Protocol version: Version 5
Date of protocol: 03 Oct 2018
Code: BIOFERULA3D

Title of the study: Feasibility study: clinical validation of 3D personalized orthopedic splints in patients with rhizarthrosis.

Product under study: "Bioférula3D", personalized 3D splint classified as a custom-made medical device.

Study population: patients with a new diagnosis of osteoarthritis of the trapeziometacarpal joint (TMJ) (rhizarthrosis).

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Study duration: 8 months

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PROYECT: BIOFERULA3D

LENGHT: 8 months

TITLE:

"Feasibility study: clinical validation of 3D personalized orthopedic splints in patients with rhizarthrosis "

Main objetive:

- Evaluate the reduction of pain in patients with regular orthoses compared to the orthosis designed using 3D technology (VAS pain scale)

Secondary objetives:

- Evaluate the functionality between both groups (DASH scale)
- Evaluate patient satisfaction between both groups (6-item scale)
- Subjectively and retrospectively evaluate the time of use between both devices
- Evaluate the strength, using grip and pinch dynamometers

Study subjects: Patients with a new diagnosis of osteoarthritis of the trapeziometacarpal joint (TMJ).

Variables: Pain, functional capacity (DASH), satisfaction, time of use, strength, age, gender, employment status, marital status and educational level.

GENERAL INFORMATION

1. STUDY IDENTIFICATION

Title: Feasibility study: clinical validation of 3D personalized orthopedic splints in patients with rhizarthrosis

Code: BIOFERULA3D

Study design: Randomized prospective follow-up

Product under study: “Bioférula3D”, personalized 3D splint classified as a custom-made medical device.

Version and date: **Version 5, 10/3/2018**

Approved by: **CREC (Clinical Research Ethics Committee) from OSI Bilbao Basurto (10/17/2018)**

Identification of the promoter and coordinator

Sponsor: Optimus 3D, S.L.

Coordinator: INNOSASUN (BIOEF)

1.1. Identification of the promoter representative

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1.2. Information of the main investigators from the participating centers

Basurto University Hospital (OSI Bilbao Basurto).

The list of researchers participating in the study is detailed in Annex I "Centers and Research Team".

Information on other services involved:

BIOEF (Innosasun): Clinical study coordination

OSI Bilbao Basurto Research Unit

OSI Bilbao Basurto CREC (Clinical Research Ethics Committee)

2. ABSTRACT

Osteoarthritis of the hand is a chronic joint disease that usually affects one or more of the finger joints and is a major cause of disability. This affectation constitutes one of the main causes of consultation for hand pain. The level of discomfort varies depending on the type of work and the idiosyncrasy of each patient and ranges from slight discomfort and limitations depending on the patient, to notable pain and impediments. In addition to the clinic, radiology is used in the diagnosis and control of evolution. The Eaton-Littler classification (Stages I-II-III-IV) is commonly used.

Treatment of stages I, II, and in some cases stage III, is conservative and is based on pharmacological and rehabilitation measures, including the use of orthoses or splints.

In an ideal situation, these devices should allow freedom of movement and functionality of the hand, being the basis for adequate completion of the treatment (adherence), which could lead to an improvement in pain and functional limitations.

There are currently several types of splints on the market made of temperature-moldable plastic material, a splint that has multiple disadvantages in terms of manufacturing.

Additive manufacturing, frequently associated with the concept of 3D printing, encompasses a set of technologies that is transforming the way of designing and manufacturing application products in many and very diverse sectors. The development of the 3D bio-splint is a project opportunity for a new 3D orthosis that will allow a qualitative leap in the search for an intelligent solution for patients with rhizarthrosis.

Splints developed using this method have a number of advantages both in manufacturing and for patients. Therefore, we proposed a proof-of-concept (feasibility) study. The objectives of this study are exploratory and seek to assess the feasibility of applying a personalized splint compared to a conventional one.

As such, the study tries to find out if the personalized splint can be suitable for the treatment of patients with osteoarthritis of the TMJ and obtain at least similar results, providing greater wearing comfort and facilitating an improvement in the development of the activities of the daily life to patients. Therefore, it is not a design aimed at evaluating the efficacy of such treatment. It is a prospective study with two arms, open with 1: 1 allocation.

The study will be carried out in the outpatient clinics of the OSI Bilbao-Basurto Orthopedic Surgery and Traumatology Service with the collaboration of the Rehabilitation Service.

