Clinical Investigation Plan (CIP)

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A single center post-market clinical follow up (PMCF) observational study evaluating the clinical performance and the safety profile of the *JuniOrtho™ Plating System™* (JPS) for the treatment of congenital deformities and fractures in lower limb of pediatric and adult patients

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By my signature below, I acknowledge that I have read this protocol and I agree that it contains all necessary details for carrying out the clinical investigation described therein. Furthermore, I agree to conduct this study in compliance with said Clinical Investigation Plan, the ICH Good Clinical Practice guideline, as well as with any and all applicable federal, state or local laws and regulations and with my contractual obligations towards *Orthofix S.r.l.* or its representatives.

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3. LIST OF ABBREVIATIONS

CRF	Case Report Form
CRO	Contract Research Organization
CV	Curriculum Vitae
DB	Database
AE	Adverse Event
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/IRB	Independent Ethics Committee/Institutional Review Board
JPS	JuniOrtho™ Plating System™
MDDs	Medical Device Deficiencies
PMCF	Post-Market Clinical Follow-up
QOL	Quality of Life
ROM	Range of Motion
SAE	Serious Adverse Event
SOA	State-of-art
WBI	Weight Baring Index

4. SYNOPSIS

TITLE	A single center, post-market clinical follow up (PMCF) observational study evaluating the clinical performance and the safety profile of the *JuniOrtho™ Plating System™* (JPS) for the treatment of congenital deformities and fractures in lower limbs of pediatric and adult patients.
ACRONYM	OCI_JPS
MEDICAL DEVICE (MD)	*JuniOrtho™ Plating System™* (JPS) JPS is a complete plating system designed to address the specific demands of advanced deformity and trauma reconstruction of the lower extremities in pediatric population. Moreover, where bones size is appropriate, JPS can also be applied on adult patients. The system was designed for the treatment of proximal femur, distal femur, proximal and distal tibia fractures, where plating is one of the options.
RATIONALE	Orthofix Srl put the JPS on the European market (2019) by the mean of a pre-market clinical evaluation made under the Medical Device Directive (MDD) requirements that were based on the analysis of the scientific literature of equivalent devices. This study has been planned as part of the Orthofix Srl post-market active surveillance plan for the collection of data on both the clinical performance and the safety profile of the JPS in a representative population of patients and users. The rationale of the proposed study is to update and support the pre-market clinical evaluation of the JPS with real-word-evidence clinical data, in order to confirm the benefit/risk ratio of this medical device and to keep the CE mark under Medical Device Regulation (MDR) requirements.
STUDY DESIGN	PMCF Study: Post-market, observational (retrospective and prospective), single-center, not controlled.
PROCEDURES	One selected site that is experienced in the treatment of pediatric and adult patients with bone deformities and fractures, where the usage of JPS is already part of the normal clinical practice, will participate in this study. Investigator will provide data for a maximum of 40 JPS implant cases satisfying inclusion and exclusion criteria (predicted drop out rate is 10%) that will contribute for at least 30 cases treated by JPS (note that some patients may contribute for more than one JPS case, according to how many JPS implants were received). For retrospective study cohort, who has previously had JPS implanted and follow-up assessment and JPS removal is done, the investigators shall purely collect clinical data from the medical record of the subjects, concerning the screening criteria, the surgery (MD application) and 4 following events: hospital discharge, first post-application control, bone consolidation assessment and device removal. Data from patients' observation are collected according to the site standard-of-care. Patients, who are prospectively enrolled in the study and have undergone JPS implantation, will have follow-up assessments, as described on Table 10.2, or until patient withdrawal.

