NCT04015167

T2 Alpha Tibia Statistical Analysis Plan (SAP)

CLINICAL INVESTIGATION TITLE:	A Post-Market Clinical Evaluation of the Treatment of Tibia Fractures with the T2 Alpha Tibia Nailing System
DEVICE NAME:	T2 Alpha Tibia Nailing System
STATISTICAL ANALYSIS PLAN (SAP) VERSION:	3
CLINICAL INVESTIGATION PLAN (CIP) VERSION:	3
INDICATIONS:	This clinical investigation will adhere to the indications and contraindications for the T2 Alpha Tibia Nailing System as are detailed in the device's Instructions For Use.
CLINICAL INVESTIGATION DESIGN:	• Post-Market, • Multicenter, • Prospective, • Non-Randomized
CONFIDENTIALITY STATEMENT:	This Statistical Analysis 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.
DATE:	July 23rd 2021

Approval Page

APPROVERS			
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1. Administrative Information

1.1. LIST OF ABBREVIATIONS

Acronym	Definition
ADE	Adverse Device Event
AE	Adverse Event
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
EU MDR	European Medical Device Regulation
FR	Final Report
ICF	Informed Consent Form
ICH-GCP	International Conference of Harmonisation Good Clinical Practice
IFU	Instructions for Use
ITT	Intent-to-Treat
Intra-Op	Intra-Operative
IR	Interim/Annual Report
IRB	Institutional Review Board
LTFU	Lost to Follow-Up
MCS	SF-36 Mental Component Summary
PCS	SF-36 Physical Component Summary
PP	Per Protocol
Pre-Op	Pre-Operative
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36v2	36-Item Short Form Health Survey
UADE	Unanticipated Adverse Device Effect

1.2. STATISTICAL ANALYSIS PLAN REVISION HISTORY

Version	Effective Date	Description	Reason
1	25MAR2020	Initial Version	
2	24JUL2020	Adjustment chapter 4.4 Timing of Outcome Assessment	CIP changes, merge of Pre-Operative and Operative/ Discharge visit.
3	23JUL2021	Distinction interim/final Analysis Amendment Table Templates section 7	Revision DQI 20-048, CIP V3

		CIP changes: chapter 2.2	

1.3. ROLES AND RESPONSIBILITIES

Role	Contributor	Affiliation
Author	Sascha Lorenzen	Stryker
(Senior) Statistician	Claudia Beimel	Stryker
Clinical Research Head (CRH)	Rebecca Gibson	Stryker
Clinical Investigation Manager (CIM)	Susanne Hoefer	Stryker

2. Introduction

2.1. BACKGROUND AND RATIONALE

The T2 Tibia Nailing System represents the latest and most comprehensive development of the original intramedullary principles presented by Professor Gerhard Kuentscher in 1940. As an addition to the T2 Nailing System, Stryker has created a new generation tibial implant that offers an efficient treatment option for multiple indications. The T2 Alpha Tibia Nail includes new locking options and the ability to utilize the advanced locking screw which creates an axial and angular stable construct. New instrumentation offers a combination of innovation, simplicity and efficiency that is designed to suit the various needs of surgeons and OR staff.

The T2 Alpha Tibia Nailing System is fully integrated into the T2 Alpha Platform. The system includes two approaches: infrapatellar approach and suprapatellar approach and allows for multiple locking configurations for stable fixation. This clinical investigation will evaluate the safety and efficacy/performance of the T2 Alpha Tibia Nailing System.

2.2. CLINICAL INVESTIGATION DESIGN

This investigation is a prospective, multicenter clinical investigation. It is anticipated that a total of 80 subjects will be enrolled at up to 5 sites. Enrollment is estimated to commence in Q4 of 2018. Neither subjects nor investigators are blinded to treatment and the clinical investigation includes a historical control which will be compared to the T2 Alpha Tibia Nailing System.

The enrollment period is expected to occur over 32 months. Total duration of enrollment, 12 month follow-up and analysis is expected to take 47 months. The clinical investigation has been designed to follow the surgeon's standard of care for tibia fractured subjects, in addition to a 12 month follow-up visit.

3. Research Goals

3.1. FRAMEWORK

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. In general, as central position parameter for quantitative

variables the mean and median will be analyzed. As variation parameter the standard deviation, 95% confidence interval of the mean, interquartile range and maximum and minimum will be calculated. All quantitative variables will be assessed for normality used the Shapiro-Wilk test. For optional visualization of quantitative variables, box-and-whisker plots will be used. Additional analyses like skewness and kurtosis measures of standard errors are also optional.

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).

3.1.1. Primary Analysis / Endpoint

This analysis is only part of the final report. The primary endpoint analysis will only be executed once at the end of the clinical investigation and will not be part of any interim or annual reports or presentations given in front of the final report.

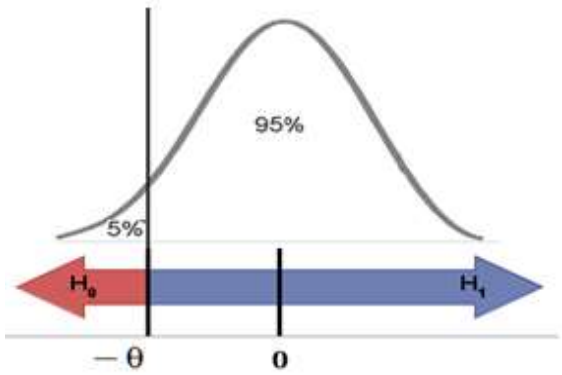
The 12 months post-operative results for subjects implanted with the T2 Alpha Tibia Nailing System will be compared to Sanders et al: Semiextended intramedullary nailing of the tibia using a suprapatellar approach: radiographic results and clinical outcomes at a minimum of 12 months follow-up. J Orthop Trauma, 2014; Sun et al: The outcome comparison of the suprapatellar approach and infrapatellar approach for tibia intramedullary nailing. Int Orthop, 2016; and Chan et al: Suprapatellar Versus Infrapatellar Tibial Nail Insertion: A Prospective Randomized Control Pilot Study. J Orthop Trauma, 2016". Specifically, the SF-36 score results reported by Wang, et al. (2017), Sanders, et al. (2014), Sun, et al. (2016) and Chan, et al. (2016) will serve as the control groups for the T2 Alpha Tibia group.

Higher SF-36 PCS and MCS score results are linked to better subject results and vice versa.

The clinical investigation endpoint is non-inferiority to the control, meaning the clinical investigation result should be equal or better than the control. In this clinical investigation, an equal or better SF-36 score result means equal or greater (≥). As only results from samples will be captured, results are mostly estimates of the true population parameter. These estimates vary by a certain area, where it is expected that the true population parameter falls within. Based on this, it is required to specify a lower limit for the acceptable difference or zone of indifference, denoted as -θ.

Hypotheses were developed to allow for a comparison of the 12 months post-operative SF-36 PCS to evaluate effectiveness / performance. The 12 months post-operative SF-36 PCS is the primary endpoint of this clinical investigation. Hypothesis tests will be one-sided with a significance level α of 5%.

Hypothesis	Equations	Interpretation
Null (H_0)	$A - B < -\theta$	Central tendency of A is inferior to the central tendency of B.
	T2 Alpha Tibia (A) – Control (B, pooled benchmark results) < -θ	
Alternative (H_1)	$A - B \geq -\theta$	Central tendency of A is non-inferior to the central tendency of B.
	T2 Alpha Tibia (A)‑ Control (B, pooled benchmark results) ≥ -θ	



Possible Evidence (p)	Possible Decisions	Possible Conclusions – SF-36 PCS
p-value > α (0.05)	Fail to reject null hypothesis (H_0)	T2 Alpha Tibia < Control (pooled benchmark results) Insufficient evidence to reject the null hypothesis (H_0: A – B < -θ) at the pre-determined significance level of 5%.
p-value ≤ α (0.05)	Reject null hypothesis (H_1)	T2 Alpha Tibia ≥ Control (pooled benchmark results) Sufficient evidence to reject the null hypothesis (H_0: A – B < -θ) at the pre-determined significance level of 5%.

