Clinical Investigation with Medical Device

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Title of the Clinical Investigation

Retrospective post-market Clinical Investigation for the evaluation of the safety and clinical benefit of Guided Growth Plate System Plus (Orthofic Srl) medical device for the treatment of lower limb bone deformities of the in growing children.

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Investigator Signature Page

By signing this document, I declare that I have read this Clinical Investigation Plan and confirm that it contains all the information necessary to conduct the Clinical Investigation as described herein. Furthermore, I confirm my intention to conduct this Clinical Investigation in accordance with the procedures outlined in this Clinical Investigation Plan, the ICH Good Clinical Practice guidelines, as well as applicable local and national laws and the obligations specified in the contract entered into with Orthofix S.r.l. or its authorised representative.

Site code: ITA 01

SIGNATURE FOR ACCEPTANCE OF THE CLINICAL INVESTIGATION PLAN

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1 SYNOPSIS

TITLE	Retrospective post-market Clinical Investigation for the evaluation of the safety and clinical benefit of Guided Growth Plate System Plus (Orthofic Srl) medical device for the treatment of lower limb bone deformities of the in growing children.
INVESTIGATIONAL DEVICE DESCRIPTION	The GGPSP consists of different sizes of eight-Plate and quad-Plate designed to accept cannulated or solid screws available in a variety of sizes. Plates and screws are available in sterile or non-sterile configuration. The device is designed for the gradual correction of pediatric congenital as well as acquired bone deformities in long bones, provided that the physis (growth plates) are not fused. The plates feature a contoured waist and low profile for pediatric usage. There is a center hole in the plates for a temporary guide pin to be implanted to aid application and removal of the plate. The plates are fixed to the bone over the growth plate by screws. These screws are not locked to the plate, but rather are allowed to swivel and diverge in their position as bone growth occurs. The implant acts like a flexible hinge, halting on one side (hemiepiphysiodesis) or on both sides (epiphysiodesis) the growth plate and thus guiding bone growth. Application and removal of the GGPSP can be performed with Orthofix general orthopaedic instrumentation.
OBJECTIVES AND ENDPOINTS	**Primary objective:** evaluate the safety profile of GGPSP. **Primary endpoint:** percentage of subjects that encountered at least one complication, to be intended as: · an expected or unexpected serious adverse effect related to the device; · an hardware failure (i.e. breaking, loosening or bending of the plate or of the screws) during follow-up period (from time of plate application to the first post-removal visit). **Secondary objective:** evaluate the clinical benefit of treatment with the GGPSP. **Secondary endpoint:** percentage of subjects that achieved the treatment goal as defined below: · for hemiepiphysiodesis, femur and/or tibia angular deformity partially or · completely corrected to standard alignment (mMPTA and mLDFA between 85° and 89°); · for epiphysiodesis, femur and/or tibia length discrepancy partially or completely corrected to the matching length of the contralateral morphologically normal limb during follow-up period (from time of plate application to the first post-removal visit).
TYPE OF INVESTIGATION	Observational, retrospective, single centre, not controlled.
RAZIONALE	Orthofix is undertaking this retrospective post-market observational Clinical Investigation to evaluate the safety and clinical performance of the GGPSP,

<table>
<tr><td></td><td>which is the second version of the GGS and incorporates minor modifications to the original design. The study is aimed to collect Real World Evidence on the usage of the products in a real life surgical setting. Therefore, a retrospective post-market study was chosen as the most appropriate study design to collect the needed data.</td></tr>
<tr><td>PLANNED

INVESTIGATION PERIOD</td><td>Preparation: 4 – 5 months for ethics committee submission preparation

Live phase: 10 months to collect the clinical data and write the statistical and clinical report.</td></tr>
<tr><td>STUDY DURATION PER

SUBJECT</td><td>Not Applicable: since this is a retrospective study, all clinical data are already in the patient files at the hospital and patients will not be involved actively in the data collection nor are they subject to further follow-up visits.</td></tr>
<tr><td>Site</td><td><table>
<tr><th>Hospital</th><th>Country</th><th>City</th><th>Principal Investigator</th></tr>
<tr><td>Istituto Ortopedico Rizzoli</td><td>Italia</td><td>Bologna</td><td>Dr. Di Gennaro</td></tr>
</table></td></tr>
<tr><td>INCLUSION CRITERIA</td><td>A patient will be included in the study who:
· Was treated with GGPSP to correct deformities of the femur and/or tibia
· Has concluded treatment with the GGPSP
· Has a data set available that would allow evaluation of the safety and clinical performance of the device</td></tr>
<tr><td>EXCLUSION CRITERIA</td><td>A patient will not be included in the study who:
· Was treated with GGPSP to correct only deformities of the upper limbs and not of the lower limbs;
· Is still undergoing treatment with the GGPSP
· Does not have a data set available that would allow evaluation of the safety and clinical performance of the device</td></tr>
<tr><td>COMPARATIVE DEVICE</td><td>I dati di letteratura disponibili per il GGP e per dispositivi equivalenti verranno utilizzati come riferimento (“Stato dell’arte”) per l’interpretazione dei dati ottenuti tramite la presente Indagine Clinica.</td></tr>
<tr><td>CLINICAL PARAMETERS</td><td>- Age at surgery
- Demographical data and BMI - Anamnesis
- Indication - Bone (femur / tibia / both)</td></tr>
</table>

	- Location (proximal / distal / both) - Side (L / R / bilateral) - Surgery details (n of implanted plates, duration, complications) - Concomitant treatments - Deformity parameters, where applicable (both at plate application and removal): Hip-knee-ankle (HKA) angle or Anatomic lateral distal femoral angle (aLDFA) or Mechanical axis deviation (MAD) or Mechanical lateral distal femoral angle (mLDFA) or Mechanical medial proximal tibial angle (mMPTA) or Lateral distal tibial angle (LDTA) or Femur-tibia rate or Tibia-fibula rate or Femur, tibia and fibula lenght - Achievement of treatment goal - Treatment time (calculated from implantation to removal) - Complications (both device related and not, leading to premature removal or an unplanned surgery or not)
SAMPLE SIZE CALCULATION	For the aim of the sample size calculation, the safety profile of GGPSP will be compared to safety data reported in the scientific literature for the treatment of lower limb deformities by the means of guided growth performed by tension band plate. The sample size, therefore, was calculated estimating the required number of subjects so that the primary endpoint of the Study for GGPSP (i.e. percentage of subjects that experienced at least one complication as above described) ranges within the state-of-art safety profile of this treatment, that is, it is within the safety data reported in the literature for its previous version (the GGS) and for equivalent medical devices. Specifically, the scientific literature reports that the percentage of patients treated by a tension band plate for a lower limb deformity that faced at least one complication is between 3% and 12% depending on the many factors, mainly the diversity of the primary diagnosis. Assuming the expected percentage of patients with at least one complication for GGPSP will be 3%, 70 implants was calculated to be the sample size of this study so that the upper limit of the 95% confidence interval for the primary endpoint, based on the exact binomial method, is under 12%. Since each patient may have been treated for the correction of multiple localized deformities in different long bones, it is understood that each eligible subject may contribute to the data collection of multiple implants (average 2). For this reason, approximately 40 patients are expected to be enrolled.

