NCT04607044

Lower Extremity Fixation In Neuropathic Patients Study (FINS) Clinical Investigation Plan

CLINICAL INVESTIGATION TITLE:	Lower Extremity Fixation In Neuropathic Patients Study (FINS)
ABBREVIATED CLINICAL INVESTIGATION TITLE:	FINS
DEVICE NAME:	HOFFMANN® LRF SYSTEM SALVATION™ EXTERNAL FIXATION SYSTEM SALVATION™ FUSION BOLTS AND BEAMS SALVATION™ 2 MIDFOOT NAIL SALVATION™ 3DI PLATING SYSTEM T2® ICF SYSTEM VALOR™ ANKLE FUSION NAIL SYSTEM
CLINICAL INVESTIGATION DESIGN:	Prospective, multi-site, multi-year post-market clinical follow-up study
INDICATIONS:	This clinical investigation will adhere to the indications and contraindications for the systems under investigation, as detailed in the devices' Instructions for Use (IFU) and Surgical Technique Manual.
CLINCIAL INVESTIGATION PLAN PHASE:	Post-Market Clinical Investigation
SPONSOR:	Stryker Orthopaedics 325 Corporate Drive Mahwah, NJ 07430 United States of America
INVESTIGATORS:	Investigators' information is on file at the Sponsor
COMPLIANCE STATEMENT:	This clinical investigation will be conducted in compliance with the Clinical Investigation Plan, International Conference of Harmonisation Good Clinical Practice (ICH-GCP), and all other applicable regulatory requirements, including the retention of essential documents. Investigators will be trained on the clinical investigation devices and surgical techniques prior to implanting clinical investigation subjects.
CONFIDENTIALITY STATEMENT:	This Clinical Investigation Plan contains confidential information, and its' use is limited to investigational staff intending to conduct the clinical investigation, Institutional Review Boards (IRBs)/Ethics Committees (ECs) and any others charged with reviewing the clinical investigation.
VERSION:	3
DATE:	27-Apr-2022

Sponsor Approval Page

APPROVERS			
Role	**Name**	**Signature**	**Date**
Medical Expert	Dr. Thomas Demuth	DocuSigned by: Name des Unterzeichners: Thomas Demuth Signiergrund: Ich genehmige dieses Dokument Signierzeit: 02-Mai-2022 | 1:01 AM PDT AE4A3F4855F64F08909D5CB4B21EEC36	02-Mai-2022 | 1:01 AM PDT
Clinical Research Head (CRH)	Rebecca Gibson	DocuSigned by: Signer Name: Rebecca Gibson Signing Reason: I approve this document Signing Time: 28-Apr-2022 | 2:15 PM EDT B69B71B0C1FA437DB21659BFBEB69FE2	28-Apr-2022 | 2:15 PM EDT
Regulatory Affairs (RA)	Val Myles	DocuSigned by: Signer Name: Val Myles Signing Reason: I approve this document Signing Time: 28-Apr-2022 | 9:01 AM PDT 3B36BC4F99D0425FB50AEAAFFC251B46	28-Apr-2022 | 9:01 AM PDT
Statistician	Jovi Quiton	DocuSigned by: Signer Name: Jovi Quiton Signing Reason: I approve this document Signing Time: 28-Apr-2022 | 7:45 AM PDT 74CDF10AA94943E682E55B884F9F9F96	28-Apr-2022 | 7:45 AM PDT

Table of Contents

1. List of Abbreviations

Acronym	Definition
AE	Adverse Event
CFR	Code of Federal Regulations
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
CV	Curriculum Vitae
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EQ-5D	A standardized health-related quality of life instrument by the EuroQuol Group
FAAM	Foot and Ankle Ability Measure
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH-GCP	International Conference of Harmonisation Good Clinical Practice
ID	Investigation Device
IFU	Instructions for Use
IRB	Institutional Review Board
LTFU	Lost to Follow-Up
PG	Performance Goal
PI	Principal Investigator
Pre-Op	Pre-Operative
PROM	Patient Reported Outcome Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UADE	Unanticipated Adverse Device Effect