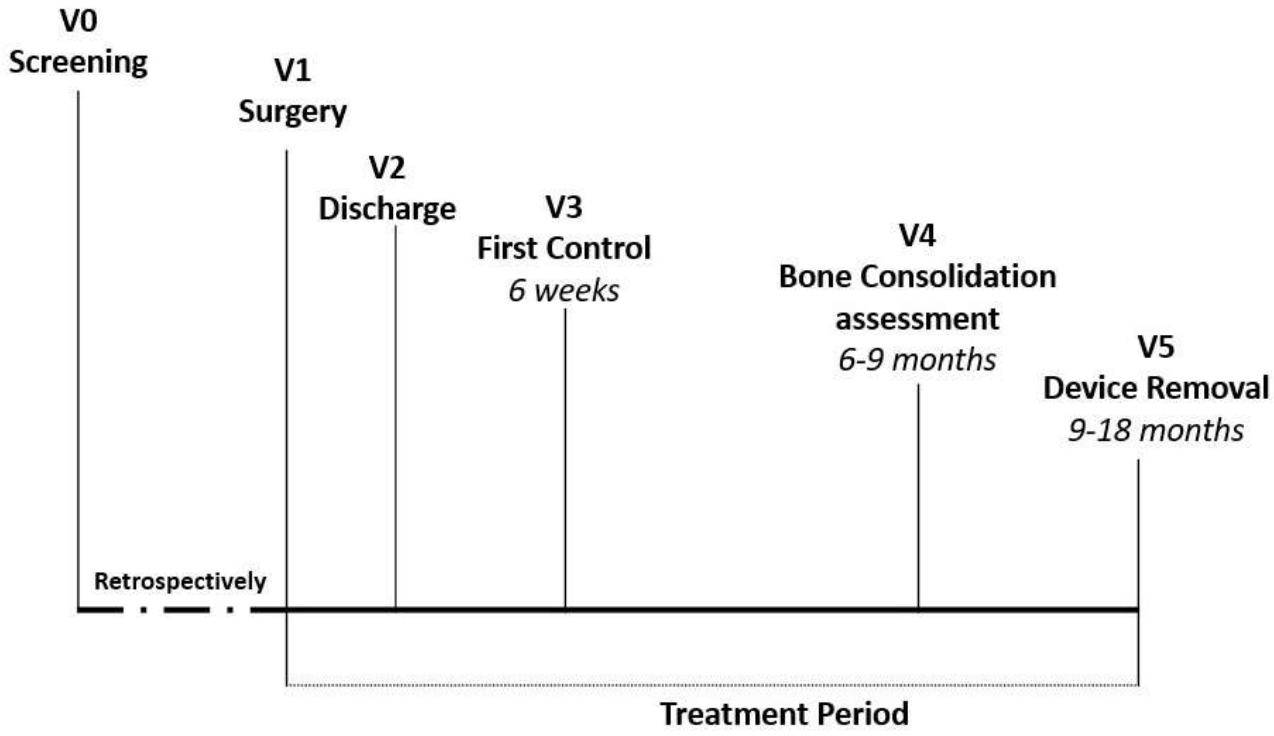
	The patient data will be systematically collected by the investigator in eCRF. As per CIP, the subjects will not undergo additional visit nor non-invasive, invasive or burdensome procedures additional to those performed under the normal clinical practice.
OBJECTIVES	The objectives of this study are to assess: - the safety profile (primary objective) - the clinical performance (secondary objective) of the JPS within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.
SAFETY ENDPOINTS	The safety profile of JPS will be assessed by the following safety endpoints: - Percentage (%) of subjects with at least one serious/not serious adverse event certainly related or possibly related to JPS (ADEs) (primary safety endpoint) at device removal follow-up (up to 18 months according to site's standard practice); - Percentage (%) of MD Deficiencies (MDDs) at device removal follow-up (up to 18 months according to site's standard practice).
EFFICACY ENDPOINTS	The clinical performance of JPS will be assessed by the following efficacy endpoints: - Percentage (%) of subjects that reached a satisfactory bone consolidation according to investigator's opinion (primary efficacy endpoint); - Percentage (%) of subjects that maintained bone correction alignment according to investigator's opinion until device removal.
PLANNED STUDY PERIOD	**First Patient in** *4Q 2022* **Last Patient in** *2Q 2023* **DB closure** *2Q 2024 (anticipated)*
STUDY DURATION FOR THE SUBJECT	Provided the study is observational. The estimated time of patient observation period is 18 months.
SITE(S) / COUNTRY(IES)	1 Investigational Site in Germany
PATIENTS / GROUPS	Clinical data to be collected only on patients with a regular indication for JPS as per IFU (no off-label use will be included): the system is intended in pediatric (excluding newborns) and small stature adult (that according investigator judgement the patient's anatomy is deemed suitable for the use of JPS plate). Pediatric patients include infants (greater than 1 month to 1 years of age), children (greater than 1 to 12 years of age), adolescents (greater than 12 to 18 years of age) and appropriate adults (where according to investigator assessment, the JPS plates fit the treated bone anatomy).
INCLUSION CRITERIA	A patient will be eligible for inclusion in the study if: • had a regular indication for surgical intervention with JPS according to the manufacturer's IFU; • underwent a surgery for bone deformity correction or trauma reconstruction of the lower extremities performed by JPS; • the clinical data registered in her/him patient chart are sufficient to assess the safety and efficacy endpoint of the study (for retrospective patients);

	• patient (or his/her legally acceptable representative) is capable of understanding the content and is willing to sign the Informed Consent Form (ICF) • patient is willing and able to participate in the data collection and comply with the protocol requirements;
EXCLUSION CRITERIA	A patient will be excluded from participation in the study if he/she: • had/has a medical condition that is a contraindication according to the manufacturer's instruction for use leaflet; • had/has a concomitant not permitted device which cannot be safely removed; • patient for whom there are other concurrent medical or other conditions that in the opinion of the participating investigator may prevent participation or otherwise render patient ineligible for the study.
COMPARATIVE DEVICE	Not applicable (the study is not controlled)
PERMITTED CONCOMITANT DEVICE	K-wires and any other concomitant devices, i.e. bone screws, that were applied to fix any bone fragments but that were not considered critical for the maintenance of treated bone alignment, are permitted during the treatment. It is understood that any necessary medical devices applied on any other bones other than the one treated by JPS are permitted as well.
QUALITY OF LIFE (QOL)	A QOL questionnaire is not performed in the normal clinical practice of the site participating this study. Provided clinical data will be retrospectively collected, it will not be possible to report a QOL questionnaire as a study result. Anyway, when available, the range of motion (ROM) of the treated limb and the weight bearing index will be collected and assessed as representative variables for the evaluation of the QOL of the enrolled Subjects.
STATISTICAL METHODOLOGY	Hypothesis to test: the observed primary safety endpoint for JPS ranges within the state-of-art (SOA) safety profile of equivalent plating systems. Primary safety endpoint: the proportion of subjects (% ± the upper and lower of limit of the 95 % confidence interval) with at least one serious/not serious adverse event surely or possibly related to JPS. State of art: The proportion of subjects with serious/not serious adverse event related or possibly related to the device reported in the scientific literature for the treatment of congenital deformities and fractures in lower limb of pediatric and appropriate adult patients by the means of equivalent plating systems is between 5.1 % and 15.0 % depending on many factors, mainly the diversity of the primary diagnosis. Assumption: for the sole purpose of the sample size calculation, it was required to assume an expected proportion of subjects for the primary safety endpoint of JPS. The sample size, therefore, was calculated estimating the required number of subjects so that the upper limit of the 95% confidence interval for the expected proportion is ranged within the SOA (i.e. 95% CI upper limit ≤ 15 %).