2 Medical Device Information

2.1 Medical Device Identification

The medical device under investigation in this Clinical Investigation is the "Guided Growth Plate System Plus" (GGPSP), also known as the "eight-Plate Guided Growth System +™", hereinafter referred to as 8-Plate Plus. 8-Plate Plus represents the new generation of the guided growth system known as the "Guided Growth System" (GGS), also referred to as 8-Plate. Although the two devices have been CE marked separately, they have been deemed equivalent based on a comparative analysis (Ref. CER-13_Rev. 04) and, as such, have been grouped into a single product family—namely, the Guided Growth Plate Systems (hereinafter GGPS, REF DMF-13), which includes both the GGS and GGPSP systems.
The 8-Plate Plus is a plate-and-screw system classified as a Class IIb medical device, manufactured and marketed by Orthofix S.r.l. in European Union markets and selected non-EU markets since May 2017.

2.2 Intended Use

Indications:
The 8-Plate Plus has been developed to guide the growth of long bones and is used to gradually correct angular deformities in growing children.
The device is indicated for the treatment of specific conditions/pathologies, including:

- knee deformities (femur and/or tibia) in varus/valgus or flexion-extension;
- ankle deformities in varus/valgus or plantarflexion.

The 8-Plate Plus is intended for professional use only. Surgeons responsible for supervising the use of the product must have comprehensive knowledge of orthopaedic fixation procedures and be familiar with the devices, instruments, and surgical technique, including both application and removal.
For further details, please refer to the "Instructions for Use" leaflet available at: https://abs.orthofix.it/db/resources/PQ_EPP.pdf

2.3 Detailed Device Description

The 8-Plate Plus system consists of plates of various sizes and shapes designed to accommodate cannulated or solid screws available in different lengths (Fig. 1). The plate with two holes for the fixation screws, which is also the most commonly used, is referred to as the "8-Plate" due to its shape and gives the name to the entire system. A version of the plate with four holes for fixation screws is also available and, due to its shape, is referred to as the "Quad-Plate" (Fig. 1).

Figure 1: Examples of plates ("8-Plate" on the left and "Quad-Plate" on the right) and screws from the 8-Plate Plus system.

The plates feature a contoured waist and low profile, making them suitable for paediatric use. Each plate includes a central hole for the insertion of a temporary guide wire, intended to facilitate both the application and removal of the plate.

The plates are secured to the bone across the growth plate using screws (Fig. 2).

Figure 2: Implantation of 8-Plate (left) and Quad-Plate (right) for hemi-epiphysiodesis.

These screws are not locked to the plate but can instead rotate and diverge under the pressure exerted by the growth plate. The implant functions as a flexible hinge (Fig. 3), inhibiting the growth plate on one side (hemi-epiphysiodesis) or on both sides (epiphysiodesis), thereby guiding bone growth.

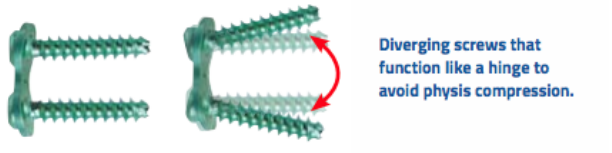


Figure 3: "Hinge-like" configuration of the implant.

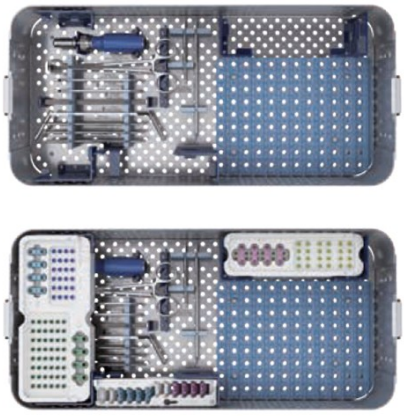
The positioning of the screws is monitored over time by radiographic imaging, and the implant is always removed before the screws reach their maximum angle of divergence. The system thus exerts pressure that temporarily inhibits growth of the growth plate.
If the growth plate is inhibited on only one side (medial or lateral), the technique is referred to as hemi-epiphysiodesis and its final effect is the correction of angular deformity of the treated limb. If, instead, the growth plate is inhibited on both sides, the technique is known as epiphysiodesis, and its final effect is to slow the growth of the treated limb, allowing the shorter contralateral limb to catch up and reduce the length discrepancy.

The implant is therefore intended as one of the surgical options for performing epiphysiodesis and hemi-epiphysiodesis in a minimally invasive manner—that is, without the need for corrective osteotomy.

The application and removal of the 8-Plate Plus can be performed using standard orthopaedic instruments (Fig. 4).

Equipment required

Instruments	
Part#	Description
GP540CE	K-Wire D 1.6mm L150mm
180005	Drill Guide
DH0455CE	Micro Ratcheting Handle with AO Connector Cannulated
GP520CE	Cannulated Drill Bit D 3.2mm with Quick Connect
180010	Cannulated Drill Bit D 2.4mm with Quick Connect
180035	Cannulated Tap D 3.5mm with Quick Connect
DH0464CE	Guided Growth Plate Holder
180015	Guided Growth Plate Bender
180020	Self-Retaining Cannulated Screwdriver Hex 3.5mm
DH0474CE	Guided Growth Screw Extractor
99-GP520CE	Cannulated Drill Bit D 3.2mm with Quick Connect Sterile
99-180010	Cannulated Drill Bit D 2.4mm with Quick Connect Sterile
99-180035	Cannulated Tap D 3.5mm with Quick Connect Sterile



Boxes	
Part#	Description
180990	Sterilization Box Empty
180990C	Sterilization Box Complete
180996	Sterilization Box Lid
180991	Eight Plate Plus Caddy Empty
180992	Quad Plate Plus Caddy Empty
180993	Extended Plus Line Caddy Empty
180997	Guided Growth System Plus Update Kit

Figure 4: Instrumentation for the application and removal of the 8-Plate Plus.

For further details regarding the instrumentation and accessories for the 8-Plate Plus, please refer to the surgical technique guide available at: https://abs.orthofix.it/db/resources/EP-1701-OPT-E0.pdf.