2. Synopsis

Title	Lower Extremity Fixation In Neuropathic Patients Study (FINS)
Treatment	HOFFMANN® LRF SYSTEM SALVATION™ EXTERNAL FIXATION SYSTEM SALVATION™ FUSION BOLTS AND BEAMS SALVATION™ 2 MIDFOOT NAIL SALVATION™ 3DI PLATING SYSTEM T2® ICF SYSTEM VALOR™ ANKLE FUSION NAIL SYSTEM
Design	Prospective, multi-site, multi-year post-market clinical follow-up study
Objective	The primary objective of this study is to compare the pooled cumulative 3-year amputation rate to a performance goal derived from a literature-based source.
Endpoints	**Primary Endpoint:** • Performance or survival of the device measured as the 3-Year Amputation Rate. **Secondary Endpoints:** • Evaluate the change in patient-report of pain, function, and social interaction for quality of life from pre-op through each annual visit as assessed by the EQ-5D-5L, the FAAM and its component scores. • Safety of the implants in terms of complications and adverse events through 5 years. • Investigator assessment of the implant including radiographic assessment of deformity correction, and fusion/consolidation time through 1 Year. • Performance or survival of the device measured as the 5-year Amputation Rate.
Target Population	Approximately 200 subjects are to be enrolled in this clinical investigation at approximately 10 sites. Enrolled subjects will be assessed at Pre-Operative, Operative/Discharge, 6 Months, 1 Year, 2 years, 3 Years, 4 Years and 5 Years after the index procedure.
Inclusion Criteria	a. Subject is a male or non-pregnant female age 18 years or older at the time of surgery; b. Subject is willing and able to give written informed consent and comply with the requirements of this Clinical Investigation Plan; and c. Subject has neuropathy and is intended to be treated for deformity with the one or a combination of the below Systems in accordance with the legally cleared/ approved IFU and Surgical Technique Manual. • HOFFMANN® LRF SYSTEM • SALVATION™ EXTERNAL FIXATION SYSTEM • SALVATION™ FUSION BOLTS AND BEAMS • SALVATION™ 2 MIDFOOT NAIL • SALVATION™ 3DI PLATING SYSTEM • T2® ICF SYSTEM • VALOR™ ANKLE FUSION NAIL SYSTEM

Exclusion Criteria	a. Subjects determined, by the investigator, to be an inappropriate candidate for the procedure indicated; b. Unable to consent to participate (written, informed consent); c. Unable to attend/complete the requested follow-up visits.

3. General Information and Administrative Structure

3.1 SPONSOR

Stryker Orthopaedics
325 Corporate Drive
Mahwah, NJ 07430
United States of America

3.2 KEY SPONSOR PERSONNEL
Jennifer Seidman
Manager, Clinical Operations
Jennifer.Seidman@stryker.com
+1 901-633-8616
Role: Clinical Investigation Manager

Rebecca Gibson
Director, Clinical Operations
Role: Clinical Research Head

Dr. Thomas Demuth
Director Medical Affairs
Role: Medical Expert

3.3 EDC SYSTEM

Information on file at the Sponsor

4 Product Information

All components of the HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems were cleared and approved for sale and use prior to starting the clinical investigation.

These Systems are to be used only for indications for which they have been approved. Please see the approved IFUs and Surgical Technique Manuals for a detailed description of the medical device(s) and instrumentation and intended use information.

Medical device product traceability will be achieved by capturing the implant lot number.

5 Risks and Benefits

This prospective, multi-center, clinical investigation is designed to examine the safety and efficacy/performance of the HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems, in accordance with the approved IFU, labeling and instrumentation. The potential risks to subjects are described in the approved IFUs and Surgical Technique Manuals. There are no additional risks anticipated, specific to participating in this study. The study is not examining any experimental procedures and participation in the study is not predicted to affect the medical treatment received by enrolled subjects

This is an observational study, so participation may not result in direct benefit to the subject. The use of information contained within the database may be of future benefit to subjects undergoing certain orthopedic procedures.

6 Introduction

Stryker introduced multiple devices to treat deformity in the neuropathic patient (lack of sensation with the 10 gram Semmes Weinstein monofilament) population. All of the devices have been cleared by the FDA. See below for the list of devices, dates of clearance, and FDA 510K numbers.

Device Name	Date of Clearance	510K Number
HOFFMANN® LRF SYSTEM	01Feb2021	K203568
SALVATION™ EXTERNAL FIXATION SYSTEM	06Jun2018	K180832
SALVATION™ FUSION BOLTS AND BEAMS	21Mar2014	K140741
SALVATION™ 2 MIDFOOT NAIL	11Jul2018	K180024
SALVATION™ 3DI PLATING SYSTEM	22May2014	K140792
SALVATION™ OSTEOPENIC SCREW	14May2014	K140408
T2® ICF SYSTEM	20Mar2020	K193366
VALOR™ ANKLE FUSION NAIL	22Oct2014	K142602

Table 6.1 Study Device FDA 510K Clearance Information

The primary outcome measure of this study will compare the pooled cumulative 3-year amputation rate derived from a Kaplan-Meier survival analysis to a performance goal derived from a literature-based source. Descriptive analyses will then compare survival curves in patients for specific devices over the entire 5-year follow-up period. Secondary endpoints include improvements in patient-reported pain, function, and social interaction for quality of life from pre-op through each annual visit as assessed by the EQ-5D-5L and the FAAM and its component scores. As well as investigator assessment of the implant including radiographic assessment of deformity correction, and fusion/consolidation time through 1 Year

The outcome measures collected in this study will be analyzed and reported as required for local, regional, and country requirements (i.e., regulatory authorities and notified bodies).