To test non-inferiority, the 12 months mean SF-36 PCS result of the T2 Alpha Tibia group will be compared to the mean estimate of the control group, 43.48 points.

To be able to identify an acceptable difference or zone of indifference (-θ), the lower 90% confidence interval (CI) of the SF-36 PCS result at 12 months post-operative in the control group (Sanders, et al.; Sun, et al.; Chan, et al.) was used as lower limit (lower 90% CI of control is 39.25 points). The maximum acceptable difference in the negative direction is 4.23 points.

Based on the underlying distribution of the data and the result of the normality assessment, either the parametric one-sample t-test or the non-parametric one-sample sign test will be used to compare the 12 months post-operative SF-36 PCS result of the T2 Alpha Tibia group against the value of 39.25 points (mean of control - θ or 43.48 – 4.23 = 39.25 points).

3.1.2. Secondary Analyses

For efficacy/performance, bone consolidation will be assessed by 12 months as measured by Investigator assessment. For Safety, the incidence of device-related adverse events/incidents by 12 months will be monitored through collection and analyses. Both analyses will be part of the final report.
Furthermore, device related adverse events/incidents and the time to (earliest) Device Related Adverse Events/incidents will be analyzed as well. Considered variables, the level of measurement and the planned analysis steps are listed in detail in the SAP.

3.1.3. Additional Analyses

Additional Analyses are outlined in the subsequent sections. Analysis details (variables, level of measurement, planned steps) are listed in-depth in the SAP.

- **Weight-bearing status**
  The weight bearing status will be evaluated and analyzed at the pre-operative visit and at 3 months, 6 months and 12 months. The within subject changes from visit to visit will be analyzed in addition. This analysis will be part of the final report.

- **External Support**
  The status of the subject using external support will be evaluated at the pre-operative visit and at 3 months, 6 months and 12 months. The within subject changes from visit to visit will be analyzed in addition. This analysis will be part of the final report.

- **Mortality**
  For analysis of the time to death or mortality, the Kaplan-Meier method will be used. The times between the date of surgery and the date of the 12 months assessment will be used together with the times between date of surgery and the date of death. This analysis will be part of the final report.

- **Reoperation**
  For analysis of the time to the reoperation, the Kaplan-Meier method will be used. The times between the date of surgery and the date of the 12 months assessment will be used together with the times between date of surgery and the date of reoperation (earliest reoperation in case that one subject experienced more than one reoperation). This analysis will be part of the final report.

- **SF-36 Total Physical Score – Within subject changes by visit**
  The within subject score changes of the SF-36 Total Score from visit to visit will be analyzed to help identify the changes on the subject level. This analysis will be part of the final report.

3.2. SAMPLE SIZE

The 12 months post-operative results for subjects implanted with the T2 Alpha Tibia Nail will be compared to a historical group and results reported by Wang, et al. (2017); Sanders, et al. (2014); Sun, et al. (2016); and Chan, et al. (2016) will serve as the control group for the T2 Alpha Tibia Nail subjects.

Hypotheses were developed to allow for a comparison of 12 months post-operative SF-36 Physical Component Summary (PCS) results and 12 months effectiveness/performance between these two populations.

Benchmark and Objectives for Planned Research	
Endpoint	Non-inferiority related to the SF-36 Physical Component Summary (PCS) for subjects undergoing infrapatellar (IP) and/or suprapatellar (SP) tibia nailing at 12 months post-operative compared to the pooled literature control.
Estimated drop-out rate	20% Source: "Stannard et al: Functional Outcome Following Intramedullary Nailing of the Tibia. A Prospective Randomized Comparison of Piriformis Fossa and Greater Trochanteric Entry Portals JBJS 2011" Stannard et al. reported a lost to follow up rate of 19.6% (11/56). Note: The source of Stannard et al. was used for T2 Alpha Tibia as well as it represents a worst-case drop-out rate.
Results as reported by Benchmark	
Non-inferiority related to the SF-36 Physical Component Summary (PCS) for subjects undergoing infrapatellar (IP) or suprapatellar (SP) tibia nailing at 12 months post-operative. The results from the sources Chan et al, Sanders et al., and Sun et al. were pooled to determine overall two-sided 90% confidence intervals of the mean SF-36 PCS (physical) and mean SF-36 MCS (mental) scores. Note: The results reported by Wang et al. seemed to be based on a different calculation method for the determination of the SF-36 scores and it was not possible to evaluate, what exactly was done by the authors. The score values reported by Wang et al. are much higher compared to what was normally reported in the literature and what was defined in country specific weights and coefficients. Wang et al. reported median	

score values whereas the other authors reported means. As summary score results usually tend to deviate from normality, means and medians might differ significantly. Therefore, the results reported by Wang et al. were not included into the pooled analysis.

Source	Subgroup	Mean SF36-PCS	Mean SF36-MCS	Pooling
Chan et al.	IP	38.00	47.00	included
Chan et al.	SP	46.00	47.00	included
Sanders et al.	SP	40.80	46.00	included
Sun et.al.	SP	49.41	44.71	included
Sun et.al.	IP	43.21	43.81	included
Wang et.al.		*79.10*	*77.00*	*excluded*

Summary of explorative analysis is listed below:

Descriptives

			Statistic	Std. Error
SF-36 PCS Physical at 12 months post-op	Mean		43,4840	1,98495
	90% Confidence Interval for Mean	Lower Bound	39,2524	
		Upper Bound	47,7156	
	Median		43,2100	
	Std. Deviation		4,43849	
	Minimum		38,00	
	Maximum		49,41	
	Range		11,41	
	Interquartile Range		8,31	
SF-36 PCS Mental at 12 months post-op	Mean		45,7040	,63333
	90% Confidence Interval for Mean	Lower Bound	44,3538	
		Upper Bound	47,0542	
	Median		46,0000	
	Std. Deviation		1,41617	
	Minimum		43,81	
	Maximum		47,00	
	Range		3,19	
	Interquartile Range		2,74	

As the mean physical score (PCS) was slightly lower, it was used for the sample size calculation.

For the clinical investigation the one-sided 95% confidence interval will be applied.

Acceptance Criteria for Sample Size Calculation

Significance Level (α)	0.05 (5%)	
Power (1-β)	0.80 (80%)	
Confidence Interval (CI)	0.95 (95%)	
Tails	1	
Path	Non-inferiority T2 Alpha Tibia (A) ≥ Benchmark (B, pooled benchmark results)	
Hypotheses Pair	Null (H_0)	$A - B < -\theta$
	Alternative (H_1)	$A - B \geq -\theta$
Benchmark Timepoint	12 months post-operative	
Benchmark Mean	**43.48 points** SF-36 PCS at 12 months (IP and SP together)	
Benchmark Std. Dev.	No standard deviation results were given by Chan et al., Sanders et al. nor by Wang et al. • Only Sun et al. reported standard deviations at 12 months postoperative for SF-36 PCS of 6.27 for the SP and of 6.52 for the IP subgroup As a worst-case, the double standard deviation reported by Sun et al. was used for the sample size calculation (2 * 6.52 = **13.04 points**)	
Benchmark 90% CI of Mean	**Lower 90% CI: 39.25** (two-sided 90% CI equals a one-sided 95% CI)	

	Upper 90% CI: 47.72
Margin (-θ)	Lower 90% CI of Benchmark: **39.25**
Software Used	IBM SPSS Sample Power V3.0

IBM SPSS Sample Power Output

One goal of the proposed clinical investigation is to test the null hypothesis that the population mean is 39.25. The criterion for significance (alpha) has been set at 0.050. The test is 1-tailed, which means that only an effect in the expected direction will be interpreted.

With the proposed sample size of 61 subjects, the clinical investigation will have power of 80.0% to yield a statistically significant result.