2.4 Surgical Procedure Related to the Use of the Medical Device

Below is a brief description of the main steps for the application and removal of the 8-Plate Plus. For more detailed information regarding the surgical steps, please refer to the surgical technique guide available at: https://abs.orthofix.it/db/resources/EP-1701-OPT-E0.pdf

Surgical Procedure:

1. Using a radiopaque instrument and a fluoroscope, identify the physis in the anatomical area where the plate and screws will be applied according to the desired correction. Mark the skin at the level of the physis and make a 1–2 cm incision.
2. Once the bone is exposed, insert the guide wire through the central hole of the plate and into the physis using a power drill, to a depth generally not exceeding 1 cm. Then confirm correct positioning of the guide wire with fluoroscopy.
3. Select the most appropriate plate size based on the patient's anatomy and the intended application. Before inserting the screws, ensure the plate is properly seated against the bone. The plate has a standard base curvature of 10°, but it can be bent an additional 10° if needed to ensure proper bone contact.
4. Plate fixation is performed using the dedicated instrumentation, following these main steps:

- Insertion of epiphyseal and metaphyseal guide wires;
- Selection of the screws and the corresponding cannulated drill bits;
- Pre-drilling of the epiphyseal hole followed by the metaphyseal hole;
- Assembly of the screwdriver and insertion of the screws;
- Removal of the guide wires;
- Wound closure with sutures.

2.5 Instructions for Medical Device Traceability

The use of the 8-Plate Plus is already part of the routine clinical practice at the participating Centre; therefore, this device is not considered an investigational product. For this reason, the supply and traceability of the 8-Plate Plus at the Centre will follow the standard commercial procedures for the provision of medical devices.

3 Background

Hemi-epiphysiodesis is a surgical procedure in which the epiphyseal (growth) cartilage of a long bone is temporarily or permanently compressed on one of its lateral aspects, to either delay or stop growth respectively, thereby allowing correction of angular deformities [1; 2; 3]. This approach is therefore often referred to as guided growth, and was first described by Stevens when achieved using an extraperiosteal plate and two screws [1].

The most common indications for hemi-epiphysiodesis include varus or valgus deformities of the knee (femur or tibia) and ankle. These pathological angular deformities of the lower limbs, when exceeding a certain

degree in children and adolescents, may lead to pain during physical activity, abnormal gait, and joint instability.

When the growth plate of a long bone is compressed bilaterally, either temporarily or permanently, the procedure is called epiphysiodesis. This technique is used to slow or arrest the growth of a morphologically normal limb, allowing the shorter contralateral limb to catch up and correct a limb length discrepancy (LLD). However, there are several techniques available for the gradual correction of LLDs [2], depending on the severity of the condition, which may significantly impair mobility [1].

LLDs can be either congenital or acquired. They can be:

- Structural (anatomical), resulting from differences in bone structure;
- Functional (apparent), where asymmetry is not associated with actual shortening of lower limb bones.

LLDs are found in approximately 70% of the population. However, there is no consensus on the threshold of clinical significance that warrants treatment, with reported cut-off values ranging from 3 mm to 60 mm. In general, 20–25 mm is often cited as an intervention threshold, though this is not absolute and depends on the individual child, as some may compensate well for discrepancies up to nearly 30 mm [1].

Congenital causes of LLDs include fibular hemimelia, tibial hemimelia, congenital femoral deficiency, hemi-hypertrophy, or other limb hypoplasias. Acquired causes typically involve damage to the growth plate due to trauma, infection, radiation, or tumours. LLDs may also result from malunion or nonunion following fractures of long bones. Additionally, hip dysplasia and dislocation can lead to LLD. Determining the skeletal age of patients is helpful for assessing the prognosis of LLDs with or without treatment.

There are multiple treatment strategies for long bone deformities [4; 5], ranging from no treatment for mild deformities to prosthetic adaptation in cases of severe LLD, or corrective osteotomy for severe angular deformities. In this context, epiphysiodesis and hemi-epiphysiodesis are considered minimally invasive treatments.

Several medical devices are available on the market to apply compression to the growth plate: staples, oblique screws, non-resorbable wires and screws, and tension-band plates.

Tension-band plates are pre-contoured, dynamic plates, often available in various lengths, combined with cannulated or non-cannulated, non-locking self-tapping screws of different lengths [6]. They are typically shaped like a number eight, hence the name "eight-Plate."

Eight-plates can be used in two main ways:

- To gradually correct abnormal deviation of the mechanical axis by applying the plate to the convex side of the deformity to inhibit growth in that portion of the physis—this is referred to as guided growth.
- To correct limb length discrepancies, by applying plates on both sides of the physis of the longer limb to slow longitudinal growth. The ability of this technique to equalise limb length depends on the residual growth potential of the unconstrained contralateral physis. The degree of correction achieved depends on the skeletal maturity of the child at the time of plate implantation (usually assessed by bone age) and the condition of the contralateral physis.

Patient advantages include the fact that the surgical procedure is often performed as a day-case, with minimal disruption to school or other activities. It has a low surgical risk and pain profile, allows for immediate mobilisation and rehabilitation, and, by compressing the physis, enables faster correction.

A clear advantage of eight-plate use is the potential reversibility of the growth-suppression effect—by removing the implanted plate once the desired correction has been achieved.

This reversibility allows for early treatment of a deformity, at a younger age than would be considered if a definitive ablative epiphysiodesis were to be performed.

The 8-Plate Plus, manufactured by Orthofix S.r.l., belongs to the family of tension-band eight-plates.

4 Rationale for the Clinical Investigation

Orthofix S.r.l. developed and placed the 8-Plate Plus on the European market after conducting an assessment of the device's clinical performance and safety based on biomechanical tests and clinical data derived from scientific publications on equivalent products, including the previous version of the 8-Plate. The 8-Plate Plus differs from the original design only in minor aspects (further details are available upon request in the DMF 13 archived with the Sponsor).

The outcome of this pre-market evaluation determined that the 8-Plate Plus meets the requirements for CE marking and, in particular, presents an acceptable risk/benefit ratio when used according to the manufacturer's intended use.
As a result, it was not necessary to carry out a pre-Clinical Investigation to address gaps in clinical data or to assess specific residual risks.

Orthofix has chosen to conduct this study as part of its proactive post-market surveillance plan, to confirm the safety and performance of the 8-Plate Plus compared to the clinical data published in the literature for its predecessor (8-Plate) and for equivalent medical devices. This will be done through the collection of clinical data from routine clinical use.

Sales data indicate that over 9,000 treatments with the 8-Plate Plus have been performed in Europe to date. The frequency of serious complications reported to Orthofix S.r.l. through the passive vigilance system is lower than that reported in the literature for equivalent plates that have been on the market for a longer period. Although this initial evidence supports the clinical effectiveness and safety of the technical features integrated into the device, it is nonetheless appropriate to supplement this indirect evidence with actively collected clinical data through the present observational investigation.

To this end, a retrospective post-market clinical follow-up study was considered the most appropriate design to obtain the required information.