7 Clinical Investigation Design

This investigation is a prospective, multicenter post-market clinical follow-up study. It is anticipated that a total of 200 subjects meeting all the eligibility criteria will be enrolled at approximately 10 sites. The enrollment period is expected to occur over 48 months. Total duration of enrollment, 5 years follow-up of subjects, and data analysis is expected to take 9 years.

The study treatment is approved for use and conforms to regulatory requirements. This investigation employs these procedures and devices for uses that are consistent with their regulatory cleared/approved labeling. The clinical investigation was designed to follow the surgeon's standard of care for treatment of deformity in the neuropathic patient in addition to annual follow-up visits through 5 years. Neither subjects nor investigators are blinded to treatment.

7.1 CLINICAL INVESTIGATION RATIONALE

The Sponsor has identified the need to collect post-market clinical follow-up data to verify the safety and efficacy/performance of the HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems. The Sponsor believes that a prospective, multi-center, post-market clinical follow-up study evaluating the on-label usage of these Systems is the most appropriate way to capture this type of data.

The primary and secondary endpoints will be used to demonstrate safety and performance/efficacy of these Systems. Efficacy will be assessed through comparing the pooled cumulative 3-year amputation rate derived from a Kaplan-Meier survival analysis to a performance goal derived from a literature-based source. Safety will be assessed through the incidence of device related intra-operative and post-operative adverse events/incidents (AEs) by 5 years.

All subjects will be followed in accordance with the Investigator's standard-of-care, with additional annual follow-up visits through 5 years. These visits may be considered outside of standard-of-care for some surgeons; however, it is necessary to provide a full assessment of the primary endpoint measure.

8 Objective

The primary effectiveness hypothesis is that the 3-year amputation rate (including both above and below the knee) is less than the performance goal (PG).

The PG was based on data summarized in Elmarsafi et al 2019. This study summarized patients with diabetic Charcot neuroarthropathy (CN). The aim of this study was to identify risk factors for major lower extremity amputations among patients who underwent osseous Charcot reconstruction. A retrospective review was performed on 331 patients with the diagnosis of CN in the foot and ankle treated over a 16-year period. Two hundred eighty-five patients were included after exclusion of those without diabetes.

Among N=285 patients, n=49 (17.2%) experienced an amputation with mean follow-up of 29.5 months (range 12.1 to 124.4). The sample estimate to be compared to the PG is the 36-month cumulative amputation rate and so is conservative relative to the mean 29 months of follow-up in the Elmarsafi et al 2019 study.

In order to derive a PG amenable to statistical testing, a small reference margin of 3% will be used. This represents a 17.4% increase above the literature-based value of 17.2%. Adding a reference margin allows there to be non-trivial power if the true event rate is at least moderately less than 17.2%. Therefore, PG is defined as 17.2% + 3% = 20.5%. If the upper bound of a one-sided 95% CI for the 3-year cumulative amputation rate as determined Kaplan-Meier analysis is less than 20.5%, the PG will be met.

8.1 PRIMARY ENDPOINT

The primary endpoint of the study is the overall performance of the devices (HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems) measured as the 3-year amputation rate.

8.2 SECONDARY ENDPOINTS

The secondary performance endpoints are:

- Improvement in patient-reported function, and social interaction for quality of life via
  - EuroQuol five dimensions (EQ-5D-5L); and
  - Foot and Ankle Ability Measure (FAAM).
- Performance or survival of the device measured as the 5-year Amputation Rate

The secondary safety endpoints are:

- Adverse events through 5 years;
- Complications; and
- Investigator assessment of the implant including radiographic assessment of deformity correction, and fusion/consolidation time through 1 Year.
- Surgical Intervention

9 Selection of Clinical Investigation Population

Subjects participating in this clinical investigation will be recruited from the investigator's standard subject population, where all neuropathic subjects presenting for treatment of deformity will be evaluated for clinical investigation participation based on the eligibility criteria listed below.

9.1 INCLUSION CRITERIA

a. Subject is a male or non-pregnant female age 18 years or older at the time of surgery;
b. Subject is willing and able to give written informed consent and comply with the requirements of this Clinical Investigation Plan (CIP); and
c. Subject has neuropathy and is intended to be treated for deformity with the one or a combination of the below Systems in accordance with the legally cleared/ approved IFU and Surgical Technique Manual.
   - HOFFMANN® LRF SYSTEM
   - SALVATION™ EXTERNAL FIXATION SYSTEM
   - SALVATION™ FUSION BOLTS AND BEAMS
   - SALVATION™ 2 MIDFOOT NAIL
   - SALVATION™ 3DI PLATING SYSTEM

