Title page

Title: Assessment of Safety and Performances of a 3D Printed Prosthetic Foot: A Pilot Study

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Study protocol

Description of the device

PROFIL (class I, Regulation EU MDR 745/2017) is a prosthetic foot made using additive manufacturing techniques (additive fabrication) in composite polymer material; it is produced through 3D printing with FFF (Fused Filament Fabrication) technology using nylon loaded with short fibers and continuous carbon fibers. The prosthetic foot is intended for lower limb amputees with a high activity level (K3 and K4) and for this reason it has been designed to allow, during the gait cycle, an adequate recovery of energy. Its shape is symmetrical on the sagittal plane (it can be used for both right and left amputations) and does not have a longitudinal division of the plantar structure. The device is equipped with a rigid pyramid-type attachment system, standard in prosthetic technique, which allows the prosthetic foot to be connected to the other prosthetic components that make up the complete prosthesis. The device is also equipped with integrated FBG (Fibre Bragg Grating) sensors for the evaluation of structural deformations. The foot, including the attachment system, has an indicative total weight of 480g for size 28.

Figure 1: PROFIL prosthesis 3D-printed with polymer and long carbon fiber. The image shows the standard metal pyramid attachment, fixed at the apex of the foot.

Intended use and target population

The device is an external foot prosthesis and is therefore intended for all subjects with unilateral or bilateral lower limb amputation who need a foot prosthesis for walking.

Manufacturer

The manufacturer is identified as CNR-IPCB, located at Via Previati 1/E, 23900, Lecco, Italy. The legal representative is the Director of the Institute, Prof. Teodoro Valente.

Traceability of the device

As these are prototype devices, each device will be assigned a unique code (e.g., PROFIL #1). The traceability of all devices produced is managed through a dedicated document, kept at the Centro Protesi Inail in Vigorso di Budrio, available to the Notified Body and the Competent Authority.

Materials in contact with the human body

The device, being a foot prosthesis, requires additional elements for connection/interface with the human body, specifically a socket for connection to the stump. There are also further connecting elements depending on the level of amputation. These parts are already in use by the subjects participating in the trial and are not the subject of the investigation. The PROFIL device therefore does not have any parts in direct contact with the human body.

Training and experience required for use of the device

The foot is a prosthetic device with functions similar to those of prostheses already on the market and used by the recruited patients. However, during the first use, the presence of qualified operators (specifically orthopedic technicians), able to position and adjust the alignments of the device under examination in relation to the specific anatomical characteristics of the subject and to provide clinical support during the experimental activities, will be necessary for the correct application and use of the device by the patients.

Review of reference literature

A dynamic energy-storing and energy-returning foot prosthesis is a type of prosthesis designed to mimic and restore the functionality and natural movement of the amputated limb. This type of prosthesis is designed to allow patients to perform daily life activities, even very dynamic ones, with greater ease and efficiency. The distinctive feature of a dynamic energy-storing and energy-returning prosthesis is the presence of a system that accumulates mechanical energy during the stance phase and returns it during the push-off phase, increasing the amount of push-off itself. This system partially compensates for the lack of the natural ankle joint and generates a smoother movement during walking and other activities for the prosthesis user.

This energy return mechanism can take different forms depending on the type of prosthesis and the level of amputation. For example, in foot prostheses, it is common to use carbon fiber blades or springs that deform during foot contact and then restore, returning elastic energy during the subsequent push-off. This helps reduce the effort required for walking and allows for smoother and more natural movements. Dynamic energy-returning prostheses can provide numerous advantages to amputee patients. These include greater comfort, increased movement efficiency, reduced stress on the surrounding healthy joints, less fatigue during physical activity, and an overall improvement in quality of life. It is important to note that dynamic energy-returning prostheses require an adaptation phase and a rehabilitation period to learn to use them correctly. Furthermore, the choice of a dynamic prosthesis depends on several factors, including the level of amputation, the desired physical activity, and the individual needs of the patient. Dynamic energy-returning prostheses represent an important development in the field of amputee rehabilitation, allowing them to resume a wide range of physical activities and improve their overall mobility and quality of life.