The study will include a recruitment visit and two follow-up visits, one at a month and another final visit at 3 months. Se incluirán pacientes con nuevo diagnóstico de artrosis de la articulación trapecio-metacarpiana. Patients with a new diagnosis of osteoarthritis of the trapezius-metacarpal joint will be included. One group of patients will wear the usual splint indicated by the Service physicians and the other group the personalized splint designed by the company OPTIMUS 3D.

The main variable is pain, which will be measured, as is usual practice, by a visual analog scale (VAS). In addition, the DASH (Disabilities of the Arm, Shoulder and Hand) questionnaire will be used in its Spanish version (DASHe) and questions about patient satisfaction with the use of splints.

3. JUSTIFICATION

Osteoarthritis of the hand is a chronic joint disease that usually affects one or more of the finger joints and is a major cause of disability (1). In relation to the hand, after the distal interphalangeal joints, the most affected joint is the trapezius metacarpal joint (TMJ) (2).

Rhizarthrosis is defined as a degenerative alteration of the trapezius-metacarpal joint (TMJ) characterized by a progressive deterioration of the articular surfaces and neo bone formation in them

Osteoarthritis of the TMJ is a disease present in a large part of the general population. The symptomatic prevalence is estimated at 6-8% of the population, although its radiological prevalence would be 29-76% depending on the series studied (3). Its diagnosis is basically clinical, although radiological tests are very useful to confirm it and to typify the evolution of the disease.

This affectation constitutes one of the main causes of consultation for hand pain. Clinically, patients present pain and decreased functional capacity, which is essentially expressed as a limitation of the range of motion and loss of grip, which generates inability to perform basic activities of life (3).

The TMJ has a great range of mobility, since it basically serves to oppose the thumb to the rest of the fingers and carry out grasping or pinching actions, which is why it is of great use and of great utility in everyday life. This range of movements is favored by being a not very congruent joint, but this fact also explains the tendency to instability, which can lead to abnormal movements between the joint surfaces, which ultimately lead to the development of osteoarthritis of the joint. Over time, a subluxation occurs and the first metacarpal tends to approach the rest of the fingers, producing an adduction. This osteoarthritis leads to pain and functional disability. The pain is usually greater when the joint is stressed, during pinching movements.

The level of discomfort varies depending on the type of work and the idiosyncrasy of each patient and ranges from slight discomfort and limitations depending on the patient, to notable pain and impediments. Besides, the degree of discomfort is usually variable over the years and one can speak of outbreaks of the disease in some cases. Work or professional activity also contributes on the degree of perception of discomfort.

On examination, limitation of joint mobility is observed, so that the degree of excursion of the first metacarpal is limited. Mobility is usually painful. As times goes by, the evolution towards a deformation with a tendency to a progressive subluxation of the first metacarpal over the trapezius is observed. The base of the first metacarpal is displaced to a dorsal subluxation. The head of the metacarpal adducts and the first phalanx hyperextended. This subluxation component adds a worse prognostic factor that influences the choice of treatment.

In addition to the clinic, radiology is used in the diagnosis and control of evolution. The Eaton-Littler classification (4) is commonly used, which proposes 4 stages:

Stage I: normal joint or slight widening

Stage II: Joint narrowing due to cartilaginous wear and osteophytes <2mm

Stage III: Joint narrowing and osteophytes> 2mm

Stage IV: Trapezioscaphoid involvement with great trapeziometacarpal narrowing

This radiological classification has therapeutic implications. Although not strictly, in stages III and IV the treatment is fundamentally surgical, with a wide range of proposed techniques, including ligament reconstruction, osteotomy of the base of the first metacarpal, interposition arthroplasty, prosthesis or arthrodesis of the joint (5).

On the other hand, the treatment of stages I, II and in some cases of stage III, is conservative and is based on pharmacological and rehabilitation measures, including functional education and joint hygiene, kinesitherapy, electrotherapy, intra-articular infiltrations and the use of orthoses or splints (6).

However, the mainstay of conservative treatment would be orthotic devices, which have been shown to reduce pain (7). Although there are no clear data to confirm this, it can be assumed that a decrease in pain could be expected to increase functional capacity (8) In an ideal situation, these devices should allow freedom of movement and functionality of the hand, being the basis for adequate treatment completion (adherence), which could lead to an improvement in pain and functional limitations (2).