This single-centre, retrospective clinical investigation represents the first clinical evaluation conducted on the 8-Plate Plus system. As such, no clinical reports or publications from previous clinical investigations—whether sponsored by the Sponsor or spontaneous—are currently available.

5 Ethical Considerations

The contents of this Clinical Investigation Plan comply with the recognised ethical principles for clinical research, the principles of Good Clinical Practice (ICH-GCP guidelines) related to clinical investigations of medical devices, and applicable standards (UNI EN ISO 14155).
The procedures described in this Clinical Investigation Plan fall within the standard clinical practice of the participating centre. In fact, this is a retrospective clinical investigation, which means it will not alter the current clinical protocols in use at the participating centre, nor will it pose any additional risks to patients or investigators.

Participation in the study is voluntary, not driven by specific interests, and motivated by a spontaneous collaborative effort to gather data of shared scientific value. The study is being conducted at a Scientific Institute for Research, Hospitalisation and Healthcare (IRCCS), where an informed consent form for healthcare services is routinely obtained from all patients receiving treatment.

Prior to the start of the Clinical Investigation, the sponsor will enter into a financial agreement with the participating centre. It should be noted that no direct compensation is foreseen for the physicians participating in this Clinical Investigation.

The Principal Investigator at the site will ensure that the Clinical Investigation is conducted in accordance with the most recent revision of the Declaration of Helsinki and with all applicable national and international laws and regulations, in order to guarantee the highest possible level of protection for the patient.

The procedures described in this Clinical Investigation Plan will be implemented only after review and approval of the study documentation by the local Ethics Committee of the participating site.

As this is a retrospective study, all clinical data are already available in the patients' medical records held at the site. Patients had already signed the site's standard informed consent form, as referenced in the "Subject Identification" section. Therefore, they will not be actively involved in data collection nor will they be subject to any additional follow-up visits.
Before data collection begins for the first patient, each Investigator will be properly trained by Orthofix S.r.l. regarding the contents of this Clinical Investigation Plan, the use of the electronic data capture system, and the investigation procedures.

Once Ethics Committee approval has been obtained, the Sponsor will notify the Competent Authority of the start of the Clinical Investigation.

5.1 Subject Identification and Confidentiality

The Investigator shall assign a unique, predefined, and sequential code to each patient deemed eligible for retrospective data collection. Only the Investigator will be able to link this code to the patient's name, either for communications related to the Clinical Investigation or for the completion of the case report form; thus, patient pseudo-anonymisation will be ensured.

As stated in Article 110, first paragraph, of the new Privacy Code, it is specified that for Scientific Institutes for Research, Hospitalisation and Healthcare (IRCCS), a study-specific informed consent form and the related personal data processing consent form are not required if the patient has already signed the standard informed consent for healthcare assistance provided by the Institution and if the study is retrospective in nature.

Therefore, as the study is monocentric, retrospective, and conducted at an IRCCS, patients deemed eligible for retrospective data collection shall not be contacted for the submission of an additional informed consent form.

In any case, all appropriate security measures, proportionate to the type of data and processing involved, will be applied to ensure confidentiality, in accordance with GDPR 679/2016 and in compliance with the "Guidelines on the processing of personal data in the context of clinical trials of medicinal products" – 24 July 2008 (Official Gazette No. 190 of 14 August 2008).

Finally, patients and/or their parents/legal guardians may exercise the rights granted under European Regulation No. 679/2016 and Article 7 of the Privacy Code (e.g., to access their personal data, supplement, update, rectify, restrict, object to processing on legitimate grounds, request data portability, etc.) by contacting the Centre directly or, through it, the Sponsor.

No additional data concerning the patient will be collected, without prejudice to the retrospective use of those already gathered during routine clinical practice, which will be used, without any modification, to evaluate the outcomes of the ongoing Clinical Investigation.

5.2 Patients Eligibility

A patient treated in the paediatric age with the 8-Plate Plus system for the correction of femoral and/or tibial deformities, whose treatment has already been completed and who has undergone at least one follow-up visit after plate removal, shall be considered eligible for participation in the clinical investigation.
As this is a retrospective study, the Investigator will verify the inclusion and exclusion criteria for patients previously treated with the 8-Plate Plus system and will select those eligible for participation in the study.
Eligible patients will be enrolled in the study, and the Investigator shall assign a unique, predefined, and sequential code to each enrolled patient.

6 Vulnerable Population

Given the observational and retrospective nature of the present Clinical Investigation, no specific procedures for the management of the vulnerable population, other than those already foreseen and implemented at the Centre through routine clinical practice during the treatment of patients who were considered vulnerable subjects, are applicable.

7 Risks and Benefits of the Medical Device, the Procedures, and the Clinical Investigation

The procedures described in this Clinical Investigation Plan, being observational and retrospective in nature, fall within the routine clinical practice of the participating Centre. The proposed clinical investigation, as it is retrospective, will not alter the practices in place at the Centre, nor will it entail any additional risks for patients or Investigators. Therefore, patients involved in this clinical investigation will not derive any benefit nor experience any disadvantage.

However, the results obtained from the investigation may provide important scientific information, both in terms of safety and clinical outcomes, regarding the use of this type of medical device in patients.

8 Information on the Clinical Investigation

8.1 Clinical Investigation Description

This Clinical Investigation is part of the active materiovigilance plan that Orthofix Srl, in agreement with its Notified Body, has implemented to actively collect clinical data on the use of the 8-Plate Plus in a representative number of users and patients (Ref. Chapter 8.7 “Number of patients expected to be enrolled”).

The data obtained from this Clinical Investigation will be used to update the pre-market clinical evaluation of the 8-Plate Plus with post-market clinical data derived from the use of the device in routine clinical practice (further details are provided in Section 4 “Rationale of the Clinical Investigation”).

8.2 Clinical Investigation Design and Justification

This Clinical Investigation is characterised as:

- **Observational** (as verified during the feasibility phase by means of a pre-study visit, the procedures described in this Clinical Investigation Plan fall within the routine clinical practice of the participating Centre);
- **Post-market** (the medical device under investigation bears the CE marking and is already used in the routine clinical practice of the participating Centre);
- **Retrospective** (clinical data will be collected from patients who have already been treated with the investigational device and who had already signed the informed consent form required by the Centre);
- **Uncontrolled** (only the investigational medical device will be observed);
- **Non-randomised** (as the investigation is observational and uncontrolled, random allocation of the medical device is not applicable);
- **Single-centre** (the investigation will be conducted at a single Centre);
- **National** (the participating Centre is located in Italy).

Accordingly, a retrospective post-market clinical follow-up (PMCF) study design has been considered the most appropriate to obtain the required information.

Given the purpose and the design described above, the present Clinical Investigation falls within the category of studies defined as *Post-Market Clinical Follow-up (PMCF) studies* (for further details, refer to MEDDEV 2.12/2 rev. 2).

