CLINICAL INVESTIGATION PLAN

CLINICAL INVESTIGATION TITLE:	A Post-Market Clinical Evaluation of the ReUnion TSA System
MEDICAL DEVICE:	ReUnion TSA System
STUDY DESIGN:	Post-Market, Multicenter, Prospective, Non-Randomized
INDICATIONS:	This study will adhere to the indications and contraindications for the ReUnion TSA System as are detailed in the device's Instructions for Use.
REGULATORY STATUS	510(k) Clearance received on 05May2011
CLINICAL INVESTIGATION PLAN PHASE:	Post-Approval Clinical Investigation
SPONSOR:	Stryker Orthopaedics 325 Corporate Drive Mahwah, NJ 07430
AUTHOR:	Lindsay Mattfolk
INVESTIGATORS:	Investigators' information is on file at the Sponsor
MEDICAL EXPERT:	Dr. Helmut Mueckter, M.D.
COMPLIANCE STATEMENT:	This clinical investigation will be conducted in compliance with the clinical investigation plan / protocol, International Conference of Harmonisation Good Clinical Practice (ICH-GCP), and all other applicable regulatory requirements, including the retention of essential documents. Investigators will be trained on the clinical investigation devices and surgical techniques prior to implanting clinical investigation subjects.
CONFIDENTIALITY STATEMENT:	This clinical investigation plan / protocol contains confidential information and its' use is limited to investigational staff intending to conduct the clinical investigation, Institutional Review Boards (IRBs) and any others charged with reviewing the clinical investigation.
VERSION:	1
DATE:	12Oct2018

Approval Page

APPROVERS			
Role	**Name**	**Signature**	**Date**
Medical Expert	Dr. Helmut Mueckter, MD	DocuSigned by: Helmut Mueckter Name des Unterzeichners: Helmut Mueckter Signiergrund: Ich habe dieses Dokument geprüft Signaturzeit: 2018-10-15 15:54:51Z (UTC) C24B3BDD5E9446ED8398FBC9B3EE30A7	15-Okt-2018 | 8 55 AM PDT
Clinical Research Head (CRH)	Georgia Mitchell	DocuSigned by: Georgia Mitchell Signer Name: Georgia Mitchell Signing Reason: I approve this document Signing Time: 2018-10-15 15:59:15Z (UTC) B2566DB498234B2182878F1BD6240617	15-Oct-2018 | 8:59 AM PD
Regulatory Affairs (RA)	Jemin Dedania	DocuSigned by: Jemin Dedania Signer Name: Jemin Dedania Signing Reason: I approve this document Signing Time: 2018-10-16 13:57:04Z (UTC) 5B8D8CF95DB14E5EA800D11CDCAB128D	16-Oct-2018 | 6 57 AM PDT
Statistician	Claudia Beimel	DocuSigned by: Claudia Beimel Signer Name: Claudia Beimel Signing Reason: I approve this document Signing Time: 2018-10-16 07:46:33Z (UTC) CF9D5AE352C545BAB2C9FF408F88CDAF	16-Oct-2018 | 1 :50 AM PD

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1. List of Abbreviations

Acronym	Definition
ADE	Adverse Device Event
AE	Adverse Event
ASES	American Shoulder and Elbow Surgeons
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
HA	Hemi-Shoulder Arthroplasty
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent-to-Treat
LTFU	Lost to Follow-Up
PP	Per Protocol
RSA	Reverse Shoulder Arthroplasty
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TSA	Total Shoulder Arthroplasty
UADE	Unanticipated Adverse Device Effect

2. Synopsis

Title	A Post-Market Clinical Evaluation of the ReUnion Total Shoulder Arthroplasty (TSA) System
Treatment	ReUnion TSA System
Design	• Post-Market • Multicenter • Prospective • Non-Randomized
Objectives	The objective of this clinical investigation is to demonstrate the safety and efficacy/performance of the ReUnion TSA System. Efficacy/performance of the procedure will be measured the American Shoulder and Elbow Surgeons (ASES) Shoulder Score. Safety of the ReUnion TSA System will be demonstrated through reporting of device-related intra-operative and post-operative Adverse Events (AEs).
Target Population	100 subjects are to be enrolled in this clinical investigation. Enrolled subjects will be assessed at Pre-Operative, Operative/Discharge, and at 6 Weeks, 6 Months, 12