Despite these facts, there are no guidelines that specify what type of orthosis is best suited for treatment (9). Studies carried out until recently have focused on clinical parameters, being necessary to incorporate other variables such as the perception of the patient, their comfort, which will lead to greater adherence to treatment and, therefore, to improve their pain and functionality.

As mentioned, in the initial treatment for rhizarthrosis, among other measures, a thumb abduction splint is usually prescribed, which seeks to put the thumb in a more physiological position (in

abduction instead of adduction) in which the articular surfaces remain in better relationship, and also seeks to stabilize the joint and relieve it of mechanical demand during daily activities.

The first axis of the hand (Trapezius (carpus) - first metacarpal - proximal and distal phalanges) tilts at the joint between the trapezius and the first metacarpal. It is a very loose joint, allowing a wide range of thumb motion. The most important movement for the functionality of the hand is that of opposition, that is, the one that allows the thumb to pivot until it is placed opposite the rest of the fingers, enabling the pincer function.

When there is a rhizarthrosis or degeneration of the trapezius-metacarpal joint, the greatest pain occurs precisely with the pinching. Biomechanically, the force or pressure exerted with the tip of the finger is transmitted by the lever arm of the aforementioned column, multiplying the mechanical demand at the base of the same, in the trapezius-metacarpal joint. This force can subluxate the joint. Both pressure and subluxation are causes of pain. Therefore, the goal of any orthosis is to immobilize and support this joint.

3.1 Conventional orthoses

Currently there are several types of splints made of temperature-moldable plastic material, a splint that has multiple disadvantages in terms of manufacture:

-Polypropylene shrinks with heat, so it must be taken into account when designing. In addition, special care must be taken when heating and thermoforming it since the orthosis can collapse more easily. If it does not heat up enough, it may not fit well.

-Rectifications cannot be made, so extreme care shoud be taken with the mold, and it is mandatory to make screeds or modifications before adapting the polypropylene, since once it has been fused, no changes can be made.

Another type of splints that exist on the market are splints made of polyethylene sheets adjustable with velcro. The disadvantage of these splints consists of their instability in immobilization: they do not hold firmly, since they do not fit perfectly to the affected area.

Given that the moments in which the patient has more pain are those in which they are exerting efforts with their hands, there is an increasing tendency to make more ergonomic and smaller models, which even allow wearing gloves on the orthosis if the worker requires it, and plastic materials that can get wet.

Additive manufacturing, frequently associated with the concept of 3D printing, encompasses a set of technologies that is transforming the way of designing and manufacturing application products in many and very diverse sectors. 3D printing is based on the creation of objects, from a computerized file, by superimposing layers of material. 3D printing or additive manufacturing is one of the main axes on which Advanced Manufacturing or Industry 4.0 is based, considered by the European Union as Key Enabling Technology (KET), and therefore, a priority line of action.

The great potential of this technology, as well as its versatility, has made it enter different markets, standing out that of Biosciences-Health. 3D printing allows the custom fabrication of anatomical models for surgical guides, surgical instruments, implants, prostheses, immobilization orthoses, etc. It can be printed on different plastic materials, resin, titanium, other metals, etc. The latest advances in health applications are based on the combination of biology, the creation of biomaterials and 3D printing, evolving to what is known as bioprinting.

Additive manufacturing, within this trend, facilitates the creation of an orthosis fully adapted to the anatomy of each patient. With the design freedom provided by 3D computing tools, the product will be lightened and manufactured in materials that can be wetted.

3.2 Advantages of the 3D orthosis

The development of the 3D bio-splint is a project opportunity for a new 3D orthosis that will allow a qualitative leap in the search for an intelligent solution for patients with rhizarthrosis.

The splints developed using this method have a series of advantages both in manufacturing and for patients, among which we can highlight:

- Increase the precision in the design of the splint to place it in the affected area.
- Reduce the weight of the splint in order to lead a more agile life.
- Improve perspiration.
- Resistance to water, which will improve hygiene, the patient can even bathe with the splint on.
- Greater mobility. The “pincer” movement will not be affected.
- Allow air circulation.
- Improve aesthetic appearance: simple splint design that can be covered if the patient considers it so, for example, with gloves.
- Manufacturing times: the 3D model is made in 3 hours and can be in use by the patient in 72 hours.
- It can be made with fully recyclable materials.