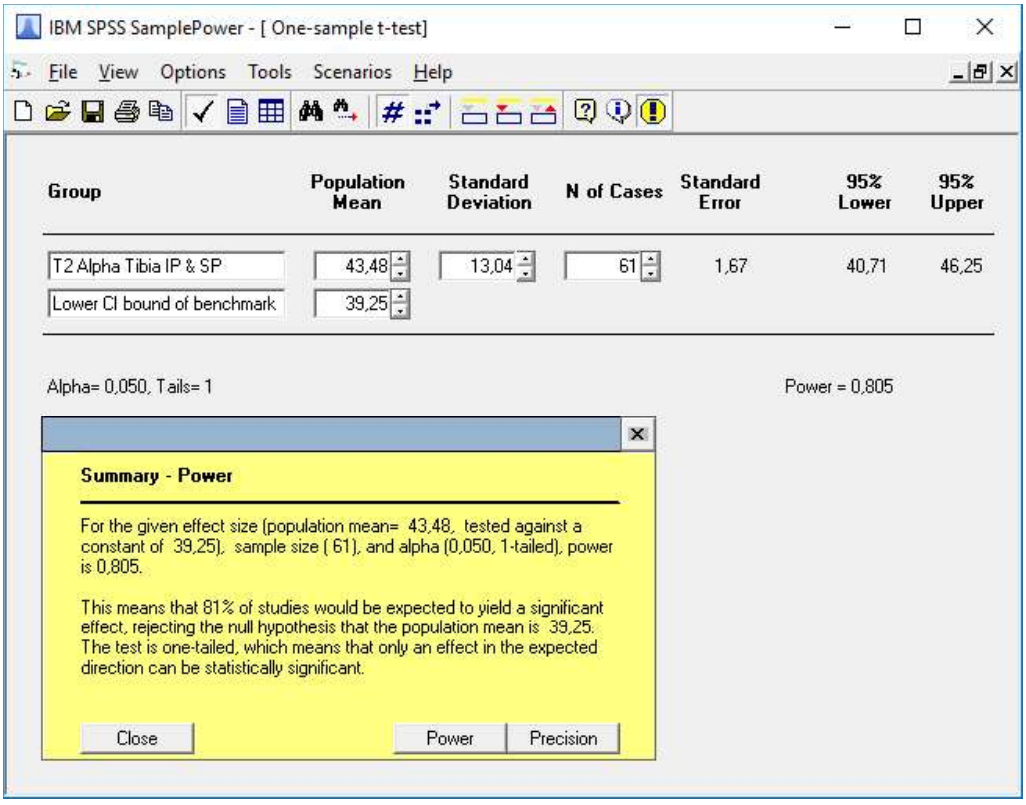
This computation assumes that the population from which the sample will be drawn has a mean of 43.48 with a standard deviation of 13.04. The observed value will be tested against a theoretical value (constant) of 39.25.

This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance.

A second goal of this clinical investigation is to estimate the mean in the population. On average, a clinical investigation of this design would enable us to report the mean with a precision (95.0% confidence level) of plus/minus 2.77 points.

The precision estimated here is the median precision. Precision will vary as a function of the observed standard deviation (as well as sample size), and in any single clinical investigation will be narrower or wider than this estimate.

IBM SPSS Sample Power Output – Screenshot



Estimated drop-out rate is 20% which leads to the requirement of enrolling additional 13 subjects into the clinical investigation.

Sample Size	**Overall number of subjects to be enrolled: 74 subjects (rounded up to 80 subjects)**

Table 3.2: Sample Size Justification

4. Methods

4.1. RANDOMIZATION

No specific methods for assigning subjects will be used for this clinical investigation. A consecutive series of subjects at each site meeting all the eligibility criteria will be enrolled in this clinical investigation.

4.2. STATISTICAL INTERIM ANALYSES AND STOPPING GUIDANCE

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.

As the primary endpoint analysis will only be conducted at the end of the clinical investigation, no adjustment of the significance level will be required.

There will be no stopping rules specified for this clinical investigation.

4.3. TIMING OF FINAL ANALYSES

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

4.4. TIMING OF OUTCOME ASSESSMENT

Subjects in this clinical investigation will be evaluated at Operative/Discharge, and at 3 Months, 6 Months and 12 Months after the index procedure. The follow-up evaluations will include assessment of device-related adverse events/incidents, evaluation per SF-36 PCS and MCS scores as well as clinical assessment of bone consolidation. Investigators should consider weight-bearing, pain and imaging when assessing bone consolidation. See the section below for visit windows and a list of assessments to be performed at each visit, given by the CIP.

Assessment	Operative/ Discharge	3 Months [a, b] (+/-2 weeks)	6 Months [a, b] (+/-3 weeks)	12 Months [b] (+/-4 weeks)
Informed Consent	X[c]			
Demographics & Medical History	X			
Inclusion/Exclusion	X			
Primary Diagnosis	X			
Surgical Procedure	X			
Clinical Assessment of Bone Consolidation [d, e]		X	X	X
SF-36v2 (PCS & MCS)	X [f]	X	X [g]	X [g]
Subject Disposition [h]		X	X	X
Device-Related Adverse Events/Incidents & Reoperations will be collected throughout the course of the Clinical Investigation.				

a. Follow-up visit schedule to reflect Institutions' Standard of Care practices
b. If the subject missed a visit and outside of visit window, every effort should be made to collect data instead of noting visit as missed. Visit windows are calculated from the index event, and not from the previous visit.
c. Informed consent must be obtained prior to enrollment in the study (i.e., prior to performance of any study-related activities).
d. Once bone consolidation is observed, assessment no longer needs to be conducted at the additional follow-up visits.
e. Investigators should consider weight-bearing, pain and imaging when assessing bone consolidation.
f. SF-36v2 evaluation must be collected post-informed consent. This can be collected post-fracture and prior to surgery or immediately post-surgery.
g. If bone consolidation is previously observed at the previous follow-up visit, evaluation is to be collected via phone.
h. Subject Disposition assessment would occur at any time point for subject withdrawal prior to the completion of the clinical investigation.

Table 4.4: Assessments and Clinical Investigation Elements

In addition, the "Operative/Discharge" visit also includes Pre-operative data, which can also be recorded post-operatively, as defined in the CIP. Pre-operative- and operative data is aggregated as "Initial Assessment" in EDC frontend, but separately listed in EDC data exports for analysis. The pre-operative data is captured at "Primary Diagnoses" assessment, operative data at "Surgical Procedure" assessment. The SAP relates to the separate designation pre-operative- and operative assessment, as given by EDC export.

4.5. STATISTICAL SOFTWARE

Statistical Analysis will be performed using IBM SPSS, IBM SPSS Sample Power as well as established standard software packages (e.g. MS Excel).

4.6. MISSING DATA

The intent is to collect as complete a dataset as possible. Nevertheless, in some situations missing data cannot be avoided. The reports and tables therefore will show the number and percentage of missing cases for each analyzed variable in relation to the enrolled cases for each post-operative assessment.

Missing data will be reported for each variable or calculation (if any) and overall totals will be reported including the proportion of missing data (if any).

4.7. CONFIDENCE INTERVALS AND P-VALUES

The following acceptance / rejection criteria were used for this clinical investigation:

Parameter	Acceptance / rejection criteria
Confidence level (1-α)	0.95 (95%)
Significance level (α)	0.05 (5%)
Power (1-β)	0.80 (80%)
Beta-level (β)	0.20 (20%)
Confidence interval of mean	95%
p-value indicating significance	≤ 0.05

Table 4.7: Acceptance / Rejection Criteria

4.8. UNITS

See analysis chapter for details related to units used for the different variables and calculations.

In case of collection of variables with non-SI units (e.g. pounds instead to kilograms), conversion of such data into SI units (and vice versa) will be ensured and both results will be reported for the full set of available subjects next to each other in the interim/annual and/or final reports.

4.9. CALCULATIONS AND TRANSFORMATIONS

Distances between times and differences between score results will be calculated. For full details of variables used for calculations and the creation of new variables based on these calculations, see analysis chapter.

4.10. ASSUMTIONS

In case of deviation from assumptions (e.g. normality), non-parametric methods will be used for analysis. No transformation of such data will be performed.

5. Population and Progress

5.1. ANALYSIS POPULATION

It is expected, that during this clinical investigation only one population for Tibia will exist and all subjects will be analyzed "Per Protocol" (PP). However, it cannot be fully avoided that in theory subjects might need to be excluded from the PP population. In this occasion, there will be two groups being fully analyzed to ensure transparency and avoid bias.

