STATISTICAL ANALYIS PLAN (SAP)

Study Details:

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Protocol Reference	17-5010-11	**Protocol Version**	2.0	**Protocol Date**	05SEP2019
Study Title	Safety and Performance of Q-Fix® All-Suture Anchor System				

SAP Version Control:

SAP Status	Final		
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1. List of Abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
AEMB	Adverse Event Monitoring Board
CI	Confidence Interval
CRF	Case Report Form(s)
CSM	Clinical Study Manager
CSR	Clinical study Report
DevD	Device Deficiency(ies)
FU	Follow-Up
IBT	Iliotibial Band Syndrome
LCL	Lateral Collateral Ligament
LL	Lower Limit
MCL	Medial Collateral Ligament
MDD	Medical Device Directive
N (or n)	Total Sample Size (or subgroup sample size)
N/A	Not Applicable
NSAE	Non-Serious Adverse Event(s)
PRO	Patient Reported Outcome(s)
QoL	Quality of Life
ROM	Range of Motion
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan

Abbreviation	Definition
SD	Standard Deviation
SLAP	Superior Labral Tear from Anterior to Posterior
TFL	Tables, Figures, and Listings
UADE	Unanticipated Adverse Device Effect(s)
VAS	Visual Analogue Scale
VMO	Vastus medialis obliquus

2. Introduction

Post-Market Clinical Follow-up is needed to address existing clinical data and gaps on the existing Q-FIX◇ device and meet existing MDD/MEDDEV requirements.

The purpose of this study to assess the safety and performance of the Q-Fix◇ All-Suture Anchor System.

This Statistical Analysis Plan (SAP) is based on protocol number 17-5010-11 version 2.0, dated 05Sep2019.

This SAP presents a detailed interpretation of the study protocol by describing the statistical analyses that will be carried out for the study in greater detail than specified in the protocol. Supporting documents used to create this SAP are the Study Protocol and the Case Report Forms (CRFs). Table, Figure, and Listing (TFL) shells will accompany the SAP.

3. Study Design

This is a retrospective, multi-center, case series to evaluate the 1-year safety and effectiveness of the Q-Fix◇ All-Suture Anchor System for arthroscopic repair when used for any of the following:

- **Shoulder**: Bankart lesion repair; superior labral tear from anterior to posterior(SLAP) lesion repair; acromio-clavicular repair; capsular shift/capsulolabral reconstruction; deltoid repair; rotator cuff repair; biceps tenodesis.
- **Hip**: Acetabular labral repair.
- **Knee**: Extra-capsular repair: medial collateral ligament (MCL), lateral collateral ligament (LCL) and posterior oblique ligament; Iliotibial band tenodesis (IBT); patellar tendon repair; vastus medialis obliquus advancement (VMO); joint capsule closure.

As the study is collecting real world data retrospectively, data may be collected on the shoulder, knee, or hip beyond the indications listed above.

Table 1 displays the information about the schedule of assessments for this study.

Schedule of Assessments

Table 1. Study Procedures by Visit

Schedule of events	Chart Review [1,2]		
	Screening	182 days post-op (±91 Days)	365 days post-op (± 91 Days)
Inclusion/Exclusion	X		
Case History Review***	X		
Implant Status[3]	X	X	X
VAS	X	X	X
ROM	X	X	X
Concomitant Medications, Procedures[4]	*	*	*
AE Assessment	*	*	*
Serious Adverse Event (SAE) / Adverse Device Effect (ADE) / Device Deficiency (DevD)	*	*	*
End of Study/Subject disposition	*	*	*

[1]Given the retrospective study design, data will be collected to the extent it is available.
[2]Informed consent/waiver of informed consent from the IRB/EC must be obtained prior to retrospective data collection.
[3]Subjects who have undergone a revision procedure of the anchor will be considered terminated from the study from the date of the revision. Study related data will not be collected following the date of the revision.
[4] Any concomitant medications/ procedures associated with an AE, SAE or SADE will be recorded.
*if applicable
*** Review of subject demographics, medical history, operative, post-op, discharge, and cumulative AE's occurring since date of surgery

4. Study Objectives

4.1 Primary Objective

The purpose of this study is to demonstrate the safety and performance of the Q-Fix® All-Suture Anchor System in hip, shoulder and knee repair.