	Sample size calculation: assuming the expected proportion of patients with at least one serious/not serious adverse event surely or possibly related to JPS will be 3 %,and assuming the worst case of each patient contributing for only one JPS implant case: 30 subjects 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 15 %. Considering that one patient can contribute for ore that one JPS implant, and considering a 10% drop out rate, the site can enroll a maximum of 40 JPS implant cases.
INTERIM ANALYSIS	An interim analysis, not planned at the start of the study, will be performed after at least 20 subjects will be enrolled and completed the "Bone Consolidation" event. The aim of this interim analysis is to verify the consistency of testing hypothesis and to confirm the historical data on the medical device safety and performance. Interim results will be used to prepare the Clinical Evaluation Report (CER). To preserve the integrity of the study results interpretation, a correction for multiplicity due to two planned analyses (interim+final) will be implemented using the approach proposed by O'Brian-Fleming for sequential design (Shein –Chung Chow et Al Sample size calculations in Clinical Research 2003, Christopher Jennison et Al Group Sequential Methods with applications to clinical Trials,2000) For this purpose, sample size will be recalculated using this approach (all details are reported in the cited bibliography): - The initial sample size will be correct by factor 1.008 for a two-sided test at 5% level and 80% power. The final sample size is 30*1.008=30.2 - The probability level will be correct by factor 1.977, at interim the P value will be 0.0052 while at the final analysis P value will be 0.048. The corresponding confidence limits will at interim 99.5% and at final analysis 95.2% In conclusion, applying the O'Brian-Fleming approach to control the type I error no great impact on sample size is observed and integrity of clinical study is preserved from any interpretation bias.

4.1 Schematic Diagram

Figure 4.1 Schematic diagram of events related to standard-of-care treatment



Notes: Timelines are estimated as average of the site normal clinical practice.

The term "Visit" and "Event" are used as synonyms to indicate the steps collected by this observational study.

5. INTRODUCTION

A manufacturer of a medical device must demonstrate that the intended purpose(s) and claim(s) made in relation to safety and performance of a Medical Device are achieved. As a general rule, such demonstration will require clinical data. Clinical data is data which is relevant to the various aspects of the clinical safety and performance of the device. This may include data from prospective and retrospective clinical investigations of the device concerned as well as market experience of the same or equivalent devices and medical procedures and information from the scientific literature.
The aim of the present study is to collect post-market clinical evidence (post-market clinical follow up - PMCF) on the use of the medical device JuniOrtho Plating System (JPS).

5.1 Background Information

Principles of bone fixation through plating systems

Plating systems are treatment options for bone fixation, indeed they are intended to provide bone fragments stabilization in case of bone fracture or osteotomy. Fixation works by blocking movements that would prevent the normal biological process of callus formation and consolidation. Excessive movement would otherwise increase the incidence of delayed union or nonunion. The very same principle is exploited when surgical fusion of bone fragments is sought, for example in joint arthrodesis or after surgical osteotomies performed to correct a limb deformity.

The JPS is a complete plating system designed to address the specific demands of advanced deformity and trauma reconstruction of the lower extremities in pediatric population and small stature adults. The system is intended for internal fixation and stabilization of fractures, osteotomies, mal-unions and non-unions of long bones of the lower limb.

Indications (as per IFU)
The JPS is intended for internal fixation and stabilization of fractures, osteotomies, mal-unions and non-unions of long bones of the lower limb.
The JPS is indicated for internal fixation and stabilization of femoral and tibial fractures, osteotomies, mal-unions and non-unions. Indications include:
• Varus, valgus, rotational and/or shortening osteotomies
• Femoral neck and/or pertrochanteric fractures
• Proximal and distal metaphyseal fractures
• Pathological and impending pathological fractures
Use of the JPS JuniOrtho Plating System™ is indicated in pediatric (excluding newborns) and small stature adult patients.

5.2 Rationale of the Clinical Investigation and justification of vulnerable group

Orthofix Srl put the JPS on the European market (2019) by the mean of a pre-market clinical evaluation made under the Medical Device Directive (MDD) requirements that was based on the analysis of the scientific literature of equivalent devices.

This study has been planned as part of the Orthofix Srl post-market active surveillance plan for the collection of data on both the clinical performance and the safety profile of the JPS in a representative population of patients and users.
The rationale of the proposed study is to update and support the pre-market clinical evaluation of the JPS with real-word-evidence clinical data, in order to confirm the benefit/risk ratio of this medical device and to keep the CE mark under Medical Device Regulation (MDR) requirements.

The uniqueness of the pediatric population manifests itself in specific indications for lower extremity reconstruction, mostly due to congenital deformities or conditions; different approach in compliance with postoperative care or need for adaptability to rapid growth and development. The JuniOrtho™ Plating System™ (JPS) is a well established, marketed device, commercially available and used as standard device in orthopedic surgeries.

The post-marketing, retrospective/prospective study with CE-marked device JuniOrtho™ Plating System™ (JPS) is designed for gathering real-world medical data from treatment of congenital deformities and fractures in lower limb of pediatric and in small stature adult patients.

All data will be collected from standard medical documentation of patients who have already been treated with JPS. Additionally, all procedures that patients underwent are justified by standard of care.

Constant identification of serious or unexpected serious risk related to the use of the device, especially in real-world experience may bring additional data, that can contribute to the safety of future patients.