In the design of dynamic prostheses with energy storage and return, several important parameters are considered to ensure optimal functioning and to meet the individual needs of the patient. Some of the key parameters include:

1. Level of amputation: The level of amputation determines the type of prosthesis and the most appropriate energy return system to use. For example, energy-return foot prostheses are suitable for below-knee amputees, while full-leg prostheses may require more complex systems.
2. Desired physical activity: The individual's needs and the type of physical activity they wish to perform influence the choice of dynamic prosthesis. For instance, prostheses for high-intensity activities such as running may require specific features to ensure adequate energy return and optimal stability.
3. Body weight: The patient's body weight can influence the choice of prosthesis type and the necessary level of energy return. Prostheses must be able to safely support the body weight and provide adequate energy return without excessive deformation.
4. Degree of foot deformation: The ability of the prosthetic foot to deform and return energy depends on its design and the characteristics of the materials used. The choice of stiffness and elasticity of the prosthetic foot can be customized according to the patient's needs and preferences.
5. Comfort and adaptation: Patient comfort is a crucial factor in choosing a dynamic prosthesis. The prosthesis should fit the patient's anatomy correctly and provide optimal comfort during use. Proper shock absorption and balanced load distribution can contribute to overall comfort.
6. Activity level and lifestyle: The patient's activity level and lifestyle can influence the choice of dynamic prosthesis. People who lead an active lifestyle and participate in sports or intense physical activities may require prostheses with greater energy return capacity and higher durability.
7. Cost: The cost of dynamic energy-return prostheses can vary depending on the type of device, the level of customization, and additional features. Cost should be considered along with other factors to ensure a balance between the patient's needs and available financial resources.

<u>Sensorization of Prostheses</u>

Wearable sensors allow communication and interaction with the external world. In the specific field of prosthetics, sensors play a fundamental role, as they ensure the interface between the prosthesis and the patient, as well as the

monitoring and control of the device. Sensorization makes the prosthesis “smart,” enabling a high level of efficiency and collaboration between the prosthesis and the patient.

Some of the sensors traditionally used in prosthetics include force sensors, electromyographic sensors, and IMUs (Inertial Measurement Units).

Compared to traditionally employed sensors, Fiber Bragg Grating (FBG) sensors offer the following qualities: low weight and small size, biocompatibility, multiplexing capability, and immunity to all electromagnetic interference. These are the reasons why the use of FBG sensors in the medical and biomedical fields has greatly increased in recent years.

Regarding the use of FBG sensors in prosthetics, the main studies focus on the sensorization of the socket to improve the interface between the residual limb and the prosthesis.

An interesting study for our research is that conducted by Bastos et al. In this case, a foot prosthesis was equipped with 9 FBGs to perform force and temperature measurements. The sensorized device was then tested on a treadmill. It was demonstrated that it is possible to multiplex several FBGs along a single optical fiber for distributed measurement throughout the prosthesis.

In particular, the best results were found in the area where the device accumulates and releases energy. However, in this study, the interrogator used was not wearable, thus limiting the applicability of the proposed solution to the laboratory setting only.

3D Printing in Orthotics and Prosthetics: Advantages, Challenges, and Manufacturing Methods

Additive Manufacturing (AM) technology is ideal for highly customized and high-value production. Orthoses and prostheses are particularly well-suited to leverage the potential of this technology. However, the lack of functional materials that meet the various design requirements—such as device structure and comfort—has limited the use of AM mainly to orthoses. AM is promising for orthoses due to its customization capabilities and lower production costs compared to traditional solutions. It also avoids the use of prefabricated solutions that often do not fit the limb perfectly during post-trauma rehabilitation.

As for prostheses, despite the complex traditional manufacturing process—which requires several steps and expert technical skills—AM has not yet reached its full potential. This is due to factors such as the lack of decision-support software for clinicians and the lack of multifunctional materials that simultaneously meet structural, functional, and durability requirements. Some research has focused on the production of lower limb prostheses using techniques such as Filament Deposition Modelling (FDM) and Selective Laser Sintering (SLS), achieving interesting results. However, prostheses produced with AM are not yet widely adopted.

In the context of prosthetic devices for sports, AM could be particularly interesting due to the smaller size and functional properties that must be optimized for individual performance. Currently, sports prosthetic devices use construction techniques and components that are very different from those of traditional prostheses. The use of innovative materials such as titanium, high-strength aluminum alloys, carbon fiber, or Kevlar with polymer resins must be combined with the choice of manufacturing technique to obtain lightweight, durable, and highly customized devices. In general, sports prostheses are made with expensive processes such as fiber and resin lamination or vacuum infusion.

AM of continuous fiber composites in thermoplastic material could represent a more economical alternative that maintains lightness, dynamic-mechanical properties, and durability. By reducing production costs, it is possible to meet a broader demand for customized products that cover a wide range of uses, both in daily life and in sports activities.