8.3 Objectives

The purpose of the Clinical Investigation is to actively collect clinical data on the use of the 8-Plate Plus in a representative number of paediatric patients (Ref. Chapter 8.7 “Number of patients expected to be enrolled”) who have already been treated with the investigational device and who have undergone at least one follow-up visit after plate removal.

- The **primary objective** of the Clinical Investigation is to evaluate the safety of the 8-Plate Plus.
- The **secondary objective** of the Clinical Investigation is to evaluate the clinical benefit of the 8-Plate Plus.

8.4 Endpoints

In this Clinical Investigation, the two variables selected as the primary and secondary endpoints, intended to measure the primary and secondary objectives of the Investigation respectively, also correspond to the treatment response measures routinely used in the standard clinical practice of the participating Centre, namely:

- **Primary endpoint (safety measure):**
  The safety of the 8-Plate Plus will be assessed by the percentage of subjects who, during the observation period — i.e., from plate implantation to the first follow-up visit after plate removal — experienced at least one complication certainly or potentially related to the investigational device. Such complications are defined as:
  - a Serious Adverse Device Effect (SADE), expected or unexpected;
  - a hardware failure (e.g., breakage, detachment, or bending of the plate or screws).
- **Secondary endpoint (benefit measure):**
  The clinical benefit of treatment with the 8-Plate Plus will be assessed by the percentage of subjects who, during the observation period — i.e., from plate implantation to the first follow-up visit after plate removal — achieved the treatment objective, defined as:
  - for hemiepiphysiodesis: partial or complete correction of the angular deformity of the femur and/or tibia towards the standard alignment direction (mMPTA and mLDFA between 85° and 89°);
  - for epiphysiodesis: partial or complete correction of femoral and/or tibial length discrepancy in relation to the morphologically normal contralateral limb length.

8.5 Methods of Endpoint Assessment

The **primary endpoint (safety measure)** of this Clinical Investigation will be assessed as follows:

- The correlation of a serious adverse event with the 8-Plate Plus will be freely determined by the Investigator according to the following options: not related / possibly related / definitely related. Serious events assessed as possibly or definitely related to the 8-Plate Plus will be included in the safety measure calculation.
- It is understood that, for serious events judged as possibly or definitely related to the 8-Plate Plus, the Sponsor reserves the right to supplement the Investigator's assessment with the opinion of an independent orthopaedic surgeon. If the independent orthopaedic surgeon subsequently identifies a surgical technique error in the primary implantation, in agreement with the Investigator, the event initially classified as possibly or definitely related to the 8-Plate Plus may be reclassified as not related and, consequently, excluded from the safety measure calculation. Similarly, serious adverse events due to use not compliant with the manufacturer's Instructions for Use (off-label use) will be excluded from the safety measure calculation.

The **secondary endpoints (benefit measures)** of this Clinical Investigation, as described above, will be assessed by comparing, for each patient, the preoperative radiographs (untreated deformity) with the radiographs collected at the plate removal visit (Visit 4).

The data related to the primary and secondary endpoints, already available in the patients' medical records, will be:

- entered into the validated electronic database provided free of charge by the Sponsor to each Investigator for data collection within the Clinical Investigation;
- analysed using descriptive and/or quantitative statistics and presented with the corresponding confidence intervals (for further details, see the *Statistics* section of this Clinical Investigation Plan).

8.6 Patients selection

A paediatric patient in the growth phase, i.e., with open growth plates at the time of treatment, affected by angular deformities and/or femoral and/or tibial length discrepancies who, in the Investigator's sole judgement, had a valid indication for surgical treatment with the 8-Plate Plus and was treated with the investigational device, will be considered eligible for retrospective data collection as defined in the Clinical Investigation Plan.

Eligible patients who meet the following inclusion criteria and none of the exclusion criteria will be deemed suitable for participation in this Clinical Investigation.

8.6.1 Inclusion criteria

A patient will be considered eligible for participation if:

- he/she has been diagnosed with an angular deformity or a femoral and/or tibial length discrepancy;

- at the time of treatment, he/she was younger than 18 years of age;
- at the time of treatment, the growth plates of the treated limb(s) were not yet closed;
- in the opinion of the Investigator, the angular deformity and/or length discrepancy represented a valid indication for surgical treatment with tension band plates;
- the deformity was treated with the 8-Plate Plus, in accordance with the manufacturer's Instructions for Use;
- the treatment with the 8-Plate Plus was completed and the patient underwent at least one follow-up visit after plate removal;
- the clinical data of the patient required for the evaluation of the device's safety and clinical benefit are still available.

8.6.2 Exclusion criteria

A patient will not be considered eligible for participation if:

- he/she was treated with the 8-Plate Plus to correct deformities of the upper limbs only and not of the lower limbs;
- his/her clinical data are no longer accessible and/or do not allow the evaluation of the safety and clinical benefit of the investigational device;
- he/she had a medical condition that constitutes a contraindication to treatment with the 8-Plate Plus according to the manufacturer's Instructions for Use;
- he/she was concomitantly treated with a non-permitted device that could not be removed without compromising the patient's safety.

8.7 Number of Patients Expected to be Enrolled

The sample size was therefore calculated by estimating the number of implants required so that the confidence limits of the study's primary endpoint for the 8-Plate Plus (i.e., the percentage of subjects who experienced at least one complication certainly or possibly related to the investigational device, as described above) fall within the safety profile of the state of the art for this treatment, namely within the safety data reported in the literature for its predecessor (the GGS) and for other equivalent medical devices.

Specifically, the scientific literature reports that the percentage of patients treated with a tension band plate for a lower limb deformity who experienced at least one device-related complication ranges from 3% to 12%, depending on several factors, primarily the heterogeneity of the primary diagnosis [7].

Assuming that the expected percentage of patients with at least one complication certainly or possibly related to the device for the 8-Plate Plus will be 3%, the sample size calculation showed that, in order for the upper limit of the 95% confidence interval for the primary endpoint (calculated using the exact binomial method) to remain below 12% (i.e., 9.94%), 70 implants are required.

As each patient may have been treated for the correction of multiple deformities located in different long bones, it is understood that each eligible subject may contribute data for more than one implant (on average 2). For this reason, approximately 40 patients are expected to be enrolled.

8.8 Enrollment Point

Each eligible patient, for whom the Investigator has verified compliance with the inclusion criteria, will be considered enrolled in the Clinical Investigation at the moment the Investigator assigns the subject a unique, predefined, and sequential study code, according to the data collection procedures described in this Clinical Investigation Plan.

8.9 Clinical Investigation Duration

Given the retrospective nature of the Clinical Investigation and considering that the consent of eligible patients had already been obtained a priori, no study-specific procedures will be required of the patient. The duration of the study therefore foresees 2 months for patient screening and 4 months for retrospective data collection.