In conclusion, patients will not directly benefit from the participation in this study but no additional risk related to the study participation is to be recognized.

6. STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of the study is to evaluate the safety profile of JPS within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.
In order to fulfill this objective, the safety profile of JPS will be assessed by the following endpoints:

- percentage (%) of subjects with at least one serious/not serious adverse event certainly related or possibly related to JPS (primary endpoint) at device removal follow-up (up to 18 months according to site's standard practice);
- percentage (%) of Medical Device Deficiencies (MDDs) at device removal follow-up (up to 18 months according to site's standard practice).

6.2 Secondary Objectives

The secondary objective of the study is to evaluate the clinical performance of JPS within the scope of its intended purpose, when used according to the manufacturer IFU on a representative population of subjects and users.
In order to fulfill these objectives the clinical performance of JPS will be assessed by the two following efficacy endpoints:

- percentage (%) of subjects that reached a satisfactory bone consolidation according to investigator's opinion;
- percentage (%) of subjects that maintained bone correction alignment according to investigator's opinion until device removal.

7. STUDY DESIGN

7.1 Research Type

This is a Post Market Clinical Follow-up (PMCF) study which is retrospective and prospective, observational, single-center, not controlled. All data from patients observation are gathered according to the site standard-of-care.

7.2 Subjects and Sites Numbers

This study will be conducted only on patients with a regular indication for JPS as per IFU (no off-label use will be included): the system is intended in pediatric (excluding newborns) and small stature adult patients. Pediatric patients include infants (greater than 1 month to 1 years of age), children (greater than 1 to 12 years of age) and adolescents (greater than 12 to 18 years of age) and appropriate adults (where according to investigator assessment, the JPS plates fit the treated bone anatomy).
This study includes only one site (monocentric) that is located in Wetter (Germany). The site was chosen for this study due to the number of subject devices already implanted, and the wideness of the indications covered by the surgeries. The site was also positively evaluated by sponsor for the appropriate qualification and competency of the investigator and of the staff, and availability of facilities and equipment.

7.3 Study duration

The follow-up period considered for this study lasts until the second surgery for JPS removal that, with the exception of clinical complications, is usually scheduled between 9 and 18 months after the surgery. (see table 10.2 “Events and Assessments Schedule”).
The estimated length of data collection period by the investigator is the time until all data is abstracted from clinical records. The data extraction from clinical record will finish after the plate removal of the last patient is completed.

7.4 End of Study (EOS)

The sponsor has the right to close this observational study at any time. The IEC must be informed.
The study will be terminated prematurely in the following cases:

- If the enrolment rate and data collection are significantly delayed;
- If the sponsor will be informed that the activities related to the study are conducted in conflict with the present protocol;
- Any other reason for the sponsor to deem that the prosecution of the study will harm the subjects’ health or rights.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 Subject Inclusion Criteria

A patient will be eligible for inclusion in the study if:

- had/has a regular indication for surgical intervention with JPS according to the manufacturer's IFU;
- underwent a surgery for bone deformity correction or trauma reconstruction of the lower extremities performed by JPS;
- the clinical data registered in her/him patient chart are sufficient to assess the safety and efficacy endpoint of the study (for retrospective patients);
- patient (or his/her legally acceptable representative) is capable of understanding the content and is willing to sign the Informed Consent Form (ICF);
- patient is willing and able to participate in the data collection and comply with the protocol requirements

8.2 Subject Exclusion Criteria

A Patient will be excluded from participation in the study if he/she:

- had/has a medical condition that is a contraindication according to the manufacturer's instruction for use leaflet;
- had/has a concomitant not permitted device which cannot be safely removed;
- patient for whom there are other concurrent medical or other conditions that in opinion of the participating investigator may prevent participation or otherwise render patient ineligible for the study.

8.3 Subject Withdrawal

Subjects must be withdrawn once he/she withdrew his/her consent for participation in the study (applicable for prospective cohort).
In all cases, subjects are withdrawn must be recorded in detail in the eCRF. Should the clinical investigation be discontinued prematurely, all clinical investigation materials (complete, partially completed and empty CRFs) will be retained.

9. TREATMENT OF SUBJECTS

9.1 Study Investigational Product(s)

General information
The JPS is a complete plating system designed to address the specific demands of advanced deformity and trauma reconstruction of the lower extremities in pediatric population and small stature adults. The system is intended for internal fixation and stabilization of fractures, osteotomies, mal-unions and non-unions of long bones of the lower limb.

Classification and Regulatory Status
The JPS is a Class IIb medical device according to the MDD 93/42.

9.1.1 Description of the Investigational Products

Device Description and Specifications
The JPS consists of 3 different plate sizes, identified as 3.0 mm, 3.5 mm and 5.0 mm, available in different lengths according to the anatomical application. Plates have been designed to accept bone screws of suitable diameters. Bone screws are available in 3 different diameters (3.0 mm, 3.5 mm and 5.0 mm corresponding to the plate size), they can be used with different lengths as well as in locking and non-locking options. Application and removal of the JPS can be performed using Orthofix general orthopedic instrumentation.

Materials
The implants are made from implant grade stainless steel AISI 316 LVM, conforming to ASTM F138 and ISO-5832.

9.1.2 Delivery and Storage Requirements

This study is a post-market investigation, therefore the dispensation of the device is through the standard market distribution. The device storage, accountability and preparation for use is under responsibility of the clinical site.