Currently, there are no examples of prostheses or aids produced exclusively using AM technologies, except at the level of scientific studies. These works clearly demonstrate the advantages of the technology, such as ease of customization, reduction in structural weight, and maximum exploitation of structural and functional properties. However, they have not yet been validated for practical application compared to commercial products made with composite materials.

Current state of the art and proposed advantages of the new device

The scientific literature reports various examples of 3D-printed prosthetic feet using FFF (fused filament fabrication) technology. These works emphasize the flexibility allowed by this technology and the possibility of making low-cost prostheses, potentially even by the user themself, if 3D printing becomes widely accessible in the future. The materials commonly used for these devices are those commonly employed in FFF, namely polylactic acid (PLA) and acrylonitrile butadiene styrene (ABS). A limitation of the proposed studies in the current state of the art lies in the mechanical properties of these materials. From this point of view, using 3D printing technologies that include the integration of continuous carbon fiber can bring an advantage to the mechanical properties of prosthetic devices. A recent study

showed that continuous carbon filament printing can lead to the creation of prostheses with dynamic and energy return characteristics similar to or even superior to commercial ones. It should be noted that most of these studies have not evaluated the acceptability of these new devices by patients. This evaluation seems relevant, since the design of these prostheses is often radically different from that of devices currently on the market.
The new device under investigation presents the advantages of foot prostheses made with additive manufacturing and therefore offers the possibility of being produced at lower costs and with more customizable characteristics compared to traditional dynamic prostheses in carbon fiber-reinforced laminates. The introduction of this type of prosthesis to the market would lead to a wider availability for users of prostheses suitable for use in medium and high activity conditions and could support easier access for people with lower limb amputations to physical activity. In addition, the new design and the characteristics of the materials used make the prosthesis particularly lightweight, which will ensure greater comfort and less fatigue during use.

Risks and Benefits
The main benefit related to the development of the PROFIL foot is the possibility of providing a high-performance prosthetic device, customizable according to the patient's needs and at lower costs compared to existing commercial solutions in the same category.
Thanks to the high level of customization of the foot, the expected benefits for the patient from using this device include achieving a good level of comfort and usability during daily activities, and the possibility of safely performing moderate physical activity. This, in turn, allows the patient to maintain good physical condition, training the residual muscles of the lower limbs, as well as the locomotor, cardiovascular, and respiratory systems.
Static and fatigue mechanical tests have been carried out, highlighting the mechanical robustness of the device. For this reason, the risks associated with its use—especially in the short term (or for the duration of the trial)—are similar to those expected from the use of any commercial foot prosthesis.
To ensure maximum risk mitigation for patients (minimizing residual risk) in this experimental clinical study, it is specified that, during the planned usage tests, patients will be supervised by an orthopedic technician and/or secured with safety systems and/or will walk in areas delimited by handrails that minimize the possibility of falls during ambulation.
Accordingly, the overall risk analysis, carried out according to ISO 14971, does not highlight any hazards associated with an unacceptable level of risk.
In the event of device failure, i.e., failure of the prosthetic foot, the patient could lose balance. Based on the preclinical tests conducted on the device, mechanical failure is considered unlikely under the expected conditions of use and, in any case, occurs gradually, with progressive deformation, which can be perceived by the user and compensated for.

Insurance Coverage
This clinical study will be covered by an ad-hoc insurance policy.

Relevance of the Clinical Investigation in the Context of the State of the Art of Clinical Practice
This pilot clinical investigation aims to provide insights regarding the safety and performance of the 3D-printed PROFIL prosthesis in a more realistic usage scenario. The current state of the art has not yet defined the performance and safety of 3D-printed prostheses made with thermoplastic materials and continuous carbon fiber. Since greater comfort and the possibility of performing physical activity more easily are expected with the use of these devices, it is considered of clinical interest to evaluate these prostheses. The application of mechanical tests according to ISO – TS 16955, which provides for mechanical characterization at characteristic angles (toe, heel, sole) separately, is considered sufficient for evaluating the mechanical robustness of the prosthesis. However, such characterization does not provide information on the performance of the prosthesis during ambulation; therefore, it is deemed necessary to characterize the response of the materials and the device as a whole (full gait cycle, including uneven terrain) during a walking test. The primary objective of the study is therefore to evaluate the safety and performance of the device during use in variable conditions (including terrains with different morphological and material characteristics). The secondary objectives concern the functional characterization of the device in enabling safe, balanced, symmetrical, and comfortable walking. All information collected, both regarding the physical properties of the device and its usability, can be used to refine the design, further improving the prosthesis to better meet the needs of the target population.