	Months, 24 Months and annually thereafter up to 10 years following the index procedure.
Endpoints	**Primary Endpoint:** The objective of the clinical investigation is to demonstrate the efficacy/performance of the device at 24 months, as measured by the ASES Shoulder Score. **Secondary Endpoints:** • Safety: Incidence of device-related intra-operative and post-operative AEs • Efficacy/Performance: Implant survivorship will be monitored
Inclusion Criteria:	a. Subject is willing to sign the informed consent. b. Subject is willing and able to comply with post-operative scheduled clinical assessments. c. Subject is male or non-pregnant female and 18 years or older at the time of surgery. d. Subject has one or more of the following: • Aseptic necrosis of the humeral head • Painful, disabling joint disease of the shoulder resulting from degenerative arthritis, rheumatoid arthritis or post-traumatic arthritis • Failed previous total shoulder replacement, resurfacing or other procedure
Exclusion Criteria:	a. Subject has an active or suspected latent infection in or about the shoulder joint. b. Subject has mental or neuromuscular disorder which would create an unacceptable risk of prosthesis instability, prosthesis fixation failure or complications in postoperative care. c. Subject has bone stock compromised by disease, infection or prior implantation which cannot provide adequate support and/or fixation to the prosthesis. d. Subject has anticipated activities which would impose high stresses on the prosthesis and its fixation. e. Subject is obese such that he/she produces a load on the prosthesis which can lead to failure of fixation of the device or to failure of the device itself. f. Subject has absent, irreparable or non-functioning rotator cuff and other essential muscles. g. Subject has concomitant disease(s) which may significantly affect the clinical outcome. h. Subject has traumatic or pathologic fracture of the proximal humerus.

3. General Information and Administrative Structure

3.1. SPONSOR

Stryker Orthopaedics
325 Corporate Drive
Mahwah, NJ 07430

3.2. KEY SPONSOR PERSONNEL

Lindsay Mattfolk
Clinical Study Manager
Role: Clinical Investigation Manager
Email: Lindsay.mattfolk@stryker.com
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Hanna Schlyter
Senior Director Clinical Affairs Trauma & Extremities
Role: Clinical Research Head

Dr. Helmut Mueckter, M.D.
Role: Medical Expert

3.3. EDC SYSTEM

Name: IBM Clinical Development
Email: icdhelp@us.ibm.com
Phone: +1 888 500 4247

4. Product Information

All components of the ReUnion TSA System have been cleared and approved for sale and use in the United States prior to starting the clinical investigation. 510(k) Clearance was received on 05May2011. This system is to be used only for indications for which it has been approved. Please see the approved Instructions for Use (IFU) and Operative Technique manuals for a detailed description of the medical device(s) and instrumentation as well as the intended use information.

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

5. Risks and Benefits

This prospective, multicenter clinical investigation is designed to examine the safety and performance of the ReUnion TSA System in accordance with the approved IFU, labelling and instrumentation. The potential risks to subjects are described in the approved IFU and Operative Technique manuals.

Potential benefits resulting for the ReUnion TSA System over other devices and procedures as demonstrated by superior scoring on the outcome survey and positive results on other clinical evaluation measurements would suggest affirmative clinical efficacy.

6. Introduction

The ReUnion TSA System is designed as an anatomical total shoulder or hemi-shoulder endoprosthesis to address advanced arthritic disorders affecting the shoulder joint in subjects having intact or repairable rotator cuff function. The ReUnion TSA System consists of a completely modular shoulder platform including a Humeral Stem, Humeral Head and Glenoid. The intended purposes of the ReUnion TSA System are to achieve pain relief, improvement of range of motion and restoration or improvement of the shoulder function while ensuring long-term replacement of the shoulder joint with sufficient stability of all endoprosthesis components.