Below is a comparative summary table of the advantages of the 3D orthoses compared to current “conventional” orthoses:

CONVENTIONAL ORTHOSES' ASPECTS TO IMPROVE		ADVANTAGES OF 3D ORTHOSES
Standard orthosis sizes.	***Comfort of the affected patient.***	-Customized splint adapted to the anatomy of each patient. (Scan to obtain 3D model of affected anatomy and fully customized CAD design).
Thermoplastic Materials / PP / Plastic Cloth (Nylon)	***Heavy orthosis. Causes excessive heat and sweating.***	-Lightened splint both with the material and its density (possibility to edit the internal density of the material). -The range of materials offered by additive manufacturing will allow testing different materials and considering the most appropriate in terms of their rigidity-flexibility.
PP manufacturing process	***Difficulty in manufacturing the PP (see section 3.1.)***	-Additional manufacturing is a simple process by which the structure of the orthosis can be manufactured without any problem by melting the plastic and creating the 3D layer by layer. This technique gives total freedom to the design, being able to create pieces unthinkable with other manufacturing methods.
Manufacturing times		Fabrication of an orthosis can be finished in 3 hours approximately.
Usually closed orthosis design	***Causes excessive heat and sweating.***	-Orthosis design freedom: openings / holes ...
Complete immobilization of the hand	***The pitching is affected. The patient cannot perform daily activities***	-Immobilization of the trapezius-metacarpal joint but nearly not affecting pitching

3.3 3D bio-splint design (3D orthosis)

Immobilization is the initial treatment for rhizarthrosis, currently carried out using an orthosis or splint made of moldable plastic material or adjustable polyethylene sheets with velcro. These orthoses have a standard size of measurements (2-3 sizes) so they do not adapt to the anatomy of 100% of the patients. In addition, they are splints that cause excessive heat, weight bearing and the impossibility of cleaning or bathing. Due to these reasons, patients tend to fail to follow the immobilization procedure prescribed by clinicians (7-10 hours a day with the splint on).

Faced with this problem, the company OPTIMUS 3D has seen the need to develop a new procedure to treat limb immobilization or orthotic external aid, providing splints with greater comfort and possibly improvement in the completion of the treatment, in addition to a better usability of the splint for the patient. The basic idea of the project is to manufacture the splint adapting it exactly to the physical configuration of the affected hand of the specific patient. The personalized splint will adapt exactly to the dimensions of the affected hand, thereby improving adherence to treatment and minimizing the discomfort derived from the use of standardized splints in sizes.

In patients with rhizarthrosis, the greatest pain appears in the fine and maintained pinch movement. For this reason, the splint should fix the trapezometacarpal joint fully and the metacarpal phalangeal joint partially. The splint will free the movement of the interphalangeal joint thanks to which you can perform daily activities that do not involve much effort. 3D printing will allow a splint design fully adapted to the anatomy of each user.

A scan will be carried out, in the orthopedist's own office, of the possible affected areas that will allow the modeling of anthropomorphic data collection to be carried out using software where a huge cloud of points obtained from the scan of each patient will be modeled. be able to obtain a fabricable 3D model, that is, a design of the bio-technical parameters of the splint, defining and taking into account when designing the custom 3D splint, all the medical and biological aspects necessary to avoid health problems and increase comfort.

OPTIMUS 3D will carry out the engineering and development of the splints using 3D printing technologies.

3.4 Product development: 3D custom splints

- Detailed modeling of the data taken in the scan. Detailed and specific modeling of the data taken by the 3D scanner will be carried out. Using the scanner, a point cloud of the model is obtained, which will be output in .stl format. This .stl file will be exported to a modifiable vector format to be refined and obtain a 3D model of the affected anatomy with which it will be worked later in 3D CAD software.
- Design using 3D software of the models necessary for the manufacture of the prototypes. The design will be made optimally based on the 3D model of the patient obtained in the scan. A design will be created that perfectly fits and wraps the 3D model of the member adjusting the immobilization zones as specified in the load book. Once the orthosis has been designed, it can be exported in STL (stereolithrography) format necessary for printing on 3D printing machines. This file is the one that is used as input or input file for 3D printers, it is the digital representation of the model to be printed, from its CAD version. In other words, the STL format (or, failing that, STP. Or IGES. Exportable to STL format) will be necessary to be able to print in 3D. These files can be obtained from various 3D CAD design software. What is needed is to make an export of the digital model that has been built and to worry about saving the file in the necessary format.