Primary objectives

- Evaluation of the safety of the prosthetic foot during use.
- Evaluation of the device's performance in terms of the quality of the motor pattern during walking and during the execution of specific functional tests.

Secondary objectives

- Evaluation of the comfort and usability of the device on different terrains and surfaces and in standing conditions.
- Evaluation of the deformations of the prosthesis structure during its use.

Type of Investigation

The nature of the study is pilot, cross-over, single-center, open-label, and non-randomized.
The study is classified as "non-profit" and aims to improve clinical practice.

Duration of the Trial

The total duration of the study is 12 months.

Primary endpoints

- Quantification and qualification of the number of failures of the PROFIL foot during experimental activities: it is hypothesized that no device failure will occur during its use in walking on flat and uneven terrain.
- Measurement of kinematic variables describing the subject's gait pattern, acquired using an optoelectronic system and commercial wearable inertial sensors, with both the device under investigation and a commercial comparator device (Össur Pro-Flex XC foot).
- Measurement of parameters describing the subject's motor quality in performing movements other than walking, such as ascending/descending stairs and ramps and sit-to-stand/stand-to-sit movements, with both the device under investigation and the commercial comparator device (Össur Pro-Flex XC foot).

Specifically, the following outcomes will be used:

- Amputee Mobility Predictor (AMP).
- L test of Functional Mobility (L-Test).
- Stair Assessment Index (SAI).
- Hill Assessment Index (HAI).
- Symmetry of load forces during sit-to-stand and stand-to-sit from chairs of different heights.
- Oscillation of the center of pressure in standing position with eyes open and closed.

It is hypothesized that the motor pattern adopted by the user of the PROFIL foot will be comparable to that adopted when using a commercial foot of the same category.

Secondary endpoints

- Ad hoc questionnaire for the evaluation of comfort and usability.
- Quantitative characterization of the deformation of the prosthetic foot structure, measured using FBGs integrated into the device.

Information on the Device Under Investigation and Any Comparator Products

Preclinical tests have been conducted on the PROFIL device, the subject of the investigation, to identify its structural characteristics and mechanical properties. Computational simulations and mechanical tests, performed according to the regulations for prosthetic feet, have shown that the behavior of the PROFIL prosthetic foot is in line with that of a commercial prosthesis of the same category and is therefore suitable for use in walking tests as required by the clinical trial.
The details of the preclinical tests are reported in the Technical File. A summary is presented below.
Figures 2 and 3, relating to mechanical tests conducted according to ISO/TS 16955, show that the displacements of the Pro-Flex XC and PROFIL feet during compression tests on inclined planes at different angles are comparable. A similar result was obtained with finite element tests (Figure 3). Likewise, the Roll-Over-Shape (ROS) (Figure 4) and the mechanical response (Figure 5) of the two feet in comparison are comparable.

In Figure 6, the PROFIL foot is compared to the Pro-Flex XC based on the classification table proposed by the American Orthotic & Prosthetic Association. Prostheses are evaluated based on their ability to store energy, indicated by their stiffness, and to return a significant amount of that energy. When the prosthesis is able to demonstrate such behavior, it is classified as Dynamic. As can be seen from Figure 6, prototype III showed the best performance, so much so that both the heel and the sole of the foot could be classified as dynamic, and it was therefore selected as the prototype for this clinical investigation