It is understood that the Sponsor, after database lock, unless otherwise agreed with the Investigators and/or the Ethics Committees, reserves a period of 4 months for end-of-study activities, namely:

- database review;
- opening and resolution of potential queries to the Investigators;
- drafting of the statistical report;
- drafting of the clinical report;
- site close-out visits;
- end-of-study notifications to the relevant Ethics Committees and Competent Authority.

8.10 Medical-Surgical Procedures and Clinical Investigation Follow-up

The Investigator will include in the study those patients who, at the selection visit (Visit 0), meet all eligibility criteria. It is understood that, given the retrospective nature of the study and considering that the consent of eligible patients was obtained a priori, patients will not attend the selection visit nor any subsequent visits. Furthermore, during the selection visit (Visit 0), the Investigator will collect the patient's demographic data and medical history.
The data to be collected are as follows:

- Demographics and BMI
- Medical history
- Indication(s) treated
- Deformity parameters:
    - hip-knee-ankle angle (HKA)
    - anatomical lateral distal femoral angle (aLDFA)
    - mechanical axis deviation (MAD)
    - mechanical lateral distal femoral angle (mLDFA)
    - mechanical medial proximal tibial angle (mMPTA)
    - lateral distal tibial angle (LDTA)
    - fibular station
    - femur, tibia, fibula length
    - tibia-to-fibula ratio
    - femur-to-tibia ratio

Subsequently, data of interest related to the surgery for plate implantation (Visit 1) and to the treatment period — i.e., the two postoperative follow-up visits (Visits 2 and 3) up to plate removal (Visit 4) — will be collected. In particular, the following data will be gathered:

- Age at surgery
- Surgical details (duration, complications, postoperative X-ray) and data related to the implanted device(s) (i.e., quantity, type, and size)
- Concomitant medications and treatments
- Achievement of the treatment objective
- Treatment duration (calculated from implantation to removal)
- Complications (both device-related and non–device-related, leading or not to premature removal or unplanned surgery).

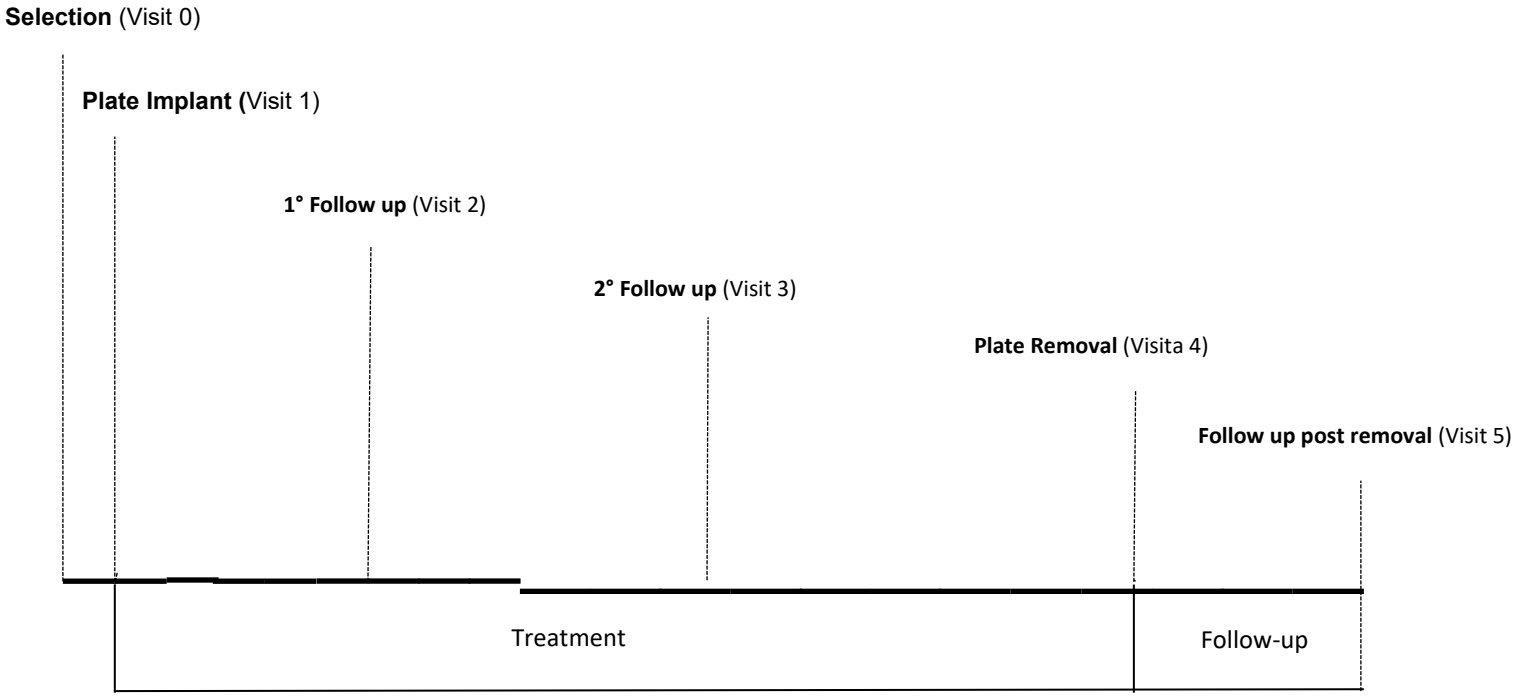
The course of treatment will be monitored as per routine clinical practice, and data corresponding to the follow-up visit, scheduled on average 4 months after plate removal (Visit 5), will be collected. At the follow-up visit, the following additional information will be recorded:

- Concomitant medications and treatments relevant to the study
- Status of the corrected deformity
- Deformity rebound
- Complications/Adverse events occurring after plate removal.

The Clinical Investigation data will be recorded in the patient's medical record and entered into a validated electronic data capture system provided by Orthofix Srl.

Note:
The visits and procedures described above are summarised in the patient treatment flowchart and in the table of procedures applicable to each visit.

8.11 Patient Treatment Flowchart



The patient treatment schedule follows the routine clinical practice of the participating Centre. However, certain visits may not be applicable depending on the type of patients included in the study.

8.12 Table of procedures

PHASE		ENROLLMENT	TREATMENT				FOLLOW UP
VISIT	Number	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Type	Selection	Implant	1° Follow up	2° Follow up	Removal	Follow up post removal
Selection Criteria Verification		x	x	x	x	x	x
Demographics		x					
Medical History		x					
X-rays		x				x	
Technical Characteristics of the Device			x				
Device Implantation			x				
Safety Measures			x	x	x	x	x
Benefit Measures		x				x	

8.13 Foreseeable Factors That Could Have Affected the Results

This Clinical Investigation is retrospective in nature; therefore, the clinical protocols observed are those applied at the participating Centre during the observation period of the Study.