9.2 Concomitant Treatments

9.2.1 Permitted Concomitant Treatments (Medications and Therapies)

K-wires and any other concomitant devices, i.e. bone screws, that were applied to fix any bone fragments but that were not considered critical for the maintenance of treated bone alignment, are permitted during the study. It is understood that, any necessary medical devices applied on any other bones than the one treated by JPS are permitted as well.

9.2.2 Not Permitted Concomitant Devices

Not permitted devices on the same JPS-treated bone: others plates providing fixation; external fixators; intramedullary nails or elastic nails.

10. STUDY PROCEDURES

10.1 Description of Procedures

Throughout the pre-study meetings, it was assessed and confirmed that the clinical data collected for the study purpose are part of the standard clinical practice for the participating investigational site. As this is an observational study, there are no change or influence to the normal clinical practice of the investigator and patients, and no interference with the local hospital standard of care guidelines and/or the internal therapeutic protocols set and established at the investigational site.
For retrospective study cohort, who have previously had JPS implemented and follow-up assessment and JPS removal is done, the investigators shall purely collect clinical data from the medical record of the subjects, concerning the screening criteria, the surgery (MD application) and 4 following events: hospital discharge, first post-application control, bone consolidation assessment and device removal. Data from patients observation are collected according to the site practice. Please note that the term “Visit” and “Event” are used as synonyms to indicate the steps collected by this observational study.
Patients from the prospective cohort, who have undergone JPS implantation, will be observed in accordance with Table 10.2 or until patient withdrawal.
The patients’ data are systematically collected by the investigator in the eCRF provided by Sponsor.

10.2 Description Event by Event

10.2.1 V0: Screening and Baseline

Prospective patients who meet the eligibility criteria will be enrolled in the study. Patients who agree to enter the study must sign the approved Informed Consent Form. Consented patients will have performed assessments as outlined in this protocol.

During the screening the investigator will evaluate the eligibility of the patients, checking all inclusion and exclusion criteria. Only those patients who meet all inclusion and exclusion criteria will be enrolled in the study. For each JPS implant a unique case number will be assigned (ID), and reported in the eCRF. Considering that each patient can contribute for more than one JPS implant: one patient can have more than one ID. In the eCRF the IDs are linked to the first ID assigned to the same patient by the clinical site. The patients not enrolled for non compliance will be considered as screening failures and will not be entered in the eCRF. Only for the enrolled patient, the Investigator will collect the demographic data and the medical history of the patient including information concerning the limb to be treated with JPS (baseline) such as the radiographic images and clinical examination.

10.2.2 V1 (Day 0): Surgery

The investigator will collect information regarding the applied components of the JPS and the surgical intervention itself, including the intraoperative application time of fluoroscopy. The investigator will also collect X-ray images to assess the treatment outcome, and the medication prescribed after the surgery. From this visit and for the rest of the visits, the

Investigator will collect information about adverse events (AEs) and medical device deficiency (MDD).

10.2.3 V2 (1 Week +/- 2 days): Hospital discharge

The investigator to collect information regarding changes in the concomitant medication, WBI; ROM (when available in the medical file) AEs and MDDs, if any.

10.2.4 V3 (6 Weeks +/- 2 weeks): 1st control visit

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any, about the functional recovery of the treated limb (by the means of the ROM and the WBI when available), and about the bone healing consolidation by X-ray images.

10.2.5 V4 (6 to 9 Months): bone consolidation

The investigator will collect information regarding changes in the concomitant medication, AEs and MDDs, if any, about the functional recovery of the treated limb (by the means of the ROM and the WBI when available), and about the bone healing consolidation process by X-ray images.

10.2.6 V5 (10 to 18 Months): device removal

The investigator will collect information regarding the surgical intervention for removal, including the intraoperative application time, and post-operative X-ray images. The investigator will collect information about changes in the concomitant medication, AEs and MDDs, if any, about the functional recovery of the treated limb (by the means of the ROM and the WBI when available).

Table 10.2: Events and Assessments Schedule

PERIODS		ENROLMENT	TREATMENT				
EVENT	Number	*V0*	*V1*	*V2*	*V3*	*V4*	*V5*
	Type	*Screening*	*Surgery*	*Discharge*	*First control*	*Bone consolidation assessment*	*Device Removal*
	Time*	*N/A*	*Day 0*	*1 Week (± 2 days)*	*6 Weeks (± 2 weeks)*	*6-9 Months*	*10-18 Months*
Inclusion / Exclusion Criteria		X					
Medical History		X					
Concomitant medication		X	X	X	X	X	X
Demographics		X					
X-ray		X	X		X	X	X
Clinical Examination		X			X	X	X
Device application			X				
Range of motion		X		X	X	X	X
Weight bearing index		X		X	X	X	X
Safety Events			X	X	X	X	X
MDDs			X	X	X	X	X

Note: * timelines are estimated as average of the site normal clinical practice.

11. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

11.1 Adverse Events

11.1.1 Definition of Adverse Event (AE)

Based on ISO 14155:2020, an “adverse event” is defined as untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

This definition includes events related to the investigational medical device or the comparator.

This definition includes events related to the procedures involved.

For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Conditions or diseases diagnosed before subject inclusion in the study that are chronic but stable should not be recorded on AE pages of the CRF (they are a part of the Medical History). Chronic diseases which are diagnosed during subject participation in the study shall be recorded as AE/SAE.

11.1.2 Definition of Serious Adverse Event (SAE)

In accordance with ISO 14155:2020, Serious Adverse Event (SAE) is an adverse event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that either resulted in users, or other persons as defined by one or more of the following:

- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function including chronic diseases, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury, or permanent
- impairment to a body structure or a body function,

c) led to fetal distress, fetal death or, a congenital abnormality, or birth defect including physical or mental impairment.