- T2® ICF SYSTEM
- VALOR™ ANKLE FUSIO NAIL SYSTEM

9.2 EXCLUSION CRITERIA

a. Subjects determined, by the investigator, to be an inappropriate candidate for the procedure indicated;
b. Unable to consent to participate (written, informed consent);
c. Unable to attend/complete the requested follow-up visits

9.3 POINT OF ENROLLMENT

Subjects will be considered enrolled in the study when they have satisfied all the below:

a. Been informed of all aspects of the study and have signed Informed Consent document
b. Acknowledged the appropriate patient data release information (included in the Informed Consent document)
c. Satisfied the Inclusion/Exclusion Criteria
d. Implanted with HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and/or VALOR™ ANKLE FUSION NAIL Systems.

Investigators should document subject enrollment in the electronic data capture system. The Source documentation should clearly state that all inclusion and exclusion criteria have been met and the patient data release and informed consent documents have been signed and appropriately dated prior to any study related activity. The subject is enrolled in the study once they have received the study device.

9.4 WITHDRAWAL CRITERIA

If, during the clinical investigation, a subject must be prematurely withdrawn, the procedures outlined in this section must be followed. These procedures should not interfere with the initiation of any new treatments that are necessary to treat a subject's condition**.** Information on all withdrawn subjects will be documented.

Subjects may be withdrawn from the clinical investigation for any of the following reasons:

a. Subject Withdrawal: A subject may voluntarily withdraw from the clinical investigation at any time and for any reason. The subject should be asked when possible, and without any form of coercion, the reason for his/her decision. If the participant withdraws from the clinical investigation completely, then data collected up until the point of withdrawal will be included in the final analysis. Subjects who decline to continue to take part will be given the opportunity to discuss/inform the research team of the reasoning behind their decision not to take part.
b. Lost to Follow-Up (LTFU): A subject will be considered LTFU after all reasonable efforts have been made to contact the subject and request his/her continued participation in the clinical investigation. All attempts to contact the subject must be documented and should include at least two attempts to contact the subject by phone and one attempt via a certified letter. Data collected up until the point where the subject is LTFU will be included in the final analysis.

c. Amputation: The discontinuation of a subject's participation in the clinical investigation due to Amputation (below the knee or above the knee) All available information concerning the amputation AEs should be provided. Data collected up until the point of amputation will be included in the final analysis.
d. Adverse Event: The discontinuation of a subject's participation due to an AEs that prohibits his/her continued participation must be fully explained. All available information concerning the AEs should be provided. Data collected up until the point of AE will be included in the final analysis.
e. Death: The discontinuation of a subject's participation in the clinical investigation due to death must be fully explained. All available information concerning the death should be provided. Removal of a subject from continued follow-up in the clinical investigation due to death will not be considered a device failure unless the death is directly caused by, or attributable to, the HOFFMANN® LRF CIRCULAR EXTERNAL FIXATION, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF INTRAMEDULLARY NAILING SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems. Data collected up until the point of death will be included in the final analysis.
f. Other: A subject may be withdrawn by the Investigator if he/she believes that it is in the best interest of the subject or the IRB/EC may determine that a subject's continued participation in the clinical investigation represents an unacceptable risk to the subject. The Sponsor must be notified immediately if this occurs. All data collected up until the point of withdrawal or IRB/EC determination will be included in the final analysis.

   A subject may also be withdrawn if the subject is non-compliant with the clinical investigation procedures or visits, or if a selection criteria violation is noted after the subject received the clinical investigation treatment and it is determined that the subject should be discontinued. All data collected up until the point of withdrawal will be included in the final analysis.

10 Clinical Investigation Evaluations, Procedures and Assessments

10.1 METHODS OF ASSIGNING SUBJECTS

No specific methods (e.g. randomization, blinding, or stratification) for assigning subjects are used in this CIP. Consecutive subjects at each site meeting all the eligibility criteria will be enrolled in this clinical investigation.

10.2 PROCEDURES

Subjects in the clinical investigation will undergo placement of the HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems. Please see the approved IFUs and Surgical Technique Manuals for a detailed description of the medical device(s) and instrumentation, intended use information and associated risks. Any additional clinically indicated procedures are permitted as deemed necessary by the clinical investigator.

10.3 FOLLOW-UP EVALUATIONS

Subjects in this clinical investigation will be evaluated at Pre-Operative, Operative/Discharge, and at 6 Months and yearly through 5 years after the index procedure. The follow-up evaluations will include assessment of device-related adverse events/incidents, evaluation per EQ-5D-5L and FAAM scores as well as surgeon surveys radiographic assessment of deformity correction, and fusion/consolidation time. Demonstration of bone consolidation in correct alignment will be measured by Investigator assessment through 1 Year. Investigators should consider weight-

bearing, pain and imaging when clinically assessing bone consolidation. See the section below for visit windows and a list of assessments to be performed at each visit.