The groups are defined as follows:

- **Intent-to Treat Population**

  The Intent-to-Treat (ITT) Population is defined to be all enrolled subjects. An enrolled subject is a subject that has signed informed consent, all screening procedures have been successfully completed, is eligible and can receive treatment. The ITT population will not be analyzed for the annual reports and will only be included in the final report.

- **Per Protocol Population**

  The Per Protocol (PP) Population is defined to be all subjects in the ITT Population with no major protocol violations. The protocol violations that will exclude a subject are as follows:

  - The subject does not receive the T2 Alpha Tibia Nail
  - The subject does not meet all eligibility criteria
  - The subject has a protocol violation that is considered likely to affect subject outcomes.

  After the clinical investigation has been completed, a review of the data will be conducted to determine which subjects are to be excluded from the PP population.

  The following tables will be created for interim/annual and final reports related to the clinical investigation populations and progress:

Evaluation Variable / Question	Level of Measurement	Analysis Plan
All Forms – Overview & Progress Report		
Counting of available subjects ***Subject Population by Site*** (Variable(s): SITENUM; SUBID)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).
Counting of available subjects ***Subject Population by Visit*** (Variable(s): SITENUM; SUBID; VISITDT)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).
Counting of available subjects ***Subject Population by Visit and by Site*** (Variable(s): SITENUM; SUBID; VISITDT)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).

Table 5.1: Populations and Progress Tables List

5.2. ELIGIBILITY

A subject is defined as eligible if all inclusion and exclusion criteria are fulfilled as it is described in the protocol. For details see CIP.

For tables to be created for the interim/annual and final reports, see chapter 6.2 and tables list 6.2.2.

5.3. WITHDRAWAL / FOLLOW-UP

If, during the clinical investigation, a subject must be prematurely withdrawn from clinical investigation, procedures are outlined in the CIP. 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.

The following tables will be created for interim/annual and final reports related to the numbers of withdrawn subjects (if any):

Evaluation Variable / Question	Level of Measurement	Analysis Plan
All Forms – Overview & Progress Report		
Counting of withdrawn subjects ***Number of Subjects Withdrawn by Site*** (Variable(s): SITENUM; COMPPROT; PRIMRSN)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).
Counting of withdrawn subjects ***Number of Subjects Withdrawn by Site by Visit*** (Variable(s): SITENUM; COMPPROT; PRIMRSN; VISITDT)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).
Comments related to ***Reasons for Subjects Withdrawn*** (Variable(s): RSNSPF)	Text, String	Listing of reasons for subjects being excluded by subject code/ID

Table 5.3: Withdrawal Tables List

5.4. ADHERENCE AND CIP DEVIATIONS

Any CIP deviations will be listed in the interim/annual and final reports. It is optional to describe this chapter in free text or present it in a tabulated format.

6. Analysis

The following tabulated analysis plan 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.

In addition, it will be defined in the text or directly in the tables below, if the variable must be included in an interim/annual report (IR) and/or in the final report (FR).

6.1. HARMS AND SAFETY

Categorization and definitions of (Serious-, Unanticipated-) Adverse Device Effects, (Serious-) Incidents are given in the CIP.

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Adverse Events / Incidents			**IR**	**FR**	**N/A**
Device-Related Adverse Event / Incident (Variable(s): AEEVENT; AEOTHER)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of other Events/Incidents.	X	X	
Describe the AE/Incident (Variable(s): AEDESCRP)	Qualitative, nominal	Listing of other Events/Incidents Description.			X
Unanticipated Adverse Device Event? (Variable(s): AEUADE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Severity (Variable(s): AESEVER)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Describe Treatment: (Variable(s): ACTTREAT)	Qualitative, nominal	Listing of Treatment Description.			X
Action Taken (Variable(s): ACTNONE; ACTMEDS; ACTSURG; ACTLABOT; ACTSHORT; ACTPROHS; ACTOTHER; ACTOTHSP)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given Other specifications.			X
AE Resolution (Variable(s): AERESOLV)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Outcome (Variable(s): AEONWOTR; AEONWTTR; AEREWOTR; AEREWTTR; AETEDISB; AEPERMD; AESUEXP)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Creation of variable ***Number of Adverse Device Effects by Site*** (Variable(s): AEEVENT; SITENUM)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Creation of variable ***Number of Adverse Device Effects per Subject and Site*** (Variable(s): AEEVENT; SITENUM; SUBID)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Creation of variable ***Number of Adverse Device Effects by Visit*** (Variable(s): AEEVENT; VISNAME)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	

Table 6.1: Adverse Events / Incidents Tables List

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Reoperation			**IR**	**FR**	**N/A**
Type of Procedure (Variable(s): TOPAMP; TOPDYNA; TOPIMPREM; TOPIRDEB; TOPRTAINTFIX; TOPINTSPF; TOPREVARTH; TOPARTHSPF; TOPRTAEXTFIX; TOPEXTSPF; TOPOTH; TOPOTHSPF)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listings of implant specifications.	X	X	
Reason(s) for Reoperation (Variable(s): DELUNION; IATRFRAC; IMPBRAK; IMPLFAIL; IMPLOOS; INFEC; MALILGN; MALUNI; NECRS; NONUNIO; PAIN; REOPOTH; REOPOTHSPF)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listings of other specifications.	X	X	

Table 6.2: Reoperation Tables List

6.2. BASELINE CHARACTERISTICS

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Pre-Operative Visit Form – Subject Eligibility – Inclusion & Exclusion Criteria			**IR**	**FR**	**N/A**
Note: Inclusion and exclusion criteria will be checked during monitoring and reported by a statement (e.g. all subjects fulfilled the inclusion criteria).					
Inclusion Criteria Questions (Variable(s): INCLA; INCLB; INCLC)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Exclusion Criteria Questions (Variable(s): EXCLA; EXCLB)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X

Table 6.2.1: Pre-Operative Visit Form - Subject Eligibility – Inclusion & Exclusion Criteria Tables List

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Pre-Operative Visit Form - Subject Demographics			**IR**	**FR**	**N/A**
*Creation of variable **Age [years]** Difference between **Date of Surgery [dd.mm.yyyy]** and **Date of Birth/DOB [dd.mm.yyyy]** in [years]* (Variable(s): BIRTHDT; VISITDT; VISNAME)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Gender (Variable(s): GENDER)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Race (Variable(s): AMERIND; ASIAN; BLKAFR; NATHAW; CAUS; RACEOTH; RACEOTHR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.	X	X	
Height [captured in inches or cm] In the analysis, all values will be reported in inches and cm next to each other. (Variable(s): HGHTM)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95%			X

		confidence interval for mean, Shapiro-Wilk Test.			
Weight [captured in lbs or kg] In the analysis, all values will be reported in lbs and kg next to each other. (Variable(s): WEIGHTKG)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.			X
Body Mass Index [kg/m^2] (Variable(s): BMI)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	

Table 6.2.2: Pre-Operative Visit Form - Subject Demographics Tables List

Evaluation Variable / Question	**Level of Measurement**	**Analysis Plan**	**Inclusion**		
Pre-Operative Visit Form – Current Relevant Medical Conditions			**IR**	**FR**	**N/A**
Current Relevant Medical Conditions (Variable(s): CURCOND; CONDSPC)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.	X	X	

Table 6.2.3: Pre-Operative Visit Form - Current Relevant Medical Conditions

Evaluation Variable / Question	**Level of Measurement**	**Analysis Plan**	**Inclusion**		
Pre-Operative Visit Form – Subject Evaluation			**IR**	**FR**	**N/A**
Tobacco Use: (Variable(s): TOBCCO)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Corticosteroids Taking: (Variable(s): CORTICO)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Affected (Study) Tibia (Variable(s): AFFCTIB)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Fracture Classification: (Variable(s): FRUCLS)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Mechanism of Injury: (Variable(s): MECHINJ; OTHSPC)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.	X	X	
Primary Indication: (Variable(s): PRIMIND)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.	X	X	
Previous History of Surgery to the Affected Tibia (Variable(s): PREVHIST)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.		X	
Procedure 1 (Variable(s): PROCNM1)	Text, String				X