4. HYPOTHESIS

3D manufactured orthoses manufactured are effective tools in the conservative treatment of rhizarthrosis in terms of pain reduction.

5. OBJETIVES

The objectives of this study are exploratory since it is a proof-of-concept or feasibility study, which seeks to assess the feasibility of applying a personalized splint compared to a conventional one. We estimate that the clinical results, pain and function of the custom splint will be at least as good as those of conventional splints, but providing greater comfort and satisfaction for the patient.

Main objective

- Evaluate the reduction of pain in patients with usual orthoses compared to the orthosis designed using 3D technology (VAS pain scale)

Secondary objetives

- Evaluate the functionality between both groups (DASH scale)
- Assess patient satisfaction between both groups (6-item scale)
- Subjectively and retrospectively evaluate the time of use between both devices
- Evaluate the strength, using pinch and grip gauges (dynamometers)

6. DESIGN OF THE STUDY

This study is a **proof of concept or feasibility study**. As such, the study tries to find out if the personalized splint can be suitable for the treatment of patients with osteoarthritis of the TMJ and obtain at least similar results, providing greater comfort of use and facilitating an improvement in the development of life activities daily to patients. Therefore, it is not a design aimed at evaluating the efficacy of such treatment.

Prospective study with two arms, open with 1: 1 allocation.

The study will be carried out in the outpatient clinics of the OSI Bilbao-Basurto Orthopedic Surgery and Traumatology Service with the collaboration of the Rehabilitation Service.

The study will include a recruitment visit and two follow-up visits, one after the first month and another final visit at the 3-month period

7. SUBJECTS OF STUDY

Patients with a new diagnosis of osteoarthritis of the trapeziometacarpal joint (TMJ) will be included according to the “recruitment plan” established in Annex III.

Inclusion criteria

- Age between 18 and 75 years
- Clinical diagnosis of rhizarthrosis
- Radiological stage of the classification of Eaton-Littler I/II
- Patients in whom a orthosis or splint is clinically indicated
- Score between 3 and 7 on the VAS pain scale (range 0 to 10)

Exclusion criteria

- Previos treatment of rhizarthrosis
- Refueses to participate in the study
- Disabilities that prevent the completion of the questionnaires
- Severe deformations in the hand
- Presence of other alterations, such as carpal tunnel syndrome, tendinitis, or chronic inflammatory arthropathies

Interventions

One group of patients will wear the usual splint indicated by the staff physicians and the other group the personalized splint designed by the company OPTIMUS 3D.
Patients will be asked to wear the splint for as long as possible, not to disrupt their normal activities (work, household, or otherwise).

Assignment to the treatment branch

Participation in the study will be offered to patients on a consecutive basis. Those patients who meet all the inclusion criteria, none for exclusion and sign the Informed Consent, will be randomized to receive the personalized splint or the control branch (conventional splint). Because the sample size is small and in order to avoid relevant imbalances in the final number of participants in each branch, the sample allocation process will follow a system of randomization by blocks (n = 4) and stratified by the level of activity of the patient. This will also try to ensure comparability between the groups in terms of the variable "activity"

Blinding

It does not apply in the present study. It is designed as an open study, since it cannot be blind, neither for patients nor for physicians, due to the fact that one branch will carry splints adapted to each patient and must be prepared by scanning the hand in the consultation itself.

8. SAMPLE SIZE

This study has not been designed to test specific statistical hypotheses, so there is no justification for the sample size, since the study is designed as a proof of concept. It is intended to include 20 patients in each treatment arm.

9. VARIABLES TO RECORD

- - The **main variable** is the pain that will be measured, as is usual practice by a visual analog scale from 0 (no pain) to 10 (excruciating pain).

Pain has been chosen as the main variable, under the hypothesis that as the splint is more comfortable it may be worn longer and this would imply a decrease in pain (Annex IV)

- As a **secondary variable**, we will use the DASH questionnaire (10) to assess functional capacity. It is a self-administered questionnaire, which consists of a central body of 30 items that measure function and symptoms. Besides, there are 2 optional modules, with 4 items each, designed to measure the impact of an upper limb injury when playing musical instruments and when doing sports or working. Each item is scored from 1 to 5, with increasing values depending on the intensity of the symptoms. The score of the items in the central body is added to obtain a total score, which can range from 30 to 150 points and which is transformed into a scale from 0 (best possible score) to 100 (worst possible score). Optional modules, where applicable, are scored separately using the same method. The DASH makes it possible to assess the disability perceived by the patient to perform various activities, including activities of daily living and symptoms such as pain, stiffness or loss of strength.