7. Clinical Investigation Design

This investigation is a prospective, multicenter clinical investigation. It is anticipated that a total of one hundred (100) subjects will be enrolled at approximately 4-7 sites. Neither subjects nor investigators are blinded to treatment and the clinical investigation does not include a contemporaneous control. The clinical investigation has been designed to follow the surgeon's standard of care for joint arthroplasty subjects, which entails clinical evaluation on a regular ongoing basis, or as needed should the subject become symptomatic in the treated joint. The enrollment period is expected to occur over 14 months.

8. Objective

8.1. PRIMARY ENDPOINT

The primary endpoint of the clinical investigation is to demonstrate non-inferiority of the device to the selected literature controls, as measured by the ASES Shoulder Score at 24 Months post-operative.

8.2. SECONDARY ENDPOINT

In addition to the principal endpoint, information on the following outcomes will be assessed up to 10 years after the index procedure:

Safety: Incidence of device-related intra-operative and post-operative AEs

Efficacy: Implant survivorship

9. Selection of Clinical Investigation Population

Subjects participating in this clinical investigation will be recruited from the investigator's standard subject population, where all subjects presenting for primary or revision total shoulder replacement will be evaluated for clinical investigation participation based on the eligibility criteria listed below.

9.1. INCLUSION CRITERIA

a. Subject is willing to sign the informed consent.

b. Subject is willing and able to comply with postoperative scheduled clinical and radiographic evaluations.

c. Subject is male or non-pregnant female and 18 years or older at the time of surgery.

d. Subject has one or more of the following:

- Aseptic necrosis of the humeral head

- Painful, disabling joint disease of the shoulder resulting from degenerative arthritis, rheumatoid arthritis or post-traumatic arthritis
- Failed previous total shoulder replacement, resurfacing or other procedure

9.2. EXCLUSION CRITERIA

a. Subject has an active or suspected latent infection in or about the shoulder joint.

b. Subject has mental or neuromuscular disorder which would create an unacceptable risk of prosthesis instability, prosthesis fixation failure or complications in postoperative care.

c. Subject has bone stock compromised by disease, infection or prior implantation which cannot provide adequate support and/or fixation to the prosthesis.

d. Subject has anticipated activities which would impose high stresses on the prosthesis and its fixation.

e. Subject is obese such that he/she produces a load on the prosthesis which can lead to failure of fixation of the device or to failure of the device itself.

f. Subject has absent, irreparable or non-functioning rotator cuff and other essential muscles.

g. Subject has concomitant disease(s) which may significantly affect the clinical outcome.

h. Subject has traumatic or pathologic fracture of the proximal humerus.

9.3. WITHDRAWAL CRITERIA

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

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

i. Subject Withdrawal: A subject may voluntarily withdraw from the clinical investigation at any time and for any reason. The subject should be asked when possible, and without any form of coercion, the reason for his/her decision. If the participant withdraws from the clinical investigation completely, then data collected up until the point of withdrawal will be included in the final analysis.

ii. Lost to Follow-Up (LTFU): A subject will be considered LTFU after all reasonable efforts have been made to contact the subject and request his/her continued participation in the clinical investigation. All attempts to contact the subject must be documented and should include at least two attempts to contact the subject by phone and one attempt via a certified letter. Data collected up until the point where the subject is LTFU will be included in the final analysis.

iii. Removal of Device or AE/Incident: The discontinuation of a subject's participation in the clinical investigation due to the removal of the ReUnion TSA System or AE/incident that prohibits his/her continued participation must be fully explained. All available information concerning the removal of the device or AE/incident should be provided. Data collected up until the point of removal or AE/incident will be included in the final analysis.

iv. Death: The discontinuation of a subject's participation in the clinical investigation due to death must be fully explained. All available information concerning the death or AE should be provided. Removal of a subject from continued follow-up in the clinical investigation due to death will not be considered a device failure unless the death is

directly caused by, or attributable to, the ReUnion TSA System. Data collected up until the point of death will be included in the final analysis.

v. Other: A subject may be withdrawn by the investigator if he/she believes it is in the best interest of the subject, or if it is determined by the IRB that a subject's continued participation in the clinical investigation represents an unacceptable risk to the subject. The Sponsor must be notified immediately if this occurs. All data collected up until the point of withdrawal or IRB determination will be included in the final analysis.
A subject may also be withdrawn if the subject is non-compliant with the clinical investigation procedures or visits, or if a selection criteria violation is noted after the subject received the clinical investigation treatment and it is determined that the subject should be discontinued. All data collected up until the point of withdrawal will be included in the final analysis.