Investigative site personnel will contact subjects prior to their scheduled follow-up evaluations to encourage compliance with clinical investigation visits and participation.

If a subject misses a visit and is outside of the visit window, every effort should be made to collect data instead of noting the visit as missed.

10.4 SCHEDULE OF EVENTS

Assessment	Pre-Operative	Operative/ Discharge	6 months [a, b] (+/-3 months)	1 Year [a, b] (+/-6 months)	2-5 years [a, b] (+/-6 months)	Study Close
Informed Consent	X					
Inclusion/Exclusion	X					
Demographics & Medical History	X					
Disease State Pre-Op	X					
EQ-5D-5L	X		X	X	X	
FAAM	X		X	X	X	
Surgical Procedure		X				
Investigator Assessment			X	X	X	
Adverse Event Assessment		X	X	X	X	
Staged Operative Information [d]						
Surgical Intervention [d]						
Subject Disposition [c]						X

a. Follow-up visit schedule to reflect Institutions' Standard of Care practices.
b. If the subject missed a visit and is outside of visit window, every effort should be made to collect data instead of noting visit as missed.
c. Subject Disposition assessment will occur at any time point for subject withdrawal prior to the completion of the clinical investigation.
d. These are not scheduled time point events but will be observed throughout the study participation

Table 10.4.1 Schedule of Events

11 Statistical Considerations

In general, the statistical analysis of will consider the combined outcome of all the devices under investigation. The population of the study will consist of all patients implanted with one or more of the devices listed Table 6.1. Subgroup analysis will be conducted for each device and device groups (i.e., devices for internal fixation only). The study required a sample size of 141 patients to provide at least 80% statistical power to reject the hypothesis that the 3-year amputation rate is less than the PG with a significance α=0.05. The final statistical analysis will occur after all subjects have completed their 3-year anniversary. Secondary effectiveness endpoints include the total and component scores of the EQ-5D-5L and FAAM. Assessment of patient-reported outcome measure (PROM) improvement will be assessed at each planned study visit. The safety endpoints will include AEs, complications and secondary surgical intervention experienced by the patients. The device- and procedure- relatedness and severity of the safety endpoints will be assessed. The clinical and radiographic surgeon assessment of fusion and consolidation at 5 years will also be assessed.

Data will be captured via the EDC system. The data will be summarized descriptively at each pre-determined clinical visit. Quantitative factors will be summarized with mean, median, standard deviation and range minimum, maximum. Frequency and percentage will be computed for categorical factors. Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier estimates with confidence limits. A significance level (α) is 0.05 will be used for all tests of hypotheses

All statistical analysis will be performed using SAS version 9.4 or higher. A Statistical Analysis Plan (SAP) that contain the details of the analysis will be developed and finalized prior to the first anniversary of the first patient enrolled in the study.

11.1 DETERMINATION OF SAMPLE SIZE

The sample size was determined by assuming a binomial distribution for the outcome of amputation to 3 years post treatment and then applying an adjustment for the maximum expected loss-to-follow-up. Based on preliminary data collected via retrospective studies that is on file with Stryker, the expected pooled amputation rate at 3 years for subjects meeting inclusion and exclusion criteria for this study is 10%.

An unadjusted chi-square test based on a 1-sided type 1 error rate of $\alpha=0.025$ has 92% power to reject the null hypothesis that $\pi amp \geq 0.202$ in favor of the alternative hypothesis $\pi amp < 0.202$ (nQuery Advisor 7.0) with N=141 subjects. This sample size is increased by 29.5% to N=200 for account for loss-to-follow-up.

11.2 ANALYSIS PLAN BY CLINICAL INVESTIGATION ELEMENT AND EVALUATION

11.2.1 Statistical Analysis

Evaluation elements are defined as the questions on the CRF/eCRF. The Statistical Analysis Plan (SAP) lists all evaluation elements and secondary elements which will be based on calculations between two or more evaluation elements.

All quantitative variables, including those based on calculations (secondary elements), will be analyzed with a case summary evaluation before the detailed characteristics and parameter can be evaluated. A case summary contains a listing of the number of valid cases/values, missing cases/values (if any) and total cases/values in the specific analysis. For quantitative variables the mean, median will be presented to summarize the average. The standard deviation, interquartile range (IQR) and range (based on maximum and minimum) will be calculated. A 95% confidence interval of the mean will also be constructed. A type 1 error $\alpha=0.05$ will be used for all statistical tests of hypothesis. All assumptions in test of hypothesis will be investigated.

All qualitative variables, including those based on summaries (secondary elements), will be analyzed listing the proportions, frequencies, column and row totals and missing proportion (if any).

The SAP reflects this approach and specifies the variables characteristics (quantitative or qualitative) in detail together with the related analysis strategy. This also includes calculation and summaries based on primary elements and the required analysis.