The choice of this variable is justified since it is the questionnaire usually used both clinically and in studies to assess functional capacity (Annex IV).

- To assess patient satisfaction, a satisfaction scale composed of 6 items will be used, each one scored from 0 to 10, that is, a scale of 11 points (11) (Annex IV)

The choice of this variable is justified by the personalized design, with which it is expected that the patients will be more satisfied in the items to be evaluated.

- The evaluation of the time of use, in hours / day, of the different splints will be done by direct question to the patient.

This variable is considered as a surrogate variable, since using the splint for a longer time may possibly improve pain and functionality.

- Finally, the grip and pinch strength will be evaluated before the splint and later, by means of a dynamometer in the consultation.

Other variables that will be included will be:

Age, gender, employment status (housekeeping, active, sick leave, retired), marital status (single, divorced, separated / married, as a couple), level of studies (no studies / primary, high school / se secondary or equivalent and higher)

10. FOLLOW-UP AND DATA COLLECTION

The data will be collected in three visits. The baseline visit, in which the inclusion / exclusion criteria are checked and the corresponding treatment is assigned.
In the control branch, the doctors prescribe the usual splint for each patient. In the intervention branch the personalized splint.
At the baseline visit, the patients will be clinically examined, an X-ray will be taken to verify the inclusion criteria, and the DASH, VAS for pain, and pressure force will be completed.
On the second visit, one month after the splint, pain, satisfaction, DASH, wearing time and grip strength will be evaluated.
At the third follow-up visit (end of the study) that will take place at the third month of follow-up (between 11-14 weeks), patients will complete the DASH questionnaire, the VAS pain scale (from 0-no pain to 10-worse imaginable pain), the pressure force, the time of use and the satisfaction questionnaire made up of 6 items, on an 11-point scoring scale, in which satisfaction will be assessed.
The data of the patients and of the study variables will be collected by the specialists of each of the centers involved in the study. These data will be collected in a data collection notebook and entered into a database designed and adapted for this study.
At the end of the data collection, the errors they may contain will be eliminated by checking logical ranges and detecting impossible codes. Likewise, any errors found will be corrected by checking the clinical history. Once it is considered that the data are refined, they will be closed for statistical analysis.

11. STATISTIC ANALYSIS

For the descriptive analysis of the quantitative variables, the mean and standard deviation, median and interquartile range will be used. For qualitative variables, frequencies and percentages will be used.

The quantitative variables, pain level and DASH score will be compared, both at baseline and at follow-up, as well as the difference between both moments, as well as time and satisfaction, between the two groups of patients using the T-test of Student or non-parametric Mann-Whitney U test, depending on whether the variables follow a normal distribution or not. The comparison of qualitative variables between both groups, such as gender, marital status, educational level or type of work, expressed as percentages, will be carried out using the Chi-square test or Fisher's exact test.

On the other hand, it will be analyzed within each group of patients if the change in pain and functionality (DASH scale) between baseline and follow-up has been significant or not using the paired t test or the non-parametric Wilcoxon test for data couplets.

Finally, the general linear model will be used to compare the decrease in pain or the improvement in functionality between the two groups of patients, adjusting for pain or baseline functionality. Changes in pain or functionality are considered as the dependent variable of the model, and the group (main independent variable) and the baseline pain or functionality scores as independent.

12. ETHICAL CONSIDERATIONS

Prior to conducting the study, this protocol will be submitted to the evaluation of the CREC (Clinical Research Ethics Committee) from OSI Bilbao Basurto. The patients included in the study will not be subjected to any risk other than that which they must suffer from the usual medical care of their disease and that due to the disease itself. No patient will be included or any study procedure will be carried out until the informed consent in writing has been obtained after written and oral information (Annex II: Information to the patient and informed consent).

The information procedure will consist of the following phases:

a) In the presence of the patient, the Information Sheet and Informed Consent will be read aloud in a clear and concise manner
b) All doubts that may arise will be clarified
c) Sufficient time will be allowed for patient to sign the Informed Consent

Participation in the study will not entail any extra expense on the part of the patient. The study will not begin in any center until the Managing Director of the same has given his express authorization to it.