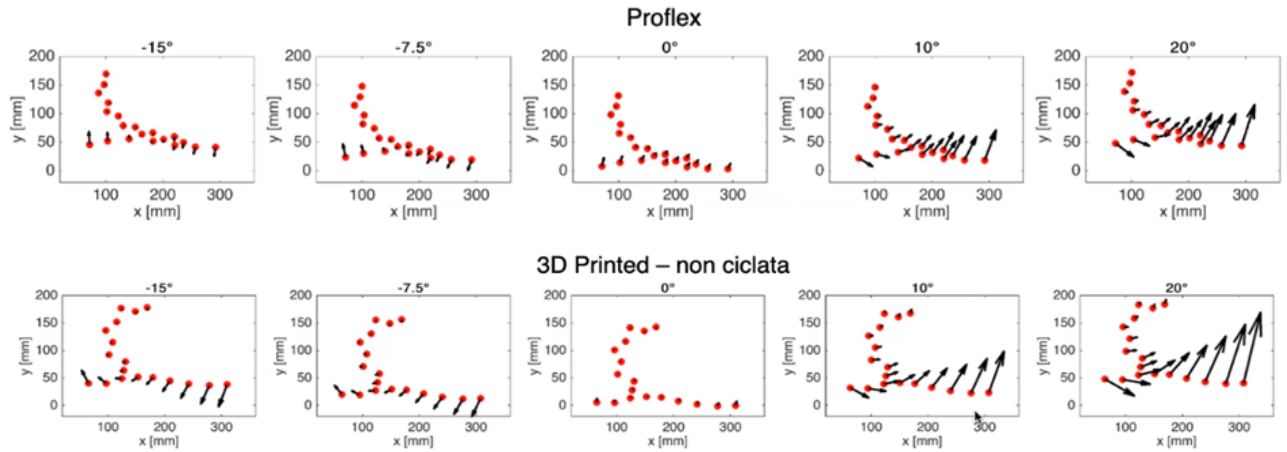

Figure 2: The figure shows that the displacements of the 3D-printed PROFIL prosthesis are similar to those of a commercial comparator prosthesis (Pro-Flex XC).

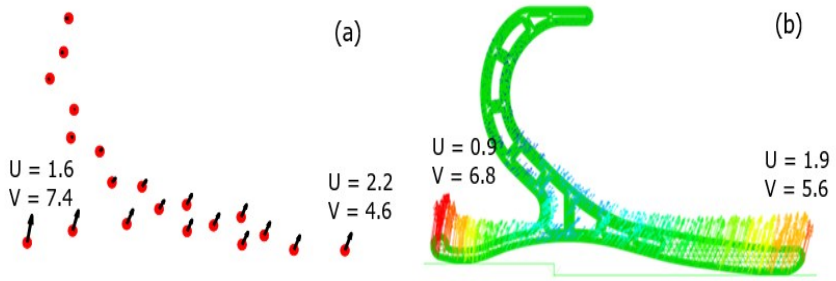

Figure 3: The figure shows that the vertical (V) and horizontal (U) displacements are consistent with those measured for the commercial comparator prosthesis (Pro-Flex XC).

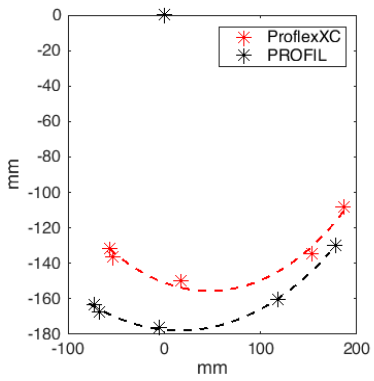

Figure 4: The figure shows the comparison between the different ROS (roll over shape, Hansen AH, Childress DS, Knox EH (2000) Prosthetic foot roll-over shapes with implications for alignment of trans-tibial prostheses. Prosthetics Orthot Int 24:205–215) of the 3D-printed prosthesis and the commercial comparator prosthesis (Pro-Flex XC).

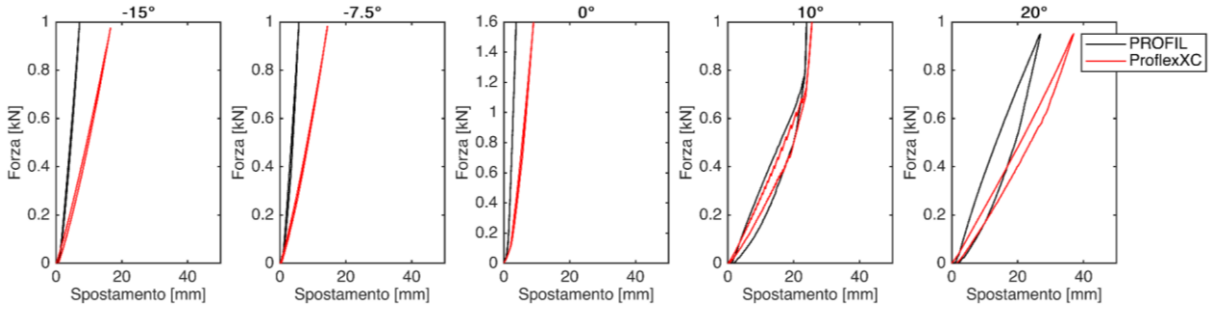

Figure 5: The figure shows the results of mechanical tests carried out at different angles as prescribed by ISO-TS 16955, comparing the 3D-printed prosthesis and the commercial comparator prosthesis (Pro-Flex XC).