5. Study Endpoints

5.1 Primary Endpoints

- Clinical success rate, defined as subjects without re-intervention at 6 months post- operative, as
- assessed by the surgeon

5.2 Secondary Endpoints

- Clinical success rate, defined as subjects without re-intervention at 12 months post- operative, as
- assessed by the surgeon
- Visual Analog Scale-pain
- ROM
- Clinical success rate in adolescents and young adults, defined as subjects ages 13-21 years of age without re-intervention at 6 and 12 months post-operative

5.3 Safety Endpoints

- Adverse events, to be evaluated by type, frequency, severity an relatedness to the study treatment
- Device-related re-intervention
- All adverse events (AEs) occurring from the time of surgery until revision or study completion
- Device related AE and SAE's

5.4 Exploratory Endpoints

- Clinical success rate as defined above, by anchor size

6. Statistical Considerations

6.1 Determination of Sample Size

Precision Analysis will be used to assess the overall proportion of success for the Q- FIX All-Suture Anchor System. Assuming a 5% lost to follow-up rate after the first year, a minimum of 90 subjects, with maximum enrollment set at 450 subjects, will be enrolled (based on the inclusion/exclusion criteria) in order to complete 84 evaluable subjects. The 90 subjects will be enrolled to allow a minimum of 28 subjects with each of the following indications to be recruited: Shoulder, Hip and Knee. Based on the results of the Byrd et al[1] study which showed a failure rate of 1.6% in the use of the Q- FIX All-Suture Anchor System, this number of subjects is sufficient to estimate the success rate to within 11% by use of the two-sided 95% confidence interval (based on an estimate of the rate of clinical success at least 95%).

6.2 Randomisation

N/A.

6.3 Interim Analysis

Not Applicable

7. Statistical Analysis

7.1 General

Smith and Nephew Global Biostatistics Department will conduct the statistical analyses for this study. Unless otherwise stated, all significance tests from the analyses will be two-sided using the 5% significance level as the threshold of establishing statistical significance. Resulting p-values will be quoted and 95% two-sided confidence intervals will be calculated where appropriate. All p-values will be rounded to three decimal places, p=values less than 0.001 will be presented as <.0001 in all tables. Categorical variables will be summarized with frequencies (n) and percentages (%). Continuous variables and ordinal endpoints (as appropriate) will be summarized with the following summary statistics: number

of observations, mean, median, standard deviation (SD), minimum and maximum values. All analysis will be performed in SAS version 9.3 or later.

7.2 Analysis Populations

Safety Population (SAF)

This includes all subjects who enroll in the study who had previously undergone arthroscopic repair using the Q-Fix™ All-Suture Anchor System i.e. subjects who only provide retrospective data.

Per Protocol Population

This includes all subjects in the Safety Population who meet the inclusion/exclusion criteria and who did not encounter major deviations leading to exclusion from study. Major protocol deviations leading to removal from the PP population will include but not restricted to the following: (1) termination from the study due to non-study related reasons such as subject lost to follow-up or death.

The final assignment of a subject to the per-protocol population will be established after a review of all protocol deviations have been evaluated and deviations that would warrant exclusion of a subject from the Safety population are identified. Subjects excluded from the per-protocol population will be documented together with their reason for exclusion.

Statistical analysis will be performed using each of the subject populations as follows: (1) Analysis of the primary and secondary endpoints will be performed separately using the Per Protocol Population.(2) All safety analyses will utilize the Safety Population.(3) The Safety Population will be additionally utilized for sensitivity analysis of the primary endpoint.

7.3 Handling of Missing, Incomplete and Repeat Data

No imputation methods are planned for missing data in this study. Only observed data will be summarized and analyzed.

7.4 Derived Data and Some Other Specific Data to be Summarized

Study Windows

6 Month window = 182 Days +/- 91 days

1 Year window = 365 Days +/- 91 days

Body Mass Index (BMI)

- BMI = weight [kg] / (height [cm]/100)^2

Change from baseline

- Change in score between baseline and follow up visits for the relevant assessments will be considered as the difference between the follow up visit and the baseline score (i.e. follow up score – baseline score) except if specifically defined otherwise.