Procedure Date 1 (Variable(s): PROCDT1)	Quantitative, ratio Date/Time	Listing of comments and dates together identified by subject code/ID			X
Procedure 2 (Variable(s): PROCNM2)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 2 (Variable(s): PROCDT2)	Quantitative, ratio Date/Time				X
Procedure 3 (Variable(s): PROCNM3)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 3 (Variable(s): PROCDT3)	Quantitative, ratio Date/Time				X
Procedure 4 (Variable(s): PROCNM4)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 4 (Variable(s): PROCDT4)	Quantitative, ratio Date/Time				X
Previous History of Surgery to the Contralateral Tibia (Variable(s): PREVHISTCONTR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given specifications.		X	
Procedure 1 (Variable(s): CONTRPROCNM1)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 1 (Variable(s): CONTRPROCDT1)	Quantitative, ratio Date/Time				X
Procedure 2 (Variable(s): CONTRPROCNM2)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 2 (Variable(s): CONTRPROCDT2)	Quantitative, ratio Date/Time				X
Procedure 3 (Variable(s): CONTRPROCNM3)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 3 (Variable(s): CONTRPROCDT3)	Quantitative, ratio Date/Time				X
Procedure 4 (Variable(s): CONTRPROCNM4)	Text, String	Listing of comments and dates together identified by subject code/ID			X
Procedure Date 4 (Variable(s): CONTRPROCDT4)	Quantitative, ratio Date/Time				X
Creation of variable ***Number of previous history of surgery to the Affected Tibia by Subject*** (Variable(s): PROCNM1; PROCNM2; PROCNM3; PROCNM4)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Creation of variable ***Number of previous history of surgery to the Contralateral Tibia by Subject*** (Variable(s): CONTRPROCNM1; CONTRPROCNM2; CONTRPROCNM3; CONTRPROCNM4)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Weight Bearing (Variable(s): WEIGTBEAR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Weight Bearing Specification (Variable(s): WEIGTSPC)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
External Support Prior to the Tibia Fracture (Variable(s): EXTRSUPP)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	

Table 6.2.4: Pre-Operative Visit Form – Subject Evaluation Tables List

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Pre-Operative Visit Form – SF-36 Score (post fracture, prior to surgery)			**IR**	**FR**	**N/A**
In general, would you say your health is (Variable(s): GH01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Compared to one year ago, how would you rate your health in general now? (Variable(s): HT_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports (Variable(s): PF01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (Variable(s): PF02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Lifting or carrying groceries (Variable(s): PF03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Climbing several flights of stairs (Variable(s): PF04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Climbing one flight of stairs (Variable(s): PF05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Bending, kneeling, or stooping (Variable(s): PF06_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Walking more than a mile (Variable(s): PF07_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Walking several hundred yards (Variable(s): PF08_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Walking one hundred yards (Variable(s): PF09_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Bathing or dressing yourself (Variable(s): PF10_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Cut down the amount of time you spent on work or other activities (Variable(s): RP01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Accomplished less than you would like (Variable(s): RP02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Were limited in the kind of work or other activities (Variable(s): RP03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Had difficulty performing the work or other activities (for example, it took extra effort) (Variable(s): RP04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Cut down the amount of time you spent on work or other activities (Variable(s): RE01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Accomplished less than you would like (Variable(s): RE02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did work or other activities less carefully than usual (Variable(s): RE03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X

During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Variable(s): SF01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
How much bodily pain have you had during the past 4 weeks? (Variable(s): BP01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Variable(s): BP02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you feel full of life? (Variable(s): VT01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you been very nervous? (Variable(s): MH01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt so down in the dumps that nothing could cheer you up? (Variable(s): MH02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt calm and peaceful? (Variable(s): MH03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you have a lot of energy? (Variable(s): VT02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt downhearted and depressed? (Variable(s): MH04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you feel worn out? (Variable(s): VT03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you been happy? (Variable(s): MH05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you feel tired? (Variable(s): VT04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? (Variable(s): SF02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I seem to get sick a little easier than other people (Variable(s): GH02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I am as healthy as anybody I know (Variable(s): GH03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I expect my health to get worse (Variable(s): GH04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
My health is excellent (Variable(s): GH05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Physical Functioning (Variable(s): PFSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95%	X	X	

		confidence interval for mean, Shapiro-Wilk Test.			
Role Physical (Variable(s): RPSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Bodily Pain (Variable(s): BPSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
General Health (Variable(s): GHSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Vitality (Variable(s): VTSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Social Functioning (Variable(s): SFSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Role Emotional (Variable(s): RESCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Mental Health (Variable(s): MHSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum,	X	X	

		standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.			
Total Physical Score (Variable(s): PCSSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Total Mental Score (Variable(s): MCSSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	

Table 6.2.5: Pre-Operative Visit Form – SF-36 Score (post fracture, prior to surgery) Tables List

6.3. INTRA-OPERATIVE CHARACTERISTICS

Evaluation Variable / Question	**Level of Measurement**	**Analysis Plan**	**Inclusion**		
Operative Visit – Operative Procedure			**IR**	**FR**	**N/A**
Date of Surgery: (Variable(s): VISITDT; VISNAME)	Date/Time	Listing the first and last surgery in the report text to describe from which date to which date subjects were operated.		X	
Date of Admission: (Variable(s): ADMINDT; VISNAME)	Date/Time	None			X
Date of Discharge: (Variable(s): DISCHRDT; VISNAME)	Date/Time	None			X
Creation of variable ***Difference between Date of Admission [dd.mm.yyyy] and Date of Surgery [dd.mm.yyyy] in / | days | /*** (Variable(s): ADMINDT; VISITDT; VISNAME)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.		X	
Surgery Start Time (24 hour clock): (Variable(s): SURGSTTM)	Date/Time	None			X
Surgery Stop Time (24 hour clock): (Variable(s): SURGSPTM)	Date/Time	None			X
Difference between Surgery Start Time and Surgery Stop Time in / | hh:mm | / (Variable(s): SURGSTTM; SURGSPTM)	Quantitative, ratio Date/Time	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.		X	
Amount of Blood Infused (Variable(s): BLOODINF)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing		X	

		cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.			
Type of Anesthesia: (Variable(s): TYPANEST)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Were there any technical difficulties during surgery? (Variable(s): SURGDIFF; SURGDESC)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given description.	X	X	
Were any concomitant procedure done during surgery? (Variable(s): CONPROC; CONPROCD)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given description.	X	X	

Table 6.3.1: Operative Visit – Surgical Procedure Tables List

Evaluation Variable / Question	**Level of Measurement**	**Analysis Plan**	**Inclusion**		
Operative Visit – Implant Specification and Locking Information			**IR**	**FR**	**N/A**
Nail Reference Number (xxxx/xxxx): (Variable(s): REFNUM)	Qualitative, nominal	None, used to populate nail details into database			X
Approach (Variable(s): APPRCH)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Proximal Locking Mode (Variable(s): PROXLOCMD)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
If Static Proximal Locking Mode (Variable(s): PRXOBLSTLSCR; PRXOBLANGSC; DISOBLSTLSCR; DISOBLANGLSCR; OBLSTLSCR; MLSTLSCR; MLSTANGLSCR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Distal Locking Screws (Variable(s): PROMLSTLSCR; PROMLANGLSCR; DISMLSTNLSCR; DISMLANGLSCR; APSTNLSCR; APANGLSCR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Was the Distal Targeting Device used? (Variable(s): DISTTARGT)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
Was an End Cap used? (Variable(s): ENDCAP)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
If yes, check which length of End Cap was used (Variable(s): ENDCAPLENTH)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	

Table 6.3.2: Operative Visit – Implant Specification and Locking Information

6.4. EARLY POST-OPERATIVE CHARACTERISTICS

N/A

6.5. POST-OPERATIVE CHARACTERISTICS

The analysis of the Postoperative data must be performed separately for each follow-up visit listed in table 4.4 in accordance to the following tables in this chapter. New Variables must be created individually for each follow-up visit.