The use of tension band plates for the treatment of angular deformities or limb length discrepancies is based on careful postoperative monitoring to avoid foreseeable complications, such as secondary deformity due to overcorrection, recurrence of deformity, or accidental physeal fusion. It is necessary to allow sufficient time for the plate to achieve its optimal effect on growth deceleration: studies suggest that its ability to slow growth is lower during the first 6–12 months, until adequate tension has accumulated across the plate to enable temporary compression of the growth plate.

In this Clinical Investigation, the enrolled patients correspond to the paediatric population without age restrictions, as indicated in the Instructions for Use. Based on these considerations, two factors are known that may compromise outcomes and the interpretation of the results, namely:

- The risk of inducing unintended physeal fusion, particularly if the plate remains implanted for more than two years. This can become a greater problem if a child is treated at a very early age, as premature unintended physeal fusion would have a significant impact on overall limb growth.
- The need for a second treatment if the procedure is performed at a very early age. This eventuality may particularly arise in cases of deformities due to metabolic or genetic disorders. Once the plate is removed, the angular deformity may recur (rebound effect).

8.14 Discontinuation and Withdrawal of Subjects from the Clinical Investigation

A patient will be considered prematurely discontinued from the study if, during the collection of data related to the visits following screening, the Investigator becomes aware that one of the inclusion or exclusion criteria is no longer fulfilled.

Patients prematurely discontinued will be recorded in the case report form through the dedicated discontinuation visit. The Investigator will be required to notify the Sponsor of all prematurely discontinued patients and, if the patient is not evaluable, i.e., discontinued before plate removal, may agree with the Sponsor on the replacement of the patient according to the procedure described below.

8.15 Patients Replacement

Subject to prior notification to the Sponsor, and no later than the study database lock, non-evaluable patients may, at the Investigator's discretion, be replaced with a patient who will be assigned a new and unique identification code.

This procedure is intended solely to increase the likelihood of achieving the planned sample size in terms of evaluable implants. It is understood that the Sponsor will also collect, retain, and analyse the data of patients who were prematurely discontinued and subsequently replaced.

9 Clinical Investigation Monitoring Plan

In order to ensure the proper conduct of the study and the accurate recording of study data, at least the following monitoring visits will be foreseen:

- site initiation visit;
- one monitoring visit during the active conduct phase of the study;
- site close-out visit.

It is understood that, if necessary, the Sponsor reserves the right to perform additional monitoring visits during the active phase of the study.

Prior to each visit, the monitor will contact the Investigator to verify availability and schedule the visit date, and will subsequently send written confirmation specifying the purpose of the visit and any documents to be made available.

At each visit, the monitor shall:

- check the updating of study documentation;
- verify that data collection related to the Clinical Investigation is being conducted appropriately and that data are recorded and reported in compliance with this Clinical Investigation Plan, Good Clinical Practice (GCP), and applicable regulations;
- verify the accuracy of the data entered into the case report form against the source data;
- implement any necessary corrective actions.

Note: Written Monitoring Plan
For this type of Clinical Investigation, which is single-centre, observational, and retrospective, a separate written Monitoring Plan is not foreseen, since all necessary information is already included in the Clinical Investigation Plan.

Note:
The Sponsor intends to monitor all reported data related to the inclusion and exclusion criteria, the study endpoint variables, and all information regarding serious and non-serious adverse events. If deemed appropriate and necessary, other study data may also be subject to monitoring.

10 Documentation

During the site initiation visit, the monitor will provide the Principal Investigator responsible for the Clinical Investigation with a file containing all the paper documentation required for study management, namely:

- Clinical Investigation Plan with related Synopsis and appendices;
- copy of the approval from the relevant Ethics Committee;
- one original copy of the signed and authorised financial agreement;
- contact details for the participating Site;
- information regarding the medical device under investigation (Instructions for Use and surgical technique);
- certification of the CE marking of the device;
- one copy of the case report form;
- access credentials for the eCRF and user manuals for the platform.

Note:
The monitor will also provide an electronic, non-modifiable copy of all study documentation for consultation and printing, as required by the Investigator.

As required by Good Clinical Practice guidelines:

- in order to prevent accidental or premature destruction of study documents, the Investigator shall store the file in a secure environment with controlled access;
- for the entire duration of the Clinical Investigation, study documentation must be kept up to date and made available during monitoring visits;
- study documentation must be retained for as long as possible and, at a minimum, for 7 years after completion or termination of the Study.

Should the Investigator rely on a third party for document archiving, he/she must notify the Sponsor of the storage location and the procedure for transferring the file.

11 Data Management

No later than the Study Initiation Visit, the Sponsor will provide, free of charge, an electronic data capture system (eCRF), named **Symphony**, in which all data pertaining to the present Clinical Investigation will be collected.

Symphony is an Electronic Data Capture (EDC) solution developed and validated by **Arithmos Srl**, a company certified according to ISO 9001 and ISO 27001 standards. Symphony therefore operates under an Information Security Management System compliant with international regulatory standards, and ensures regulatory adherence by monitoring and archiving the audit history directly within the platform.

For further details, please contact:

ARITHMOS Srl
Via Roveggia 122 – 37136 Verona, ITALY
Tel.: +39 045 58549
Fax: +39 045 8209471
E-mail: info@arithmostech.com

No later than the Study Initiation Visit, the Sponsor will provide Investigators with the necessary training for the proper use of Symphony. If required, the Sponsor will also maintain a free help desk service throughout the duration of the Clinical Investigation to support Investigators.

Each Investigator will be able to access Symphony via the internet using personal login credentials and will only have visibility of the data relating to patients enrolled at their own site.

The clinical data collected within the present Clinical Investigation will be processed by the Sponsor in an anonymised form, in compliance with European data protection legislation, namely Regulation (EU) 2016/679 – the General Data Protection Regulation (GDPR).

12 Quality Assurance

In order to ensure the proper conduct of the Clinical Investigation in compliance with Good Clinical Practice, UNI EN ISO 14155:2019 and subsequent updates, and in accordance with the provisions of the present Clinical Investigation Plan, the Sponsor:

- has established a monitoring plan (as described above);
- furthermore, if deemed necessary, either during or after the active phase of the Investigation, the Sponsor's Quality Assurance Department (as well as national or international regulatory authorities) may conduct an audit at the Site, with at least 15 days' prior notice.

13 Protocol Deviations

All deviations from the present Clinical Investigation Plan, whether identified by the monitor during site visits or spontaneously reported by the Investigator, will be recorded by the Sponsor and retained within the study-related documentation.

Each deviation will be assessed by the Sponsor and classified as either a major or a minor deviation. Following this evaluation, the Sponsor will implement corrective actions as required by Good Clinical Practice (GCP) to prevent recurrence and, if necessary, will promptly inform all Investigators and the relevant Ethics Committee.