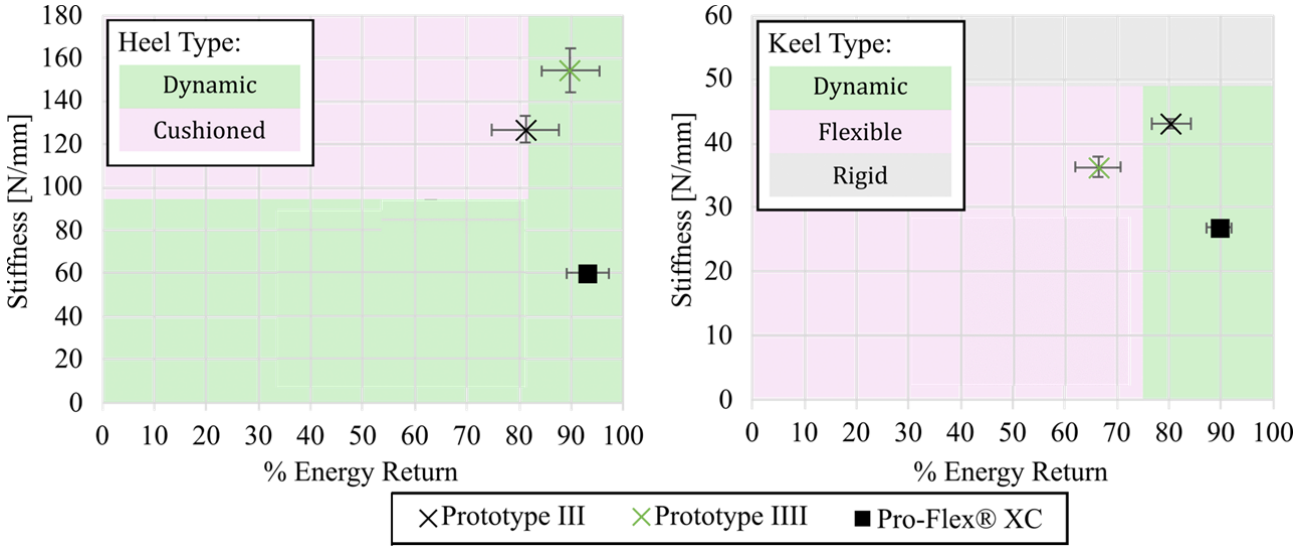

Figure 6: The graphs, referring to the classification of prosthetic feet by AOPA (https://www.aopanet.org/wp-content/uploads/2013/12/Prosthetic_Foot_Project.pdf), show the characteristics of energy return relative to the stiffness of the prosthesis for the device under investigation compared to the commercial Pro-Flex XC prosthesis. In the figure, a reduction in the performance of prototype IIII can be observed, which deteriorated due to a mobilization of the attachment to the pylon—different from prototype III—which led to significant deformations at the connection and, consequently, a loss of energy. This solution adopted in prototype IIII was later corrected to ensure full stability of the prosthesis-pylon connection. The final solution used for the PROFIL prototype is consistent with that of prototype III.

Information on Subjects

The study will involve a total of 3 patients. Given the exploratory nature of the study and considering the maturity level of the technology, although the device is intended for the entire population of lower limb amputees, this study will include only patients with unilateral transtibial amputation.

Patient screening will be carried out by a multidisciplinary team and will aim to determine the eligibility of the subject according to the following inclusion and exclusion criteria.

Inclusion Criteria

- Unilateral transtibial amputation.
- Stable clinical conditions.
- Activity level K3 or K4.
- Adult subject aged between 18 and 65 years.
- Patient already able to use a prosthesis adequately for the experimental activities (experienced user).
- Collaborative patient.
- Weight not exceeding 100 kg.

Exclusion Criteria

- Pregnancy.
- Inability to understand written text.
- Problems with the residual limb.

Drop-out Criteria

- Voluntary withdrawal of the subject.
- Inability of the subject to continue the experimental activities.
- Loss of eligibility to continue with the experimental activities as assessed by the principal investigator.