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Post-Operative Visit Form – Physical Exam			**IR**	**FR**	**N/A**
Date of Visit:	Date/Time	None			X
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of Visit [dd.mm.yyyy] In /| days |/*** (Variable(s): VISITID; VISNAME)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.		X	
Is the subject weight bearing? (Variable(s): WEIGHTBEAR)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Specify, Full or Partial (Variable(s): FULPART)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Is the subject using an external support? (Variable(s): EXTRSUPP)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).	X	X	
Has the bone consolidated (consider weight-bearing, pain and imaging)? (Variable(s): BONECONS; EXPLN)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any). Listing of given explanations.	X	X	

Table 6.5.1: Post-Operative Visit Form – Physical Exam Tables List

Evaluation Variable / Question	Level of Measurement	Analysis Plan	Inclusion		
Post-Operative Visit Form – SF-36 Score			**IR**	**FR**	**N/A**
In general, would you say your health is (Variable(s): GH01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Compared to one year ago, how would you rate your health in general now? (Variable(s): HT_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports (Variable(s): PF01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf (Variable(s): PF02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Lifting or carrying groceries (Variable(s): PF03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Climbing several flights of stairs (Variable(s): PF04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Climbing one flight of stairs (Variable(s): PF05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Bending, kneeling, or stooping (Variable(s): PF06_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Walking more than a mile (Variable(s): PF07_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Walking several hundred yards (Variable(s): PF08_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X

Walking one hundred yards (Variable(s): PF09_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Bathing or dressing yourself (Variable(s): PF10_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Cut down the amount of time you spent on work or other activities (Variable(s): RP01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Accomplished less than you would like (Variable(s): RP02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Were limited in the kind of work or other activities (Variable(s): RP03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Had difficulty performing the work or other activities (for example, it took extra effort) (Variable(s): RP04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Cut down the amount of time you spent on work or other activities (Variable(s): RE01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Accomplished less than you would like (Variable(s): RE02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did work or other activities less carefully than usual (Variable(s): RE03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Variable(s): SF01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
How much bodily pain have you had during the past 4 weeks? (Variable(s): BP01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Variable(s): BP02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you feel full of life? (Variable(s): VT01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you been very nervous? (Variable(s): MH01_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt so down in the dumps that nothing could cheer you up? (Variable(s): MH02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt calm and peaceful? (Variable(s): MH03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you have a lot of energy? (Variable(s): VT02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you felt downhearted and depressed? (Variable(s): MH04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Did you feel worn out? (Variable(s): VT03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Have you been happy? (Variable(s): MH05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X

Did you feel tired? (Variable(s): VT04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)? (Variable(s): SF02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I seem to get sick a little easier than other people (Variable(s): GH02_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I am as healthy as anybody I know (Variable(s): GH03_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
I expect my health to get worse (Variable(s): GH04_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
My health is excellent (Variable(s): GH05_RESPONSE)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).			X
Physical Functioning (Variable(s): PFSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Role Physical (Variable(s): RPSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Bodily Pain (Variable(s): BPSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
General Health (Variable(s): GHSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Vitality (Variable(s): VTSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum,	X	X	

		standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.			
Social Functioning (Variable(s): SFSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Role Emotional (Variable(s): RESCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Mental Health (Variable(s): MHSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Total Physical Score (Variable(s): PCSSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	
Total Mental Score (Variable(s): MCSSCORE)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.	X	X	

Table 6.5.2: Post-Operative Visit Form – SF-36 Score Tables List

6.6. ANALYSIS OF CI ENDPOINTS

Evaluation Variable / Question	Level of Measurement	Analysis Plan
Endpoints – Primary Endpoint		
Use variable ***SF-36 Total Physical Score 12 Months [points]:*** Based on the underlying distribution of the data and the result of the normality assessment, either the parametric one-sample t-test or the non-parametric one-sample sign test will be used to compare the 12 months post-operative SF-36 score results of the T2 Alpha Tibia group against the value of 39.25 points. The complete available SPSS tables content related to either the one-sample t-test or the one-sample sign test will be included in the final report (under no circumstances, creation of this analysis in any interim/annual report). (Variable(s): VISITDT; PCSSCORE)		

Table 6.6.1: Endpoints – Primary Endpoint Tables List

Evaluation Variable / Question	Level of Measurement	Recode and Analysis Plan	Inclusion		
All Assessments – Fracture Healing			**IR**	**FR**	**N/A**
3 Months - **4. Has the bone consolidated (consider weight-bearing, pain and imaging)?** (Variable(s): VISITDT; BONECONS)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
6 Months - **4. Has the bone consolidated (consider weight-bearing, pain and imaging)?** (Variable(s): VISITDT; BONECONS)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	
12 Months - **4. Has the bone consolidated (consider weight-bearing, pain and imaging)?** (Variable(s): VISITDT; BONECONS)	Qualitative, nominal	Proportions, frequencies, column and row totals, missing proportion (if any).		X	

Table 6.6.2: Endpoints – Secondary Endpoint Fracture Healing Tables List

Evaluation Variable / Question	Level of Measurement	Recode and Analysis Plan	Inclusion		
Adverse Events – Time to (earliest) Device Related Adverse Event / *Incident*			**IR**	**FR**	**N/A**
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of First Device Related Adverse Event [dd.mm.yyyy] in /| days |/*** (Variable(s): VISITDT; VISNAME; AEONSTDT)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.		X	
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of 12 Months Visit [dd.mm.yyyy] in /| days |/*** (Variable(s): VISITDT; VISNAME)	Quantitative, ratio	N/A (Analyzed above), used for survivorship		X	
Create new variable ***"Grouping variable – First Device Related Adverse Event"*** (Variable(s): AEEVENT)	Qualitative, nominal	- censored = survivors - events = first (earliest) Device Related Adverse Event		X	
Create new variable ***"Combined Time – First Device Related Adverse Event"*** (Variable(s): AEONSTDT)	Quantitative, ratio	- Use time between surgery and 12 months visit for surviving subjects - Use time between surgery and first device related adverse event for subjects with device related adverse event		X	
Use variables ***"Combined Time – First Device Related Adverse Event"***	Qualitative,	Case summary with number and percentage of valid		X	

and ***"Grouping variable – First Device Related Adverse Event"***	nominal Quantitative, ratio	cases/values, missing cases/values (if any) and total cases/values. Kaplan-Meier survival analysis: subject ID, time, status, cumulative proportion, Kaplan-Meier estimate, standard error of KM estimate, number of cumulative events, number of remaining cases, mean for survival time with 95% confidence interval, survival graph, hazard graph.			

Table 6.6.3: Endpoints – Secondary Endpoint Time to (earliest) Device Related Adverse Event / Incident Tables List

6.7. ADDITIONAL ANALYSIS

6.7.1. SF-36 Total Physical Score Comparison

Evaluation Variable / Question	Level of Measurement	Analysis Plan
All Assessments – SF-36 Total Physical Score Comparison		
Use ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 3 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 3 Months [points]"*** to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)		
Use ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 6 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 6 Months [points]"*** to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)		
Use ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 12 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total Physical Score Pre-Op [points]"*** *and* ***"SF-36 Total Physical Score 12 Months [points]"*** to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)		
Use ***"SF-36 Total Physical Score 3 Months [points]"*** *and* ***"SF-36 Total Physical Score 6 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total Physical Score 3 Months [points]"*** *and* ***"SF-36 Total Physical Score 6 Months [points]"***:to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)		
Use ***"SF-36 Total Physical Score 3 Months [points]"*** *and* ***"SF-36 Total Physical Score 12 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total Physical Score 3 Months [points]"*** *and* ***"SF-36 Total Physical Score 12 Months [points]"***:to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)		
Use ***"SF-36 Total Physical Score 6 Months [points]"*** *and* ***"SF-36 Total Physical Score 12 Months [points]"***: Based on the underlying distribution of the data in both groups and the result of the normality assessment, either the parametric paired samples t-test or the non-parametric Wilcoxon test will be used to compare ***"SF-36 Total***		

Physical Score 6 Months [points]" *and* ***"SF-36 Total Physical Score 12 Months [points]"***:to evaluate the SF-36 PCS score change by subject (improvement or decrease). The complete available SPSS tables content related to either the paired samples t-test or the Wilcoxon test will be included in the final report. (Variable(s): VISITDT; PCSSCORE)

Table 6.7.1: All Assessments – SF-36 Total Physical Score Comparison Tables List

6.7.2. Weight-bearing status

As listed above, the weight bearing status will be evaluated and analyzed at the pre-operative visit and at 3 months, 6 months and 12 months. The within subject changes from visit to visit will be analyzed in addition. This analysis is part of the final report.