11.2.2 Primary Analysis / Endpoint

The primary effectiveness hypothesis will be tested on the basis of a confidence interval derived from a Kaplan-Meier analysis of cumulative amputation rates over time. The null and alternative hypotheses to be tested are as follows:

Ho: πamp ≥ PG vs Ha: πamp < PG

πamp is the pooled 3-year cumulative rate of amputations, A Kaplan Meier survival estimate with confidence limits of the PG will be constructed for the time to amputation These hypotheses will be tested by comparing the upper bound (UB) of a 1-sided 97.5% confidence interval (CI) at the 3-year to the target performance (PG). The null hypothesis (Ho) will be rejected If UB < PG, and it will be concluded that the performance of the device(s) achieved the PG. This is approximately equivalent to specifying a 1-sided type 1 error rate of α=0.025. A 1-sided type 1 error rate of α=0.025 rather than α=0.05 is specified to increase the robustness of the statistical evidence. A chart to depict the survival function with confidence limits will be presented.

11.2.3 Secondary Analyses

Improvements in subject quality of life after surgery will be assessed by constructing 95% confidence interval for the mean change from baseline score in EQ-5D-5L and FAAM total and component scores to each annual visit with focus on the 3-year endpoint for consistency with the primary endpoint.

11.2.4 Safety Analysis

All subjects enrolled in the study will be assessed for safety. AEs and other safety evaluations will be reported as frequencies and rates as appropriate, cumulative over the different follow-up schedules.

Safety endpoints will include all AEs, serious AE (SAE), device related adverse effect (DRAE), procedure related adverse effect (PRAE), serious device-related adverse effect (SDRAE), serious procedure-related adverse effect (SPRAE), unanticipated adverse device effects (UADEs) and type of surgical intervention as a consequence of the AE occurence. For each type of AE and intervention type, total counts and per subject incident rates with 95% exact binomial confidence intervals will be reported. Counts of AE's will also be reported according to incidence time intervals.

11.2.5. Additional Analysis

There are two types of fixation, external and internal. External fixation devices are always removed. Survival analysis of time to external fixation removal with Kaplan-Meier survival estimates and corresponding confidence limits will be presented. Internal fixation breakage will be reported as an AE.

Subgroup analysis of patient reported outcome improvement scores (EQ-5D-5L and FAAM) will be conducted for i.) patients with external fixation only, ii.) patients with internal fixation only, iii.) patients with external and/or internal fixation. In addition, subgroup analysis will be conducted by device type (HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, THE SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL).

MISSING DATA For the primary endpoint analysis, subjects that have not experienced the event (i.e., amputation) at the last day of follow-up will be censured in the survival analysis. Patients that dropped out for any reason before their 3-year anniversary will also be censored at the last known date. A sensitivity analysis will be conducted that will exclude patients that dropped out from the study for reasons other than amputation prior to their three-year anniversary.

For the patient reported outcomes (EQ-5D and FAAM), statistical summaries will be computed only for available data. No imputation for missing data will be conducted.

11.3 REPORTS

11.3.1 Interim Analysis and Reports

Interim analyses will be performed on a yearly basis. The progress of the clinical investigation will be reported together with the interim results on the variable level according to the analysis plan. The only exception is the analysis of the primary endpoint will not be part of the interim reports.

11.3.2 Final Analysis and Reports

The full final report with complete analysis and progress and conduct reporting will be created at the end of this clinical investigation.

12 Clinical Investigation Plan Deviations

A CIP deviation is a departure from the approved CIP that is not implemented or intended as a systemic change. All CIP deviations are recorded and reported to the Sponsor and each site's IRB/EC in accordance with the respective site's IRB/EC policies. Investigators should not deviate from the study protocol except to deliver emergency care or to eliminate an immediate hazard to the subject.

13 Adverse Events

An Adverse Event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related

A Serious Adverse Event (SAE) is any AE that:

- Led to death
- Led to serious deterioration in the health the subject, that either resulted in
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, 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,
- Led to fetal distress, fetal death or congenital abnormality or birth defect.

An Adverse Device Effect is defined as any untoward or unintended response to the clinical investigation treatment; and/or a medical response which may have a causal relationship to the treatment.

- **An Incident** is defined as any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.
- **A Serious Adverse Device Effect** is defined as any DRAE that results in consequences characteristic of a SAE or might lead to the consequences if suitable action or intervention is not taken; causes considerable interference with the subject's usual activities and may be

incapacitating or life-threatening, including those events resulting in a subject's disability or permanent damage, or required intervention to prevent disability or permanent damage; results in a life-threatening illness or injury; and/or results in death (fatal).