10. Clinical Investigation Evaluations, Procedures and Assessments

10.1. METHOD OF ASSIGNING SUBJECTS

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

10.2. PROCEDURES

Subjects in the clinical investigation will undergo placement of the ReUnion TSA System. Please see the approved IFU and Operative Technique manuals for a detailed description of the medical device(s) and instrumentation, intended use information and associated risk. Any additional clinically indicated procedures are permitted as deemed necessary by the clinical investigation investigator.

10.3. FOLLOW-UP EVALUATIONS

Subjects in this clinical investigation will be evaluated at Pre-Operative, Operative/Discharge, and at 6 Weeks (4 weeks – 8 weeks), 6 Months (24 weeks – 28 weeks), 12 Months (48 weeks- 56 weeks), 24 Months (100 weeks – 108 weeks) and annually after the index procedure. The follow-up evaluations will include assessment of device-related AEs/incidents, radiographs and ASES Shoulder Score.

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

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

10.4. SCHEDULE OF EVENTS

Assessment	Pre-Operative	Operative/ Discharge	6 Weeks [a, b] (+/- 2 weeks)	6 Months [a, b] (+/- 3 weeks)	12 Months [a, b] (+/- 4 weeks)	24 Months [a, b] (+/- 4 weeks)	Annually [b]
Informed Consent	X						
Demographics & Medical History	X						

Inclusion/Exclusion	X						
Physical Exam	X		X[c]	X[c]	X[c]	X[c]	X[c]
Surgical Procedure		X					
ASES Shoulder Score	X		X[d]	X[d]	X [d]	X [d]	X [d]
Image Evaluation [e, f]	X	X	X	X	X	X	X
Subject Disposition [g]			X	X	X	X	X
	Device-Related AEs/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 misses a visit and is outside of the visit window, then every effort should be made to collect data instead of noting visit as missed. c. Evaluation may be collected when subject presents in-clinic for study visit. d. Evaluation can be collected via phone. e. Radiograph collection should follow Institution's Standard of Care practices and no additional x-rays should be made for study purposes. f. CT scans may be collected if part of Institution's Standard of Care practices. g. Subject Disposition assessment will occur at any time point for subject withdrawal prior to the completion of the clinical investigation.						

Table 1: Schedule of Events

11. Statistical Methods

The 24 months post-operative results for subjects implanted with the ReUnion TSA System will be compared to a historical group and results reported by respective clinical outcome data in the scientific literature. The benchmark sources and values will serve as the control group for the ReUnion TSA System subjects.

Hypotheses are developed to allow for a comparison of 24 months post-operative ASES Shoulder Score results and 24 months effectiveness/performance between these two populations.

The Statistical Analysis Plan (SAP) lists all variables/questions within this clinical investigation. Therefore, no additional "evaluation" chapter is required nor needed for this CIP.

Data will be captured via IBM Clinical Development electronic data capture (EDC) system and statistical analysis will be performed using IBM SPSS. All statistical hypotheses tests will be with confidence levels (1-α) of 95% and power (1-β) of 80%. The significance level (α) is 0.05 and the beta-value (β) is set to 0.20. Therefore, p-values ≤ 0.05 will indicate statistical significance.

Results will be presented using summary tables and optionally supported by graphs. For detailed information per variable, see SAP.