13. DESCRIPTION OF THE TECHNIQUE TO BE USED IN THE STUDY

The project will be carried out in the outpatient clinics of the OSI Bilbao-Basurto Orthopedic Surgery and Traumatology Service with the collaboration of the OSI Rehabilitation Service.

This study will include a recruitment visit and two follow-up visits, one at first month and another final visit at 3 months.

Patients with a new diagnosis of osteoarthritis of the trapeziometacarpal joint will be included. One group of patients will wear the usual splint indicated by the staff physicians and the other group, the personalized splint designed by the company OPTIMUS 3D.

The main variable is pain, which will be measured, as is usual practice, by a visual analog scale (VAS). In addition, the DASH (Disabilities of the Arm, Shoulder and Hand) questionnaire will be used in its Spanish version (DASHe) and questions about patient satisfaction with the use of splints.

In the first recruitment visit, following the criteria and specifications of the "Recruitment Plan in relation to patient participation" (Annex III), Optimus 3D will scan the patient with rhizarthrosis to obtain the necessary information with which the model will be created.

The patient, seated, will keep the arm extended on a table, leaving the area of the wrist and hand in the air without support. The wrist will be kept in a functional position, simulating holding a glass. When the clinician verifies the correct position of the affected limb, the scan will begin.

The Optimus 3D technician will rotate the 3D scanner of the ASORCAD equipment around the patient's arm for approximately 1 minute. The scanner connected to a laptop will collect the anatomical data generating a point cloud that will be exported as a mesh (.stl format). This model will be used to begin the custom splint design process.

14. LIMITATIONS OF THE STUDY

The limitations of the study include the following:

- - The Eaton-Litter classification is subject to intra-observer and inter-observer variability. This fact can affect the classification of patients. However, it is the most used in the literature.
- The standard splint does not consist of a single model, but there are several available to patients. This fact means that the control group can contain different models. However, this is what happens in routine clinical practice.
- Being a proof of concept study, the comparisons are exploratory.

15. DURATION AND FOLLOW-UP OF THE STUDY

Prior to the beginning of the study, a representative of the promoter or coordinating center will contact the principal investigator and the services involved in the study at each center to review the Protocol together with the data collection notebook (DCN). The objective is to clarify any doubts that may arise prior to the start of the study.

During the course of the study, follow-up visits will be made periodically by a coordinator to check the progress of the study, control the documentation generated, help gather the required data and answer any questions that may arise.

The objective of this procedure is to verify that all documentation and files are up-to-date and guarantee compliance with all protocol requirements and applicable local and national regulations, as well as the competent authorities.

The phases in this study will be:

Tasks	**Months**					
	1-2	**3**	**4-6**	**6-7**	**7-8**	**8**
1.- Documentation: Protocol and DCN						
2.- AEMPS and CREC						
3.- Recruitment and follow-up of patients						
4.- Debugging of the database						
5.- Data analysis						
6.- Results presentation						

16. REFERENCES

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ANNEXES

Annex I:

Participating Centers and Research Team

CENTER	SERVICE	COLLABORATING RESEARCHER
Basurto University Hospital (OSI Bilbao Basurto)	Orthopedic Surgery	Iñigo Cearra Guezuraga MD, PhD
		Félix Manuel Silió Ochandiano MD, PhD
		Borja Cuevas Martínez, MD
	Rehabilitation	Mª Lourdes Vadillo Jáuregui, MD
	Research Unit	Antonio Escobar Martínez MD, PhD
		Iñigo Gorostiza Hormaetxe MD, PhD
		Amaia Bilbao MD, PhD
Optimus 3D, S.L.	I+D+i	Mr Fernando Oharriz
		Mr Alberto Ruiz de Olano
		Mrs Izaskun Arriaga

Annex III:

Recruitment plan related to patient participation

1. All members of the Orthopedic Surgery and Rehabilitation services will be informed, in the morning session, that initially ALL patients with a first diagnosis of rhizarthrosis in the outpatient clinic must be referred to the Hospital's Outpatient Traumatology Consultations, with symptomatic treatment and with recommendation of relative rest and analgesics. The clinics included are: Dr Areilza, Rekalde, Deusto, Txurdinaga, Santutxu, Javier Sáenz de Buruaga, Begoña and Bombero Etxaniz.