- **A Serious Incident** is defined as any incident that directly or indirectly led, might have led or might lead to any of the following:
    - the death of a patient, user or other person;
    - the temporary or permanent serious deterioration of a patient's, user's or other person's state of health;
    - a serious public health threat

- **An Unanticipated Adverse Device Effect (UADE)** is defined as an AE not described in the informed consent, CIP or device labeling which has resulted in any of the consequences of a SAE or which might have led to any of the consequences of a SAE if suitable action had not been taken, intervention had not occurred, or if circumstances had been less opportune. Anticipated AEs will be those listed in the HOFFMANN® LRF CIRCULAR EXTERNAL FIXATION, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF INTRAMEDULLARY NAILING SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems device labeling (Surgical Technical Manual and IFU).

13.1 RELATIONSHIP TO THE DEVICE

The relationship of the AE to the study device or the implant procedure should be reported on the AE data collection form.

- Device Related: an AE that results from the presence or performance of the device.
- Procedure Related: an AE that occurs as a result of the implant procedure.

13.2 FORESEEABLE DRAE AND SDRAE

DRAEs, SADREs and incidents which may be expected as part of the surgical interventions include:

- Infection or painful, swollen or inflamed implant site
- Fracture of the implant
- Loosening or dislocation of the implant requiring revision surgery
- Bone resorption or over-production
- Allergic reaction(s) to implant material(s)
- Untoward histological responses possibly involving macrophages and/or fibroblasts
- Migration of particle wear debris possibly resulting in a bodily response
- Embolism
- Abnormal pain and sensations due to the device
- Infection
- Neurologic complication with possible palsy
- Pseudarthrosis

A complete listing of foreseeable ADREs may also be found in the HOFFMANN® LRF SYSTEM, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems device labeling and Informed Consent Form.

13.3 ADVERSE DEVICE EVENT/INCIDENT REPORTING

In the event that a SADRE, UADE or serious incident occurs, the Investigator is required to notify the Sponsor within 24 hours of being made aware of the event. The Investigator is also required to notify their IRB/EC in accordance with the policies of their local laws and regulations. The

investigator is required to notify the Sponsor within 3 business days of becoming aware of all adverse events.

14 Reoperations

Reoperations and reason(s) for reoperations will be collected throughout the course of the clinical investigation. A reoperation may include, but not limited to, amputation, revision surgery, and/or implant removal.

15 Ethics

This clinical investigation is to be conducted according to International Conference of Harmonisation of Good Clinical Practice (ICH-GCP), applicable regulations, institutional research policies and procedures, Declaration of Helsinki, local regulatory requirements and in compliance with the CIP. Investigators will be trained on the clinical investigation devices and surgical techniques prior to implanting clinical investigation subjects.

This CIP and any amendments will be submitted to a properly constituted independent ethics board, in agreement with local legal prescriptions, for formal approval of the clinical investigation conduct. The decision of the ethics board concerning the conduct of the clinical investigation will be made in writing to the Site Principal Investigator before commencement of this clinical investigation. Clinical investigations shall not begin until the governing regulatory authority has provided full, unconditional approval. Off-label use of the HOFFMANN® LRF CIRCULAR EXTERNAL FIXATION, SALVATION™ EXTERNAL FIXATION SYSTEM, SALVATION™ FUSION BOLTS AND BEAMS, SALVATION™ 2 MIDFOOT NAIL, SALVATION™ 3DI PLATING SYSTEM, T2® ICF INTRAMEDULLARY NAILING SYSTEM, and VALOR™ ANKLE FUSION NAIL Systems is not permitted.

15.1 INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE (EC)

It is the responsibility of the principal investigator at each participating site to obtain prospective approval of the study protocol, protocol amendments, subject information sheets, Informed Consent documents and any other relevant documents, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the site's Investigator Master File**.** Copies of IRB/EC approvals should be forwarded to the Sponsor or its designated representative prior to enrolling subjects. The Investigator must immediately report to the Sponsor or its designated representative if the IRB/EC withdraws its approval of the study for any reason.

15.2 INFORMED CONSENT

The Investigator, or qualified clinical investigation personnel designated to perform this task, will explain the nature of the clinical investigation to the subject, and answer all questions regarding participation in this clinical investigation. Prior to any clinical investigation procedures being performed, the Informed Consent Form (ICF) will be reviewed, signed and dated by the subject, and by the person administering the informed consent. A copy of the ICF will be given to the subject, and the original will be placed in the subject's clinical investigation records. Subjects will need to sign updated versions of the ICF if required by the Investigator's IRB/EC during the course of the clinical investigation.

16 Data Collection Process

The Sponsor will collect clinical data for this clinical investigation utilizing eCRFs through an EDC system. All clinical data is entered into the EDC system by designated personnel at each of the Investigator sites. All data entered in the eCRFs are supported by source documentation.