Description of Clinical Procedures and Diagnostic Methods Related to the Clinical Investigation

The subject tests will take place in the laboratories of the Centro Protesi Inail at the Vigorso di Budrio (BO) site.
Below are the experimental activities planned for each session.
It is not considered necessary to set a training period for the use of the PROFIL prosthetic foot, as this device has characteristics entirely equivalent to those of the prosthetic foot normally used by the recruited subject (Pro-Flex XC).
The timeline of all activities is as follows:

T1. Arrival of the subject at the Prosthesis Center and signing of consent forms.
T2. Registration and alignment of the Pro-Flex XC prosthesis.
T3. Gait Analysis.
T4. Functional tests.
T5. Registration and alignment of the PROFIL prosthesis (device under investigation).
T6. Gait Analysis.
T7. Functional tests
T8. Completion of the acceptability and usability questionnaire.

An orthopedic technician will be responsible for the adjustment and correct alignment of each prosthesis during activities 2 and 5. During all experimental tests, the patient may wear IMUs (Inertial Measurement Units), commercial and CE-certified wearable sensors (e.g., Xsense MTi-10 IMU, Xsense Technologies B.V, NL) for monitoring motor patterns.
Below are the details of the experimental activities planned for T3/T6 and T4/T7.

<u>T3/T6: Gait Analysis</u>

The optoelectronic analysis acquisition system (Vicon) is equipped with 9 infrared cameras, 3 video cameras, and 3 force platforms arranged along a path 20 meters long (smooth and homogeneous surface). Data on marker positions and ground reactions will be saved in Nexus format (Vicon proprietary software) for subsequent analysis.
Passive reflective markers will be applied to the patient's skin and the surface of the prosthesis, following a standard marker protocol widely used at the Centro Protesi Inail.
The protocol during Gait Analysis includes:

- Walking at normal (self-selected) speed with shoes: baseline measurement (three repetitions).
- Walking at sustained (self-selected) speed with shoes: measurement at high dynamic load intensity (three repetitions).

These tests will be repeated three times.
All tests in the Gait Analysis laboratory will be performed with the support of a harness, to prevent possible accidental falls of the subject.

<u>T4/T7: Functional Tests</u>

In this phase, some kinematic parameters will be evaluated during activities other than walking. In particular, the following will be assessed:

- Functional status using the Amputee Mobility Predictor (AMP): the therapist assigns a score on a graduated scale to the subject's functional abilities with the prosthesis during 21 simple motor tasks. The maximum score is 47 points: the higher the final score, the greater the patient's functional abilities.
- Dynamic balance using the L test of Functional Mobility (L-Test), which involves standing up and sitting down from a chair, four changes of direction, and walking a total distance of 20 meters. This test is used to assess the individual's physical functions, such as dynamic balance abilities. The execution time is measured.

- Quality of stair ascent/descent using the Stair Assessment Index (SAI): the therapist assigns a score on a graduated scale to the subject's functional abilities after ascending and descending 4 flights of stairs (2 floors), with a maximum score of 13 points.
- Quality of ramp ascent/descent using the Hill Assessment Index (HAI): the therapist assigns a score on a graduated scale to the subject's functional abilities after ascending and descending a 20-meter ramp with an 8% slope, with a maximum score of 11 points.
- Symmetry of load forces during sit-to-stand and stand-to-sit from chairs of different heights. The patient starts from a seated position with both feet on two separate force platforms. At the start signal, the patient stands up while keeping both feet on the platforms. After 5 seconds standing, the patient sits down again.
- Oscillation of the center of pressure in standing position with eyes open and closed. The patient stands on the force platform with arms at their sides, in a stable and comfortable configuration. At the start signal, the patient maintains the position for 60 seconds with eyes open. At the second start signal, the patient repeats the exercise with eyes closed.

At the end of this testing phase, the subject will be asked to complete the acceptability and usability questionnaire (T8).

Monitoring Plan

For proper monitoring of the clinical investigation, data collection will take place in both paper and electronic formats. The paper CRF will record all activities planned in the study and the dates of all evaluations performed, thus serving as the main tracking document for the entire study. Electronic data, including instrumental data, will be stored on a server with access restricted to the investigators.

The study provides for the appointment of a monitor for the purposes outlined in UNI EN ISO 14155. The monitor will carry out control and supervision of the study through an on-site visit plan agreed upon with the principal investigator.

Enrolment Points

Participants in the study will be recruited from among the patients of the Centro Protesi Inail in Vigorso di Budrio (BO).

Statistics

Given the nature of the study, no inferential statistical analysis will be performed.

Regarding the results of instrumented tests, only qualitative comparative analyses between the PROFIL foot and the standard prosthesis in use will be conducted.