Furthermore, at the conclusion of the Clinical Investigation, the list of deviations will be reviewed to determine whether any of them may have compromised the interpretation of the affected results.

14 Amendments

In the event that amendments to the present Clinical Investigation Plan become necessary, the Sponsor shall:

- classify the nature of the amendments as substantial or non-substantial;
- revise the Clinical Investigation Plan and any study documentation impacted by the amendments, ensuring that all changes are appropriately tracked;
- in the case of non-substantial amendments, promptly notify in writing the participating Site and the corresponding Ethics Committee for information purposes, providing copies of the revised documents;
- in the case of substantial amendments, suspend the Clinical Investigation until a new favourable opinion has been issued by the relevant Ethics Committee.

15 Adverse events

The foreseeable adverse events related to the use of the 8-Plate Plus, as identified through the risk analysis performed during product design, are described in the section *"POSSIBLE ADVERSE EFFECTS"* of the device's Instructions for Use (http://abs.orthofix.it/db/resources/PQ_EPP.pdf).

This Clinical Investigation is a retrospective observational study and, therefore, does not pose additional risks to patients or Investigators.

Definitions:

- An *adverse event (AE)* is any undesirable experience associated with the use of the device in a patient.
- An *adverse event* is defined as a *serious adverse event (SAE)* when, as a consequence of such event, the patient:
    - dies;
    - experiences a life-threatening event;
    - requires prolongation of hospitalisation;
    - requires re-hospitalisation;
    - suffers permanent disability;
    - experiences a congenital anomaly or birth defect.

Expected Serious Adverse Device Effects (SADEs) — i.e., those already reported in the device Instructions for Use — are further classified as **E(SADE)** (*Expected SADE*). Conversely, Serious Adverse Device Effects not previously reported in the device Instructions for Use are further classified as **U(SADE)** (*Unexpected SADE*).

All adverse events and adverse device effects associated with the use of the device that occurred during the entire observation period of the Clinical Investigation will be classified and reported to the Sponsor via the electronic database provided by the Sponsor.

Since this is a retrospective Clinical Investigation, serious adverse events (SAEs), having already followed the reporting procedures of the vigilance system, are not subject to prompt notification upon awareness, as otherwise required by GCP (Section 4.11.1).

16 Statistics

The safety profile of the 8-Plate Plus, as measured in the present Clinical Investigation, will be compared with the safety data reported in the scientific literature for the treatment of lower limb deformities by guided growth performed with equivalent tension-band plates.
The sample size calculation was performed in order to estimate the confidence intervals for the primary endpoint (safety outcome related to treatment response) of the 8-Plate Plus and to enable a reliable comparison with the data reported in the literature.
Accordingly, the sample size was determined by estimating the number of implants required so that the confidence intervals for the study primary endpoint with the 8-Plate Plus would fall within the established safety profile for this treatment, namely within the range of safety data reported in the literature for its predecessor (the GGS) and for equivalent medical devices.
Specifically, the scientific literature indicates that the proportion of patients treated with a tension-band plate for lower limb deformity who experience at least one device-related complication ranges between 3% and 12%, depending mainly on the heterogeneity of the underlying diagnosis.
Assuming that the expected proportion of patients experiencing at least one complication with the 8-Plate Plus is 3%, the sample size calculation showed that, in order for the upper limit of the 95% confidence interval for the primary endpoint (calculated using the exact binomial method) to remain below 12% (i.e., 9.94%), a total of 70 implants (in approximately 40 patients) are required.
The clinical data collected during the present Clinical Investigation will be analysed using descriptive statistics:

- the primary endpoint will be presented as a percentage value with its corresponding 95% confidence interval;
- the secondary endpoint will be presented as a percentage value with its corresponding 95% confidence interval.

The clinical data obtained from this Clinical Investigation will be used to complete the evaluation of the clinical performance and safety of the 8-Plate Plus, with the objective of confirming that the device can be considered safe and effective as hypothesised during its development, based on the preclinical evaluations conducted for CE marking.

17 Publication of Results

The Investigators and the Sponsor agree to maintain the clinical data collected during the present Clinical Investigation as confidential until such information is made publicly available, in anonymised form, by the Sponsor at the conclusion of the Investigation.
Within four months of the last site close-out visit, the Sponsor will be responsible for making the Investigation data public through the preparation of the final clinical report, containing aggregated and analysed site data, which will be provided to the Investigators, the involved Ethics Committee, and the Competent Authority.
Furthermore, within six months of the finalisation of the clinical report, the Sponsor reserves the right to publish a manuscript containing the aggregated and anonymised data from the monocentric study.
At the end of the Investigation, the Sponsor will make available to the Site the results pertaining to the patients enrolled in the study for publication purposes.
The Sponsor reserves the right to present the results of this study at scientific meetings and to submit these data to national and international authorities. At the same time, the Sponsor acknowledges the right and interest of all participating Investigators to publish scientifically, or to disseminate at congresses and meetings, the results obtained from the present Clinical Investigation.

18 Data Publication Policy

The Sponsor undertakes to share with all Investigators, for information and review, any preliminary version of the manuscript prior to publication.

Any publication by an Investigator may take place only after the potential publication by the Sponsor. It is understood that:

- the Investigator may initiate a publication prior to the Sponsor's publication only with the Sponsor's written consent;
- if, within six months from the finalisation of the clinical report, the Sponsor has not initiated any publication, the Investigator shall be free to publish the results obtained at his/her Site without requiring the Sponsor's written consent.

Prior to any publication or presentation of results, Investigators agree to submit in due time (in any case not less than 30 days before publication or presentation) the manuscript/abstract/presentation to the Sponsor for review and approval. The Sponsor undertakes to provide feedback within 15 days of receipt of the draft.

It is understood that the Sponsor's review is intended to ensure the accurate elaboration and presentation of the Investigation results. Any modifications proposed by the Sponsor shall in no way interfere with the scientific nature and content of the publication.

The identity of the Sponsor and the nature of its contribution to the present Clinical Investigation shall be clearly disclosed in any publication or presentation at congresses or meetings, in full respect of data transparency in clinical research.

19 Authorship

In compliance with the *"Uniform Requirements for Manuscripts Submitted to Biomedical Journals"* of the International Committee of Medical Journal Editors (ICMJE) [8], authorship of the manuscript will be granted to all individuals who meet the following criteria:

a) have made a substantial contribution to the conception or design of the study, or to the acquisition, analysis, or interpretation of data;

b) have made a substantial contribution to drafting the article or to critically revising it for important intellectual content;

c) have provided final approval of the version to be published.

All other participants who contributed to the study (either by enrolling patients or in other ways) will be acknowledged in the *Acknowledgements* section of the manuscript. For any other circumstance, the guidance provided by the ICMJE [8] will be followed and respected.

20 References

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