17 Clinical Investigation Monitoring

It is the responsibility of the Site Principal Investigator to oversee the safety of the clinical investigation at his/her site, to include the careful assessment and appropriate reporting of AEs as noted above as well as the implementation of site data safety. The Sponsor, or designee, will monitor the sites to ensure informed consent has been documented appropriately, to ensure the information documented on the completed case report forms match the medical records and to resolve any differences. The Sponsor will take all steps necessary to ensure data integrity. The Sponsor will also review significant new information, including UADEs and ensure that such information is provided to all Investigators, their IRBs/ECs, and applicable regulatory authorities. Additionally, a quality assurance check will be performed to ensure the investigator is complying with the CIP and applicable regulations in the collection of all clinical investigation data.

18 Data Handling and Record Keeping

Information about clinical investigation subjects will be kept confidential. In the event a subject revokes authorization to collect or use protected health information, the Site Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. The Health Insurance Portability and accountability Act (HIPAA) will apply in order to ensure data protection and document anonymization. Records are to be stored in a secure location. Retention of records shall be maintained through the clinical investigation duration as well as specified years following the clinical investigation completion as required by local regulatory authority.

19 Reports

Analysis will be executed, and interim reports will be prepared on a yearly basis. Upon the completion of all subject's final post-operative assessment, data freeze will take place and the final report will be prepared.

20 Public Registration

The clinical investigation and summary of results will be registered on ClinicalTrials.gov.

21 Completion of the Clinical Investigation

The Investigator will conduct this clinical investigation in compliance with the CIP and will complete the clinical investigation within the timeframe specified in the contract. Continuation of the clinical investigation beyond this time must be mutually agreed upon in writing by both the Investigator and Stryker. The Investigator will provide a summary of the clinical investigation results in accordance with the IRB/EC guidelines.

Stryker may terminate this clinical investigation prematurely, either in its entirety or at this site, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the clinical investigation at their site for reasonable cause, after providing written notice to Stryker a reasonable time in advance of the intended termination. If Stryker terminates the clinical investigation for safety reasons, it will immediately notify the Investigator by telephone and subsequently provide written instructions for clinical investigation termination.

22 Essential Documents

All essential documentation will be stored as specified under the Sponsor's Standard Operating Procedures.

23 Publication Policy

Refer to the clinical investigation agreement for the publication policy.

24 References

21 CFR Part 11:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1

21 CFR Part 50:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1

21 CFR Part 54:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=54&showFR=1

21 CFR Part 56:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56&showFR=1

Elmarsafi T, Anghel EL, Sinkin J, Cooper PS, Steinberg JS, Evens KK, Kim PJ, and Attinger CE. Risk Factors Associated With Major Lower Extremity Amputation After Osseous Diabetic Charcot Reconstruction. The Journal of Foot & Ankle Surgery 2019, 58:295-300.

EQ-5D-5L Questionnaire; EQ-5D™ is a trade mark of the EuroQol Research Foundation.

EU Regulation 2017/745, also known as the EU Medical Device Regulation (EU MDR)
https://publications.europa.eu/en/publication-detail/-/publication/83bdc18f-315d-11e7-9412-01aa75ed71a1/language-en/format-PDF/source-58036705

GCP Guidelines:
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Hansson T, Hansson E, Malchau H. A comparison of common elective orthopaedic surgical procedures. SPINE 2008; 33; 25; 2819-283.

ICH E6 4.8.10(m): https://ichgcp.net/48-informed-consent-of-trial-subjects/

ISO 14155:2020: https://www.iso.org/standard/71690.html

Maher A, Kilmartin, T. An analysis of Euroqol EQ5D and Manchester Oxford Foot Questionnaire. Journal of Foot and Ankle Research 2012; 5; 7

Martin RL, Irrgang JJ, Burdett RG. Evidence of Validity for the Foot and Ankle Ability Measure (FAAM). Foot & Ankle International 2005; 26; 11; 968-983

25 Clinical Investigation Plan Signature Page

Lower Extremity Fixation In Neuropathic Patients Study (FINS)

I have read this Clinical Investigation Plan and agree that this clinical investigation is ethical. I agree to conduct this clinical investigation in accordance with this Clinical Investigation Plan, as well as all applicable regulations and guidelines. I agree to maintain the confidentiality of all information received or developed in connection with this Clinical Investigation Plan.

_____ _____

Signature of Investigator Date of Signature

_____

Name of Investigator (Printed)

26 Document Version History

Version	Effective Date	Description	Revised/Created by
1	07-Oct-2021	Initial version	Jennifer Seidman
2	11-Mar-2022	• Updated to Stryker CIP template and language • Added Hoffman LRF and T2 ICF devices to the study • Updated Statistical Considerations language	Jennifer Seidman
3	27-Apr-2022	• Corrected intended population language from treating neuropathy to treating deformity in neuropathic patients	Jennifer Seidman