The variable capturing weight bearing will be used with "yes" (including partial and full) versus "no" weightbearing.

Evaluation Variable / Question	Level of Measurement	Recoding
All Assessments - Weight-bearing status		
Recode initial weightbearing status at pre-op visit into new variable ***"Pre-Op Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	The initial variable capturing weight bearing pre-op will be recoded with "yes" (including partial and full) versus "no" weightbearing.
Recode initial weightbearing status at pre-op visit into new variable ***"3 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	The initial variable capturing weight bearing at 3 months will be recoded with "yes" (including partial and full) versus "no" weightbearing.
Recode initial weightbearing status at pre-op visit into new variable ***"6 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	The initial variable capturing weight bearing at 6 months will be recoded with "yes" (including partial and full) versus "no" weightbearing.
Recode initial weightbearing status at pre-op visit into new variable ***"12 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	The initial variable capturing weight bearing at 12 months will be recoded with "yes" (including partial and full) versus "no" weightbearing.

Table 6.7.2.1: All Assessments – Weight-bearing status Recoding

New variables (10) will then be created for each possible pair/comparison. Negative changes (from "yes" to "no") will be coded with "negative change" and positive changes (from "no" to "yes") with be coded with "positive change". If there is no change (from "yes" to "yes" or from "no" to "no"), the coding will be "no change".

Evaluation Variable / Question	Level of Measurement	Coding and Analysis Plan
All Assessments - Weight-bearing status		
Create new variable ***"Weightbearing status change between pre-operative visit and 3 months"*** *based on comparison of* ***"Pre-Op Weightbearing Dichotomous"*** *with* ***"3 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).

*Create new variable **"Weightbearing status change between pre-operative visit and 6 months"** based on comparison of **"Pre-Op Weightbearing Dichotomous"** with **"6 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
*Create new variable **"Weightbearing status change between pre-operative visit and 12 months"** based on comparison of **"Pre-Op Weightbearing Dichotomous"** with **"12 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
*Create new variable **"Weightbearing status change between 3 months and 6 months"** based on comparison of **"3 Months Weightbearing Dichotomous"** with **"6 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
*Create new variable **"Weightbearing status change between 3 months and 12 months"** based on comparison of **"3 Months Weightbearing Dichotomous"** with **"12 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
*Create new variable **"Weightbearing status change between 6 months and 12 months"** based on comparison of **"6 Months Weightbearing Dichotomous"** with **"12 Months Weightbearing Dichotomous"*** (Variable(s): VISITDT; WEIGHTBEAR)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).

Table 6.7.2.2: All Assessments – Weight-bearing status Tables List

6.7.3. External Support

As listed above, the status of the subject using external support will be evaluated at the pre-operative visit and at 3 months, 6 months and 12 months. The within subject changes from visit to visit will be analyzed in addition. This analysis is part of the final report.

The variable capturing "Is the subject using an external support" will be used and recoded into a new variable for each visit with the options "no" (using no support at all) versus "yes" (including Walker, Cane, One Crutch or Two Crutches).

Evaluation Variable / Question	**Level of Measurement**	**Recoding**
All Assessments – External support status		
*Recode initial external support status at pre-op visit into new variable **"Pre-Op External Support Dichotomous"*** (Variable(s): EXTRSUPP)	Qualitative, nominal	The variable capturing "Is the subject using an external support" will be used and recoded into a new variable for each visit with the options "no" (using no support at all) versus "yes" (including Walker, Cane, One Crutch or Two Crutches).
*Recode initial external support status at pre-op visit into new variable **"3***	Qualitative, nominal	The variable capturing "Is the subject using an external support" will be used and recoded into a new variable for each visit with the options "no" (using no support at all)

Months External Support Dichotomous" (Variable(s): VISITDT; EXTRSUPP)		versus "yes" (including Walker, Cane, One Crutch or Two Crutches).
Recode initial external support status at pre-op visit into new variable ***"6 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	The variable capturing "Is the subject using an external support" will be used and recoded into a new variable for each visit with the options "no" (using no support at all) versus "yes" (including Walker, Cane, One Crutch or Two Crutches).
Recode initial external support status at pre-op visit into new variable ***"12 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	The variable capturing "Is the subject using an external support" will be used and recoded into a new variable for each visit with the options "no" (using no support at all) versus "yes" (including Walker, Cane, One Crutch or Two Crutches).

Table 6.7.3.1: All Assessments – External Support Recoding

New variables (10) will then be created for each comparison listed below. Negative changes (from "no" to "yes") will be coded with "negative change" and positive changes (from "yes" to "no") with be coded with "positive change". If there is no change (from "yes" to "yes" or from "no" to "no"), the coding will be "no change".

Evaluation Variable / Question	Level of Measurement	Coding and Analysis Plan
All Assessments - External support status		
Create new variable ***"External support status change between pre-operative visit and 3 months"*** *based on comparison of* ***"Pre-Op External Support Dichotomous"*** *with* ***"3 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
Create new variable ***"External support status change between pre-operative visit and 6 months"*** *based on comparison of* ***"Pre-Op External Support Dichotomous"*** *with* ***"6 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
Create new variable ***"External support status change between pre-operative visit and 12 months"*** *based on comparison of* ***"Pre-Op External Support Dichotomous"*** *with* ***"12 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
Create new variable ***"External support status change between 3 months and 6 months"*** *based on comparison of* ***"3 Months External Support Dichotomous"*** *with* ***"6***	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change"

Months External Support Dichotomous" (Variable(s): VISITDT; EXTRSUPP)		Proportions, frequencies, column and row totals, missing proportion (if any).
Create new variable ***"External support status change between 3 months and 12 months"*** *based on comparison of* ***"3 Months External Support Dichotomous"*** *with* ***"12 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).
Create new variable ***"External support status change between 6 months and 12 months"*** *based on comparison of* ***"6 Months External Support Dichotomous"*** *with* ***"12 Months External Support Dichotomous"*** (Variable(s): VISITDT; EXTRSUPP)	Qualitative, nominal	- Negative changes (from "yes" to "no") = "negative change" - Positive changes (from "no" to "yes") = "positive change" - No change (from "yes" to "yes" or from "no" to "no") = "no change" Proportions, frequencies, column and row totals, missing proportion (if any).

Table 6.7.3.2: All Assessments – External support status Tables List

6.7.4. Mortality

For analysis of the time to death or mortality, the Kaplan-Meier method will be used. The times between surgery and the 12 months assessment will be used together with the times between surgery and the date of death. This analysis is part of the final report.

Evaluation Variable / Question	Level of Measurement	Recode and Analysis Plan
All Assessments - Mortality		
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of Death [dd.mm.yyyy] in [| days |]*** (Variable(s): VISITDT; DOSEDD)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of 12 Months Visit [dd.mm.yyyy] in [| days |]*** (Variable(s): VISITDT)	Quantitative, ratio	N/A (Analyzed above), used for survivorship
Create new variable ***"Grouping variable - Mortality"*** (Variable(s): PRIMRSN)	Qualitative, nominal	- censored = survivors - events = death
Create new variable ***"Combined Time - Mortality"*** (Variable(s): VISITDT; DOSEDD)	Quantitative, ratio	- Use time between surgery and 12 months visit for surviving subjects - Use time between surgery and death for deceased subject

Use variables ***"Combined Time - Mortality"*** *and* ***"Grouping variable - Mortality"***	Qualitative, nominal Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Kaplan-Meier survival analysis: subject ID, time, status, cumulative proportion, Kaplan-Meier estimate, standard error of KM estimate, number of cumulative events, number of remaining cases, mean for survival time with 95% confidence interval, survival graph, hazard graph.

Table 6.7.4: All Assessments – Mortality Tables List

6.7.5. Revision Surgery

For analysis of the time to the revision surgery, the Kaplan-Meier method will be used. The times between surgery and the 12 months assessment will be used together with the times between surgery and the date of revision (earliest revision in case that one subject experienced more than one revision). This analysis is part of the final report.