2. To facilitate the appointment, patients will be referred with PREFERENCE and directed to ORTHOPEDIC SURGERY - RHIZARTHROSIS CLINIC. When doing it in this way, the specific day of the consultation is not given by the administrator of each outpatient clinic, but the request documents are sent by fax to the Hospital's Outpatient Clinics, where the administrators are aware of the study and the days available for citation. In the outpatient clinic, then, the patient receives the information that the appointment will be notified by mail or telephone, and it will take place within a maximum period of 15 days.

3. The administrative staff of the Hospital's Outpatient Clinics will have, each month, at least two consultation spaces for the study of rhizarthrosis, so that no patient waits more than 15 days. These days will be determined with one month in advance, depending on the availability of the doctors, the consultation spaces, and the needs of the service. These inquiries will be notified, also within one month, to the company Optimus 3D. It is not expected to have more than 5 patients each day. The Orthopedic Surgeons who will attend these consultations are doctors Iñigo Cearra and Borja Cuevas. It is estimated to need about 20 minutes per patient.

4. In the office, it will be determined, from among all the patients, which ones meet all the inclusion criteria and none of the study exclusion criteria. The randomization will be carried out by the Hospital Research Unit. The patients in the experimental group will be scanned the same day of consultation by Optimus 3D company, with the objective of delivering the orthosis as soon as possible, estimating the time from scanning to delivery in 5 working days. Patients who are unable or unwilling to enter the study will be treated according to normal practice.

5. Follow-up consultations will be carried out at one month and at three months, after this first consultation, to evaluate the result of the treatment.

Annex IV:

Variables in data collection notebook (DCN).

PAIN VAS

0	1	2	3	4	5	6	7	8	9	10
No pain										Maximum pain

DASH QUESTIONNAIRE

DISABILITIES OF THE ARM, SHOULDER AND HAND

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

DISABILITIES OF THE ARM, SHOULDER AND HAND

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = $\left[\left(\frac{\text{sum of n responses}}{n}\right) - 1\right] \times 25$, where n is equal to the number of completed responses.

A DASH score may <u>not</u> be calculated if there are greater than 3 missing items.

DISABILITIES OF THE ARM, SHOULDER AND HAND

WORK MODULE (OPTIONAL)

The following questions ask about the impact of your arm, shoulder or hand problem on your ability to work (including home-making if that is your main work role).

Please indicate what your job/work is:_____

❒ I do not work. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for your work?	1	2	3	4	5
2. doing your usual work because of arm, shoulder or hand pain?	1	2	3	4	5
3. doing your work as well as you would like?	1	2	3	4	5
4. spending your usual amount of time doing your work?	1	2	3	4	5

SPORTS/PERFORMING ARTS MODULE (OPTIONAL)

The following questions relate to the impact of your arm, shoulder or hand problem on playing *your musical instrument or sport or both*. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you.

Please indicate the sport or instrument which is most important to you:_____

❒ I do not play a sport or an instrument. (You may skip this section.)

Please circle the number that best describes your physical ability in the past week. Did you have any difficulty:

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. using your usual technique for playing your instrument or sport?	1	2	3	4	5
2. playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
3. playing your musical instrument or sport as well as you would like?	1	2	3	4	5
4. spending your usual amount of time practising or playing your instrument or sport?	1	2	3	4	5

SCORING THE OPTIONAL MODULES: Add up assigned values for each response; divide by 4 (number of items); subtract 1; multiply by 25.
An optional module score may <u>not</u> be calculated if there are any missing items.

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PATIENT SATISFACTION

1. What is your level of satisfaction with the splint?
2. Has the splint helped decrease your pain?
3. Has the splint helped you maintain your daily activities?
4. Has it improved your quality of life?
5. How comfortable was the use of the splint?
6. How easy has it been to follow the instructions for using the splint?

Answers are on a scale from 0 to 10

0	1	2	3	4	5	6	7	8	9	10
Not satisfied at all										Very satisfied
Has not helped me at all										Has helped me a lot
Has not helped me at all										Has helped me a lot
Has not improved at all										Has improved a lot
Not confortable at all										Very confortable
Not easy at all										Very easy

Annex V: Declaración of Helsinki

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964; amended by the 29th WMA General Assembly, Tokyo,
Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong,
September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA
General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, ''The health of my patient will be my first consideration,'' and the International Code of Medical Ethics declares that, ''A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.''
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The
researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent

should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient–physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.