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP without serious deterioration in health, is not considered a serious adverse event. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be recorded as the event.

Hospitalizations for the following reasons will not be recorded as SAEs:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions if not associated with the new occurrence of AE/SAE

- Hospitalization or prolonged hospitalization required to allow outcome measurement for the study if not associated with the new occurrence of AE/SAE
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study if not associated with the new occurrence of AE/SAE.

11.1.3 Relationship between an AE/SAE and the use of the medical device

All AE/SAE will be judged by both the reporting Investigator and the sponsor as having a reasonable causal relationship to the investigational medical device. The relationship between the AE/SAE and the investigational medical device is considered

- **Certain** when the AE/SAE occurs in a plausible time relation to the application of the device and cannot be explained by a concurrent disease or other devices, drugs or chemicals. The response to withdrawal of the device (de-challenge) should be clinically plausible. The event must be definitive using a satisfactory re-challenge procedure if necessary;
- **Possible** when the AE/SAE occurs with a reasonable time relation to the application of the device, but it could also be explained by a concurrent disease or other devices, drugs or chemicals. Information on device withdrawal (de-challenge) may be lacking or unclear;

The AE/SAE is **Not Related** to the use of the investigational device in case of:

- existence of a clear alternative explanation, and/or
- unreasonable temporal relationship between application and/or
- non plausibility.

11.1.4 Medical Device Deficiency (MDD)

A “device deficiency” is defined as an “Inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.” A Medical Device Deficiency (MDD) is a device deficiency related to the device used for the clinical investigation (for the present study it is the JPS) and, when applicable, related to the comparative devices as well (for this CI it is not applicable because it is a not controlled study).
Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling, also related to the ancillary devices provided with the MD..
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11.1.5 Procedures for Reporting and Recording AE, SAE and Medical Device Deficiencies

For the retrospective cohort the investigator will only collect AEs and MDDs already reported in medical file occurred since the application to the removal of the device.

For the prospective cohort, the investigator will follow the standard clinical practice to record data in the medical file, will follow the CA reporting procedure for any applicable case of AE and the manufacturer instruction to report any MDDs or AE as appropriate. Only after that, he will also record the AEs and MDDs in the eCRF.

For both cases the investigator, when reporting the event in the eCRF will assess:

- whether or not it is Serious and
- whether or not it is related to the use of the investigational device

, The investigator from surgery to device removal will record the AE on the Patient eCRF as appropriate. When applicable, the investigator should also provide any available information and diagnostic measurements (laboratory test, X-ray etc) related to the AE and store it in the eCRF.

In case of a serious adverse event related or possibly related to the investigational device, in addition to the recording of the adverse event in the eCRF, the investigator will send the compiled Safety Reporting Form (PO218-02 provided by the sponsor) to the following email addresses:

safetyclinicalstudiesintl@orthofix.com

Notification to Authorities by the sponsor

All SAEs related to an investigational procedure leading to death or imminent threat to death, a serious injury or disease, requiring a rapid corrective action must be notified by the sponsor to Competent Authority immediately or within 2 days at the latest.

In addition, as this is a PMCF observational study regarding a CE-marked device, the sponsor will comply with Articles 87 to 90 of MDR and detailed in MDCG 2023-3 (published in February 2023)

According to mentioned articles and guidelines, the sponsor will report to the competent authority all incidents that will occur during the use of the medical device covered by this study by specific reporting. For serious incidents with the most urgency, the reporting will be through Manufacturer Incident Report MIR 7.2.1 and sent to the competent authority with the most urgency and in any case no later than 10 days as well as to the local EC. For all other incidents, this timeline is within 30 days.

12. STATISTICS

12.1 Hypothesis

Hypothesis to test:
the observed primary safety endpoint for JPS ranges within the state-of-art (SOA) safety profile of equivalent plating systems.

State of art:
The proportion of subjects with serious/not serious adverse event surely or possibly related to the device reported in the scientific literature for the treatment of congenital deformities and fractures in lower limb of pediatric patients by the means of equivalent plating systems is between 5.1 % and 15.0 % depending on many factors, mainly the diversity of the primary diagnosis.

Assumption:
for the sole purpose of the sample size calculation, it was required to assume an expected proportion for the primary safety endpoint of JPS. The sample size, therefore, was calculated estimating the required number of subjects (considering the case the each patient contributes for only one JPS implant) so that the upper limit of the 95 % confidence interval for the expected proportion is ranged within the SOA (i.e. 95 % CI upper limit ≤ 15 %).

12.2 Sample size calculation

Assuming the expected proportion of patients with at least one serious/not serious adverse event surely or possibly related to JPS will be 3 %, 30 subjects (considering the case the each patient contributes for only one JPS implant) 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 15 %.

12.3 Safety and Clinical Performance endpoints

12.3.1 Efficacy endpoints

The clinical performance of JPS will be assessed by the following efficacy endpoints:

- percentage (%) of subjects that reached a satisfactory bone consolidation (primary efficacy endpoint);
- percentage (%) of subjects that maintained bone correction alignment until device removal (secondary efficacy endpoint).

12.3.2 Safety Variables

The safety profile of JPS will be assessed by the following safety endpoints:

- percentage (%) of subjects (± the upper and lower of limit of the 95 % confidence interval) with at least one serious/not serious adverse event surely or possibly related to

JPS (ADEs) (primary safety endpoint). Exact limits will be calculated by Chi-square test with Clopper option.