Evaluation Variable / Question	Level of Measurement	Recode and Analysis Plan
Adverse Events / Revision Surgery		
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of First Revision [dd.mm.yyyy] in [| days |]*** (Variable(s): VISITDT)	Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***Difference between Date of Surgery [dd.mm.yyyy] and Date of 12 Months Visit [dd.mm.yyyy] in [| days |]*** (Variable(s): VISITDT)	Quantitative, ratio	N/A (Analyzed above), used for survivorship
Create new variable ***"Grouping variable – First Revision"*** (Variable(s): VISITDT)	Qualitative, nominal	- censored = survivors - events = first (earliest) Revision
Create new variable ***"Combined Time – First Revision"*** (Variable(s): VISITDT)	Quantitative, ratio	- Use time between surgery and 12 months visit for surviving subjects - Use time between surgery and first revision for subjects with revision(s)
Use variables ***"Combined Time – First Revision"*** *and* ***"Grouping variable – First Revision"***	Qualitative, nominal Quantitative, ratio	Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Kaplan-Meier survival analysis: subject ID, time, status, cumulative proportion, Kaplan-Meier estimate, standard error of KM estimate, number of cumulative events, number of remaining cases, mean for survival time with 95% confidence interval, survival graph, hazard graph.

Table 6.7.5: All Assessments – Revision Surgery Tables List

6.7.6. SF-36 Total Physical Score – Within subject changes by visit

The within subject score changes of the SF-36 Total Physical Score from visit to visit will be analyzed to help identifying the changes on the subject level. This analysis is part of the report.

Evaluation Variable / Question	Level of Measurement	Coding and Analysis Plan
All Assessments - SF-36 Total Physical Score Within Subject Changes		
Creation of variable ***"SF-36 Total Physical Score change between pre-operative visit and 3 Months [points]"***	Quantitative, interval	Calculate difference (could be negative or positive).

Difference between ***"SF-36 Total Physical Score Pre-Op [points]"*** *with* ***"SF-36 Total Physical Score 3 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)		Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***"SF-36 Total Physical Score change between pre-operative visit and 6 Months [points]"*** *Difference between* ***"SF-36 Total Physical Score Pre-Op [points]"*** *with* ***"SF-36 Total Physical Score 6 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)	Quantitative, interval	Calculate difference (could be negative or positive). Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***"SF-36 Total Physical Score change between pre-operative visit and 12 Months [points]"*** *Difference between* ***"SF-36 Total Physical Score Pre-Op [points]"*** *with* ***"SF-36 Total Physical Score 12 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)	Quantitative, interval	Calculate difference (could be negative or positive). Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***"SF-36 Total Physical Score change between 3 Months and 6 Months [points]"*** *Difference between* ***"SF-36 Total Physical Score 3 Months [points]"*** *with* ***"SF-36 Total Physical Score 6 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)	Quantitative, interval	Calculate difference (could be negative or positive). Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***"SF-36 Total Physical Score change between 3 Months and 12 Months [points]"*** *Difference between* ***"SF-36 Total Physical Score 3 Months [points]"*** *with* ***"SF-36 Total Physical Score 12 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)	Quantitative, interval	Calculate difference (could be negative or positive). Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.
Creation of variable ***"SF-36 Total Physical Score change between 6 Months and 12 Months [points]"*** *Difference between* ***"SF-36 Total Physical Score 6 Months [points]"*** *with* ***"SF-36 Total Physical Score 12 Months [points]"*** (Variable(s): VISITDT; PCSSCORE)	Quantitative, interval	Calculate difference (could be negative or positive). Case summary with number and percentage of valid cases/values, missing cases/values (if any) and total cases/values. Mean, median, interquartile range, maximum, minimum, standard deviation, 95% confidence interval for mean, Shapiro-Wilk Test.

Table 6.7.6: All Assessments – SF-36 Total Physical Score Within Subject Changes

7. Table Templates (Tables, Figures, Listings - TFL)

Tables must consist of at least a headline, the variable/analysis-object label and column headers. Furthermore, the table headline must contain the "Analysis Section"(e.g. Demographics, Operative) the variable label (e.g. Gender, Age) as well as the table type (Frequencies, Listing). If the table is referring to a subgroup, a notification must be entered in the headline as well. Figures (if any) must be clearly labeled and numbered by a figure number and title in addition to the axis and category labeling created by software packages (e.g. IBM SPSS).

7.1. FREQUENCIES

All answered response options must be listed with the appropriate label, other response options do not have to be displayed necessarily. In the event of missing answers, the frequencies must be included in an extra row as well ("*Missing*"). All given answers must be added up in an extra row ("*Total*"). In addition to the number of frequencies, percentages must be displayed in a separate column.

"Analysis Section" – "Variable Label" – Frequencies

Characteristic		**n**	**%**
"Variable Label"	"Response A"	*"xxx"*	*"xxx"*
	"Response B"	*"xxx"*	*"xxx"*
	Missing	*"xxx"*	*"xxx"*
	Total	*"xxx"*	*"xxx"*

Table 7.1.1: Frequencies Table Template

If multiple subgroups/clusters (e.g. Sites, Visits) should be displayed in one table, an extra column ("*Group X*") and/or extra rows ("*Group Y*") must be added. Same applies to (sub-) questions, which can be merged in one table. It is recommended to add an extra "Total" column and row, for adding up the subgroups, if possible, from a statistical point of view. In addition, subgroups must be named in the headline as well ("*by Group X and by Group Y*").

"Analysis Section" – "Variable Label" – Frequencies – by "Group X" and "Group Y"

Characteristic		***"Group X1"***		***"Group X2"***		**Total**	
		n	**%**	**n**	**%**	**n**	**%**
"Group Y1"	*"Response A"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	"Response B"	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Missing	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Total	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
"Group Y2	*"Response A"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	"Response B"	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Missing	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Total	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
Total	*"Total Response A"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	"Total Response B"	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Missing	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*
	Total	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*	*"xxx"*

Table 7.1.2: Grouped Frequencies Table Template

7.2. DESCRIPTIVE STATISTICS

Descriptive Statistic tables must contain the items listed in Table 7.2.1. Furthermore, the associated unit must be displayed. If the values are referring to a subgroup (n) and not to the overall population (N), a notification must be entered in the headline("*n = xxx*").

"Analysis Section" – "Variable Label" – Descriptive Statistics (n = "xxx")

Characteristic		**["*unit*"]**
"Variable Label"	Mean	*"xxx"*
	Median	*"xxx"*
	SD	*"xxx"*
	IQR	*"xxx"*
	Max	*"xxx"*
	Min	*"xxx"*

Table 7.2.1: Descriptive Statistics Table Template

7.3. LISTINGS

Listing tables must contain one unique identifier (e.g. Subject ID). Furthermore, an additional column must be added, if the specification/description is not referring to one single variable or response option("*Response Option*"), which is already named in the headline. If multiple specifications/descriptions exist for one variable/response (e.g. Drug1, Drug2, Drug3…), further columns must be added ("*Specification/Description A*", "*Specification/Description B*"). Subgroups can be implemented as described in chapter 7.1.

"Analysis Section" – "Variable Label" – Listing

"Unique Identifier"	**Description**	
	"Response Option"	***"Specification/Description A"***
"xxx"	*"xxx"*	*"xxx"*
"xxx"	*"xxx"*	*"xxx"*
"xxx"	*"xxx"*	*"xxx"*

Table 7.3.1: Listing Table Template

8. References

a. ISO 14155 - Clinical Investigation of Medical Devices for Human Subjects

b. ICH-E6 Harmonized Tripartite Guidelines for Good Clinical Practice

c. ICH-E9 Statistical Principles for Clinical Trials

d. Declaration of Helsinki

e. Gamble C et. al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. AMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

f. DQP 20-001 Clinical Investigation

g. DQI 20-001 Clinical Investigation - Clinical Investigation Plan

h. DQI 20-004 Clinical Investigation - Master CRF, eCRF and Database Development

i. DQI 20-009 Clinical Investigation - Reports

20210723_T2 Alpha Tibia_SAP

Final Audit Report 2021-07-23

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