Instructions for the creation of the following tables:

- Reason for Revision, Reason for Revision will be derived from the Study Device Revision CRF.
- Study Device Revision, if multiple Reasons for Revision then include and separate with a comma.

7.4.1 Derived Data for the Primary Endpoint

The final count of re-interventions for the 6 month post-operative time point will be defined as any revision that occurred before the end of the 6 Month window (273 days),

i.e. if (Date of Revision – Date of Surgery) < 273 days,

where the Date of Revision is obtained from the Implant Revision CRF and the Surgery Date is obtained from the Operative Data CRF.

7.4.2 Derived Data for the Secondary Endpoints

The final count of re-interventions for the 12 month post-operative time point will be defined as any revision that occurred between the end of the 6 Month window (273 days) and the end of the 12 Month window (456 days) i.e. if (273 days< = Date of Revision – Date of Surgery < = 456 days). Where the Date of Revision is obtained from the Implant Revision CRF and the Surgery Date is obtained from the Operative Data CRF.

7.4.3 Derived Data for the Exploratory Endpoints

N/A

7.4.4 Derived Data for the Safety Endpoints

Time to Event will be defined as: Start Date – Operative Date

Duration = End Date - Start Date

Start Date for AE will be based on Original AE Report Date. For AEs where resolution has occurred:

End Date for AE will be based on the AE Stop Date or Death Date.

When there is a Follow-up AE, the end date will come from the AE Stop Date or Death Date on the latest or highest numbered Follow-up AE.

For the Serious AE listing,

Duration = End Date - Start Date

Start Date for SAE will be based on SAE Report Date. For SAEs where resolution has occurred:

End Date for SAE will be based on the AE Stop Date or Death Date as found in the Related AE.

When there is a Follow-up AE, the end date will come from the AE Stop Date or Death Date on the latest or highest numbered Follow-up AE.

Also, a check will be performed for all bilateral knee subjects to remove from the AE summaries the double entries referencing the same Adverse Event for a single implant twice. Where an AE CRF is filled out regarding the contralateral knee after an AE has already been reported for the ipsilateral knee.

An ADE is defined as an Adverse Event that is Possibly or Probably Related to Device or Procedure.[1]

The Expectation variable on the AE CRF is only to be filled out for Serious ADEs.

All Adverse Events will be assessed by the Investigator to determine relatedness and severity. The AEMB may subsequently classify events into SAEs, ADEs, SADEs, UADEs, USADEs etc. All safety Tables will presented based on the Investigator's and/or AEMB classifications.

7.5 Baseline Data

7.5.1 Demographics and Baseline Characteristics

Patient demographics including age, gender, and body mass index (BMI) will be summarized using appropriate descriptive summary characteristics.

7.5.2 Medical History

Primary Diagnosis, previous surgeries, Joint Involvement, and pre-operative mechanical alignment will be summarized using appropriate descriptive summary characteristics.

7.5.3 Operative

Intervention, Skin to skin summarized using appropriate descriptive summary characteristics.

7.5.4 Discharge Information

Prophylactic Antibiotics given, DVT Prophylaxis given, and other pertinent discharge information will be summarized using appropriate descriptive summary characteristics.

7.6 Disposition of Subjects

Patient accounting will be presented as follows:

- Complete Data Per Protocol: Subjects with complete data for the primary endpoint, evaluated per protocol, in the window time frame.
- Any Data: Subjects with any follow-up data reviewed or evaluated by investigator ("all evaluated" accounting).
- Theoretically Due: Number of subjects that would have reached the beginning of the study window associated with each visit if all subjects returned.
- Not Yet Overdue: Subjects who have not yet returned visited but whose visiting window is still open.
- Deaths: Cumulative number of subjects that died during or prior to the study visit.
- Revision: Cumulative number of subjects that failed (revision) during or prior to the study visit.
- Expected Visit: Theoretical subjects minus the number of deaths and revisions.
- % Follow-up: Any Data/Expected*100
- % Follow-up Per Protocol: Complete Data Per Protocol / Expected *100

Additionally information on subjects discontinued from the study prematurely will be presented, with a breakdown of the reasons for discontinuation as reported in the CRF. The disposition table will be based on the population from the Safety Population. A Disposition table will also be created in order to summarize the outcomes in terms of implants.