Data Management and Storage

The ownership of the results derived from the data collected during the trial is shared among the clinical center and the sponsor, according to the terms detailed in the collaboration agreement signed by the Parties. Clinical and functional data recorded during the trial will be collected in the CRF in a pseudonymized manner and will be treated as confidential. An information sheet on the study has been prepared, containing a description of the activities involving the patient as well as information on the processing of personal data, which will be provided together with the relevant informed consent forms. Data will be managed in accordance with current regulations on personal data management (GDPR 2016/679).

Documentation Storage

All paper data related to the study will be stored in archives located in areas with access restricted to investigators only, while electronic data will be stored according to the procedures established by Inail within its own IT infrastructure with restricted and controlled access. The data will be kept by the data controllers under their responsibility, together with the code identifying the data subject, for 7 years after the end of the study. Once the retention period has expired, the data will be deleted or anonymized so that it is no longer possible to trace, directly or indirectly, the identity of the data subject. Anonymized data may be reused for future research and therefore may be retained by the joint controllers indefinitely.

Information on Amendments to the Clinical Investigation Plan

Any amendments or additions to this protocol will be subject to an amendment process as required by the competent Ethics Committee (EC) and will not be implemented without specific authorization.

Statement of Compliance with Ethical Principles

The study will be conducted in accordance with Italian legislation and the principles of the Declaration of Helsinki. Reference ethical code: (1) Helsinki: articles 4, 5, 7; (2) Helsinki: article 6; (3) Helsinki: articles 9, 10, 11.

The study will be conducted in compliance with Good Clinical Practice, UNI EN ISO 14155, and as described in this protocol.

The sponsor will provide all required documentation to the reference EC to request approval.

The study may only begin after formal approval by the EC.

The trial will start after notification of a positive outcome of the document review by the Ministry of Health, which the sponsor undertakes to submit after any approval by the EC.

Description of Informed Consent

Patients will be called for an interview by the principal investigator, who will explain the purposes of the clinical study and provide the information sheets on participation and data processing. For this purpose, an information sheet on the study has been prepared, containing a description of the activities involving the patients, as well as information on the processing of personal data, which will be provided together with the relevant consent forms.

Safety Reports and Management of Adverse Events

During the trial, any adverse events of varying severity, undesirable events (such as incidents or near misses), deficiencies, or adverse events related to device functionality (if they occur) will be recorded, and it will be the sponsor's responsibility to report them immediately via the electronic system referred to in Article 73 of Regulation EU MDR 2017/745 (EUDAMED). If the EUDAMED electronic system is not yet active, such adverse events will be promptly reported by the principal investigator, coordinator of the clinical study, to the device-vigilance officer of the USL Area Vasta Emilia-Centro Companies of the Emilia-Romagna Region, in accordance with Article 80 of Regulation EU MDR 2017/745 and the European guideline MDCG 2020-10/1 Rev1 - Safety reporting in clinical investigations of medical devices under Regulation EU MDR 2017/745 October 2022.

Adverse events will be recorded in the CRF following the completion procedures described in the guidelines, and the completed form will be sent by email, in Excel or equivalent format, to the competent authority. The principal investigator coordinating the study must submit the notification no later than 2 days after the event, in the case of a Serious Adverse Event (SAE), and no later than 7 days after the event for other events included in the category of adverse events.

Criteria and Procedures for Follow-up of Subjects After Completion, Temporary Interruption, or Early Termination of the Trial and Follow-up of Subjects Who Withdrew Consent or Dropped Out

Early termination and suspension of the clinical evaluation may occur in the following cases: (i) explicit request by the patient, (ii) inability to continue due to device-related problems, (iii) the principal investigator considers that such a decision is in the subject's interest or if the subject is no longer eligible according to the inclusion/exclusion criteria. In addition, interruptions or suspensions of the study may be decided by the sponsor or the competent EC if events related to the conduct of the study or the medical device under investigation may affect the safety of subjects receiving the experimental treatment. In all cases, the reasons and date of withdrawal will be recorded in the subject's CRF, and no additional assessments will be performed. Data collected up to that point will be retained and analyzed according to the study's assumptions. The sponsor will communicate this to the EC. The communication sent will contain detailed information regarding the date of suspension or early termination, the centers involved in the suspension, and the reasons that led to the suspension or interruption of the trial.

At the regular end of the trial, no further follow-up is planned.

Data Publication Policy

The publication of data and project results will be planned and decided taking into account the objectives and the dissemination plan, safeguarding intellectual property and confidentiality rights. Each publication will be discussed and approved by the parties involved as established by the existing agreements.

Publication of data and results will be ensured regardless of whether the outcome of the study is positive or negative.

References

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