- percentage (%) of medical device deficiency (secondary safety endpoint). Exact limits will be calculated by Chi-square test with Clopper option.

- percentage (%) of implants where a serious/not serious adverse event certainly related or possibly related to JPS is registered on total surgical implants performed (up to 18 months according to site's standard practice). Exact limits will be calculated by Chi-square test with Clopper option.

12.4 General methodology

Clinical data collected throughout this study will be analyzed by descriptive statistics to assess the hypothesis to test and the study objectives. Descriptive statistics will be provided in summary tables according to the type of variable summarized:
- Quantitative variables will be summarized by using n (sample size), arithmetic mean, standard deviation (SD), median, minimum and maximum;
- Categorical variables will be summarized by using frequency distribution and percentages.

Although the clinical performance and the safety of JPS vary with many factors i.e. the primary diagnosis, the anatomical site (tibia and/or femur), the population (pediatric or adult), the concomitant diseases and the quality of the treated bone, no sub-group descriptive statistics will be done due to the limited sample size; data will be processed as whole entity to precent any interpretation bias.

12.5 Interim Analysis

An interim analysis, not planned at the start of the study, will be performed after at least 20 subjects will be enrolled and completed the "Bone Consolidation" event.
The aim of this interim analysis is to verify the consistency of testing hypothesis and to confirm the historical data on the medical device safety and performance. Interim results will be used to prepare the Clinical Evaluation Report (CER).
To preserve the integrity of the study results interpretation, a correction for multiplicity due to two planned analyses (interim+final) will be implemented using the approach proposed by O'Brian-Fleming for sequential design. (*Shein –Chung Chow et Al Sample size calculations in Clinical Research 2003, Christopher Jennison et Al Group Sequential Methods with applications to clinical Trials,2000*)
For this purpose, sample size will be recalculated using this approach (all details are reported in the cited bibliography):
- The initial sample size will be correct by factor 1.008 for a two-sided test at 5% level and 80% power. The final sample size is 30*1.008=30.2
- The probability level will be correct by factor 1.977, at interim the P value will be 0.0052 while at the final analysis P value will be 0.048. The corresponding confidence limits will at interim 99.5% and at final analysis 95.2%

In conclusion, applying the O'Brian-Fleming approach to control the type I error no great impact on sample size is observed and integrity of clinical study is preserved from any interpretation bias.

13. ETHICS AND REGULATORY REQUIREMENTS

This investigation will be performed according to the following guidelines:

- World Medical Association Declaration of Helsinki;

13.1 Regulatory Approval

Prior to the initiation of this investigation and first data collection, the CIP and all other relevant documents as required by the relevant Independent Ethics Committee/Institutional Review Board (IEC/IRB) will be submitted for review and approval.

Any amendment to the CIP will be submitted to the IEC/IRB for notification and/or approval, before implementation, as applicable.

13.2 Subject Information and Consent

The aim of the study is to collect clinical data based on medical records for patients treated with the JPS system in the past for whom follow-up assessment and JPS removal is already done (retrospective group) and for patients who has undergone JPS implantation and will have follow-up assessments and JPS removal (prospective group).

All subjects should give informed consent to participate in this study. Prior to being enrolled into the study, each patient (if he/she is adult at the time of the screening visit), or his/her parents/legal representative (if he/she is minor at the time of the screening visit), will be required to give his/her written and dated informed consent to participate the study and to collect and process their clinical data, and to anonymously store the data electronically. Also minors patients will be informed as far as possible by the investigators about the study and will be given an age dedicated informed form. Their willingness or refuse to participate to the study, if expressed, must be taken into consideration by the investigator.
Each patient/parents/legal representative will have the opportunity to discuss the informed consent with the Investigator prior to sign it. The Investigator or his/her designee will inform all patient/parents/legal representative regarding the purpose of the study and the clinical data that will be collected. The Investigator will deliberate that, considering this is an observational Study, there are no foreseeable risks resulting from study participation as well as potential benefits that may result from participating in the study.
Each patient/parents/legal representative will be informed by the Investigator that he/she is free to refuse to participate in the study and, if he/she choose to participate, that he/she may withdraw from the study at any time without providing reasons. In addition, the patient/parents/legal representative will be informed that, in some necessary cases, the Investigator may prematurely terminate their participation providing an appropriate reason.
The Investigator will provide the patient/parents/legal Representative with contact details in case they need further information after ICF signature.
Each patient/parents/legal representative will be informed that his/her medical records will be subjected to review by the Sponsor representatives, and may be subjected to review for the

auditor and regulatory authorities, and that the information will be used during the analysis of the results.
The data gathered for this group at the visits and assessment during the follow-up period, will be systematically collected by the investigator in eCRF.

Subjects will not undergo additional visits nor invasive or burdensome procedures additional to those already performed under the normal clinical practice. The scope of data collection is limited to the available data in the patients' charts.

13.3 Subject Confidentiality

All information and data sent to parties involved in study conduct concerning patients or their participation in this study will be considered confidential per the requirements of EU GDPR regulations and local requirements. The Informed Consent shall describe the process of subject data protection in details. Each JPS implant will be assigned a unique case number (ID), and reported in the eCRF. Considering that each patient can contribute for more than one JPS implant: one patient can have more than one ID. In the eCRF the IDs are linked to the first ID assigned to the same patient by the clinical site. Records of the subject/study ID number relationship will be maintained by the study center. The study ID number is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document other than the Informed Consent Form and the patients screening log. In the event a subject's name is included for any reason, it will be blinded as applicable.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

14. STUDY MANAGEMENT AND ADMINISTRATION

14.1 Supplies

After the required approval will be obtained before the site will be initiated, the sponsor will provide the site with the following supplies:

- A paper and electronic copy of this CIP;
- Blank copies of the ICFs to be signed by the enrolled subjects;
- The Investigator Site File (ISF) containing all the study related documents;
- An eCRF platform and the credential to enter the system to upload clinical data;
- An appropriate training on study procedures and eCRF management.