7.7 Protocol Deviations

A protocol deviation is defined as an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include, but are not limited to: study visits outside the window or missed, failure to capture patient reported outcomes at defined time points, failure to conduct radiologic or clinical evaluation at defined time points, failure to collect adverse events at defined time points, and failure to withdraw subjects defined by protocol withdrawal measures. Specificity and determination of deviations that would warrant exclusion of subjects from the PP population will be finalized prior to database lock.

A listing of all protocol deviations encountered on-study will be provided.

7.8 Multiplicity

N/A

7.9 Evaluation of Efficacy

7.9.1 Analysis of Primary Endpoint

- Overall clinical success rate at 6 months will be summarized using count (n) and percentage (%). A 95% Confidence Interval (CI) for the percentage of subjects with clinical success at 6 months will be computed using exact methods.[2] This same analysis will be repeated by the position, i.e. the hip, shoulder and knee will be reported. These analyses will be carried out using the per protocol population as the primary analysis population with the safety population used for sensitivity analyses.

7.9.2 Analysis of Secondary Endpoints

- Clinical success rate at 12 months will be analyzed using the same type of analysis carried out on the primary endpoint.
- Clinical success rate at 6 months and at 12 months for subjects 13 to 21 years of age will be analyzed using the same type of analysis carried out on the primary endpoint.
- Device-related re-intervention. All the above variables will be categorical in nature hence frequencies together with percentages will be tabulated for the entire sample as well as by the indication. Available data will be summarized and summary statistics tabulated. For both the ROM and VAS secondary endpoints a 95% Confidence Interval (CI) for the percentage of subjects with clinical success at 6 months and 1 year will be computed using exact methods[3)]

7.9.3 Exploratory Analysis

- Clinical success rate at 6 months and at 12 months for all subjects will be analyzed by anchor size.

7.9.4 Safety Analysis

The total number of AEs, and the total number of subjects experiencing an AE will be presented by Classification from the Investigator and the AEMB as per the tables below. [3]

Number of Adverse Events by Classification

ADVERSE EVENTS	NON DEVICE-RELATED	DEVICE-RELATED	
NON-SERIOUS	ADVERSE EVENT (AE)	ADVERSE DEVICE EFFECT (ADE)	
	<device>	<device>	
	<#> x%	<#> x%	
SERIOUS	SERIOUS ADVERSE EVENT (SAE)	SERIOUS ADVERSE DEVICE EFFECT	
		ANTICIPATED	UNANTICIPATED
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)
	<device>	<device>	<device>
	<#> x%	<#> x%	<#> x%

Number of Patients Experiencing Adverse Events, by Classification

ADVERSE EVENTS	NON DEVICE-RELATED	DEVICE-RELATED
	ADVERSE EVENT (AE)	ADVERSE DEVICE EFFECT (ADE)

NON-SERIOUS	<device>	<device>	
	<#> x%	<#> x%	
SERIOUS	SERIOUS ADVERSE EVENT (SAE)	SERIOUS ADVERSE DEVICE EFFECT (SADE)	
		ANTICIPATED	UNANTICIPATED
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)
	<device>	<device>	<device>
	<#> x%	<#> x%	<#> x%

Secondly, a listing from the AE CRFs will be created to display the Severity, Investigator's Assessment of Relationship to Study Device, Investigator's Assessment of Relation to Study Procedure, Investigator's Assessment of Seriousness, Investigator's assessment of Event Expectation, Outcome of each AE, Duration, AE Category and Investigator's Classification. The Duration will be calculated as indicated in the Derived Data section for Safety Endpoints. There will be a listing for the SAE/SADE, USADE CRFs as well.

7.10 Interim Analysis

N/A

7.11 Changes in Analysis Methods Specified in the Protocol

N/A

8. References

1. Byrd, J.W. Thomas, Kays S, et al. Acetabular All-Suture Anchor for Labral Repair: Incidence of Intraoperative Failure due to Pullout. Arthroscopy: The Journal of Arthroscopic & Related Surgery, Volume 34, Issue 4, April 2018, Pages 1217-1218
2. Clopper, CJ & Pearson ES. (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 26, 404–413.
3. ISO 14155:2011 Clinical investigation of medical devices for human subjects – good clinical practice.