombosi venosa/ arterial. Data: _____

☐ Pèrdua parcial del penjoll. Data: _____

☐ Hematoma. Data: _____

☐ Infecció. Data: _____

☐ Dehiscència de la ferida. Data: _____

☐ Altres: _____ Data: _____

EN L'ALTA

- **Total dies estada hospitalària / al servei de cirurgia plàstica:** _____ dies

PRIMERA VISITA – MES 1

- **Supervivència del penjoll**: ☐ Sí ☐ No
- **Puntuació de l'escala LEFS:** _____ punts
- **Necessitat de rehabilitació**: ☐ Sí ☐ No

SEGONA VISITA – MES 3

- **Supervivència del penjoll**: ☐ Sí ☐ No
- **Puntuació de l'escala LEFS:** _____ punts
- **Necessitat de rehabilitació**: ☐ Sí ☐ No

TERCERA VISITA – MES 6

- **Puntuació de l'escala LEFS:** _____ punts
- **Necessitat de rehabilitació**: ☐ Sí ☐ No

QUARTA VISITA – MES 9

- **Puntuació de l'escala LEFS:** _____ punts
- **Necessitat de rehabilitació:** ☐ Sí ☐ No

CINQUENA VISITA – MES 12

- **Puntuació de l'escala LEFS:** _____ punts
- **Necessitat de rehabilitació**: ☐ Sí ☐ No

ANNEX 6 – LOWER EXTREMITY FUNCTIONAL SCALE

Escala Funcional de la Extremidad Inferior

Estamos interesados en saber si el problema de su extremidad inferior, por lo cual usted busca atención hoy, le esta causando dificultades con las actividades alistadas debajo. Proporcione una respuesta para cada actividad.

Hoy, le causa o le pudiera causar dificultad con: (Circule un número en cada línea)

Actividades	Extrema dificultad o incapaz de realizar la actividad	Bastante Dificultad	Dificultad Moderada	Un poco de Dificultad	No Dificultad
a. Cualquier trabajo usual, trabajo domestico, o actividades de la escuela.	0	1	2	3	4
b. Sus pasatiempos usuales, actividades recreativas o deportivas.	0	1	2	3	4
c. Entrar o salir del baño.	0	1	2	3	4
d. Andar entre cuartos.	0	1	2	3	4
e. Poniendo sus zapatos o los calcetines.	0	1	2	3	4
f. Ponerse en cuclillas.	0	1	2	3	4
g. Levantar un objeto, como una bolsa de comestibles del piso.	0	1	2	3	4
h. Realizar actividades ligeras domesticas.	0	1	2	3	4
i. Realizar actividades pesadas domesticas.	0	1	2	3	4
j. Entrar o salir de un coche.	0	1	2	3	4
k. Caminar 2 cuadras.	0	1	2	3	4
l. Caminar una milla.	0	1	2	3	4
m. Subir o bajar 10 escalones (cerca de 1 escalera completa).	0	1	2	3	4
n. Estar de pie por 1 hora.	0	1	2	3	4
o. Estar sentado por 1 hora.	0	1	2	3	4
p. Correr sobre suelo plano.	0	1	2	3	4
q. Correr sobre suelo desigual.	0	1	2	3	4
r. Hacer vueltas bruscas cuando corre rápidamente.	0	1	2	3	4
s. Saltar.	0	1	2	3	4
t. Darse la vuelta en la cama.	0	1	2	3	4
COLUMN TOTALS (para el uso de fisioterapeuta)					

Score is the sum of all circled items. (range = 0-80) **Score: ___/80**

ANNEX 7 – CHARLSON COMORBIDITY INDEX

Charlson Comorbidity Index (51)

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno-deficiency syndrome (AIDS)	6