14.2 Monitoring

The sponsor planned to perform a 100% source data verification (SDV), on inclusion/exclusion criteria and on the endpoints variables. On the remaining data the SDV will be performed by random spot check. Before each visit the monitors will contact the investigator/centre to schedule the visit and will send a written confirmation and the related agenda.
In order to fulfill its responsibility of assuring the proper conduct of the study regarding adherence to the CIP and the completeness and accuracy of the data recorded on the case report forms, the sponsor planned to perform at least the following monitoring visits:

- Site Initiation Visit (SIV), to be performed after EC approval;
- 6 monitoring visits throughout the life phase of the study and according monitoring plan;
- Close Out Visit (COV), after the last patient's data are entered into eCRF.

In case of need the investigational site is subjected to additional monitoring visits. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

14.3 Direct Access to Source Data/Documents

With all efforts to ensure that patients' pseudo-anonymity and confidentiality is respected, the Investigator will permit the clinical monitors to have direct access to all study records that are the eCRF, the ISF and all the source data.

14.4 Audit

There may be a possibility that the Quality Assurance Department of the sponsor may audit the compliance to CIP procedures according to the company Standard Operating Procedures.

The investigator will permit to be audited by sponsor personnel during and after the study has been completed.

14.5 Adherence to Protocol

CIP deviations will be reported to the sponsor who will assess their significance (Major and Minor). All deviations will be reported and discussed in the clinical investigation report.

In case of a CIP amendment, before the suggested modifications will be implemented, the sponsor will notify to the relevant IEC/IRB the new version of the CIP, specifying whether the modifications are substantial/not-substantial and, if applicable, will put the study on hold until the re-approval will be obtained.

14.6 Data Handling and retention

The sponsor and the investigator assume the responsibility to assure that the clinical data will be collected according to the CIP requirements (no additional data will be collected), local laws and obligations and the World Medical Association Declaration of Helsinki. The clinical data obtained as a result of this study is considered confidential between the site and the sponsor: disclosures to third part are prohibited or, if necessary for example to perform statistical analysis with contracted vendors, will be protected by non-disclosure agreements.

Before the Site Initiation Visit, the sponsor will provide a validated eCRF system and will train the Investigators about the data entry procedures, data clearing and queries resolution. Only the data recorded in the eCRF will be considered for the statistical analysis. The clinical data entered in the eCRF must come from the source data, that is all information in original (or certified copies) patients' clinical records, records of clinical findings, investigator's observations/assessment.
The investigator assumes the responsibility to assure that the last data will be entered within 2 week from the plate removal of the last patient.

The investigator will have to keep all study related documentation for the longest possible duration, but at least for 15 years after the completion or premature termination of the study. No data should be destroyed without agreement of the sponsor. The Sponsor will maintain all documentation pertaining to the study for the lifetime of the product.
Sponsor and investigators shall take measures to prevent accidental or premature destruction of these documents and they may rely on a third part for documents retention by a non-disclosure agreement to protect data confidentiality.

14.7 Clinical Study Report

The clinical study report shall be completed by the sponsor, or a designed delegate by the means of a non-disclosure agreement, even if the clinical investigation will be terminated prematurely, only after:

- all queries concerning the eCRF will be closed;
- the database will be locked;
- the statistical report will be written and approved.

The sponsor will draft the clinical study report within 2 months after the statistical report will be finalized. That report will be reviewed and approved by the investigator and, as soon as available, shall be provided to the relevant IEC/IRB, to the regulatory authorities (when applicable). For all statistical details related to Interim Analyses please refer to section 12.5.

14.8 Insurance and Liability

No additional procedures for patients nor for the investigational team members are planned for the present observational study with respect to the normal clinical practice, that actually comprises a retrospective and prospective data collection. The sponsor, therefore, is not requested to put in place an additional dedicated liability insurance covering this study.

14.9 Financial Disclosures

Assumed this is a sponsored study, after the IEC/IRB approval, the sponsor will put in place with the hospital administration of the site an agreement that will allow to pay the involved department for study execution. It is understood that, considering study procedures consist of a observational (prospective and retrospective) collection of clinical data, the sponsor will pay the time used by the Investigator to screen the eligible patients, as well as the time to fulfil and handle the clinical database.

14.10 Publication

The sponsor and the investigator intend to compile a comprehensive publication of study results in a peer review journal, appropriately addressing contributions of co-authors.
The sponsor recognizes the right and interest of co-authors, to scientifically publish the results obtained from the study for non-commercial purposes, even if the effects ascribed to the investigational product fail to materialize.
The sponsor, together with the investigator, reserves the right to publish and present the results of this study at scientific congresses, to submit these clinical trial data to national and international Regulatory Authorities, and to register the study in a publicly accessible database.

Prior to any publication or presentation of study results, co-authors may submit a manuscript/abstract of the intended publication or presentation to the sponsor for review. Proposals for changes and modifications raised by sponsor will be taken into consideration by the participating Investigators if such proposals do not interfere with the scientific nature and content of the publication.

The identity of the sponsor and the nature of his contribution to this study shall be disclosed in any publication or presentation.

15. REFERENCES

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