The primary endpoint of the clinical investigation is to demonstrate non-inferiority of the device to the selected literature controls, as measured by the ASES Shoulder Score at 24 Months post-operative. Specifically, the proposed study will test the null hypothesis that the population mean is 82.16 points. The criterion for significance (alpha) is set at 0.05. With the sample size of 10 cases, the clinical investigation will have power of 80.3% to yield a statistically significant result. This computation assumes that the population from which the sample will be drawn has a mean of 82.16 points with a standard deviation of 16.76 points. The observed value will be tested against a theoretical value (lower limit -θ) of 65.40 points. To account for an estimated appropriate overall drop-out rate, Stryker intends to enroll the calculated number of subjects, multiplied by the number of cleared indications (5) to reflect the underlying subject population adequately.

11.1. DETERMINATION OF SAMPLE SIZE

For details of the sample size determination, see Table 2.

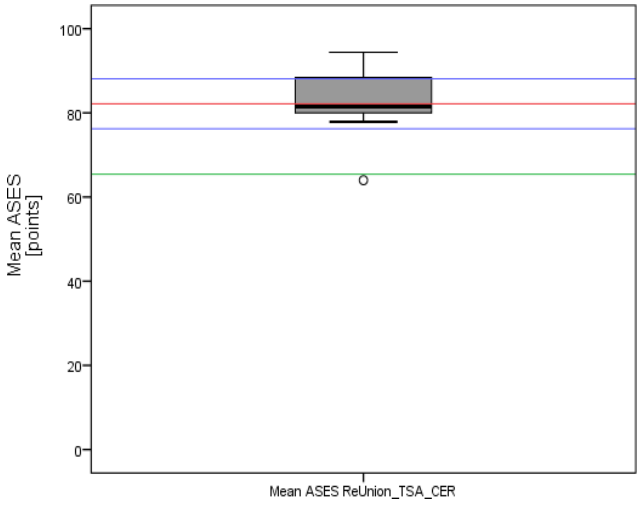
Benchmark and Objectives for Clinical Investigation					
Endpoint	Non-inferiority (equal or better) of the ASES Score in relationship to the officially cleared indications in comparison to respective clinical outcome data in the scientific literature.				
Estimated drop-out rate	56% (confirmed by Medical Expert, see Cuff et al. [1])				
Benchmark Sources & Values ASES [points]					
Source		**n**	**Mean**	**Std. Dev.**	**Comments No.**
No.	**Title**				
1	Irlenbusch et al. [2]	73	77.9	N/A	Conflict related to Follow-Up times in abstract vs method vs result section.
2	Flurin et al. [3]	73	90.3	14.6	Not clear if SD or 95% CI
3	Press et al. [4]	34	82.6	19.4	
4	Hsu et al. [5]	25	94.4	N/A	
5	Kiet et al. [6]	40	80	21	N changed from 45 to 40
6	Steen et al. [7]	96	80.4	22.4	Not clear if SD or 95% CI
7	Gulotta et al. [8]	40	80.1	10.1	
8	Petri et al. [9]	43	83.5	13.1	
9	Schoch et al. [10]	78	88.4	16.7	
10	Alentorn-Geli et al. [11]	38	64	N/A	TSA und HA combined.
Identified Cleared Indications					
No.	**Indication**				
1	Post-traumatic arthritis				
2	Degenerative arthritis				
3	Rheumatoid arthritis				
4	Revision of previous unsuccessful total shoulder replacement, resurfacing or other procedure				
5	Aseptic necrosis				
Explorative Meta-Analysis - ASES (single group)					
Acceptance Criteria					
Confidence Interval (CI)					0.95 (95%) two-sided
Software Used					IBM SPSS V20

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Mean ASES ReUnion_TSA_CER	10	100,0%	0	0,0%	10	100,0%
Std.Dev. ASES ReUnion_TSA_CER	7	70,0%	3	30,0%	10	100,0%

Descriptives

			Statistic
Std.Dev. ASES ReUnion_TSA_CER	Mean		16,7571
	95% Confidence Interval for Mean	Lower Bound	12,6353
		Upper Bound	20,8790
	Median		16,7000
	Std. Deviation		4,45678
	Minimum		10,10
	Maximum		22,40
	Interquartile Range		7,90
Mean ASES ReUnion_TSA_CER	Mean		82,1600
	95% Confidence Interval for Mean	Lower Bound	76,2372
		Upper Bound	88,0828
	Median		81,5000
	Std. Deviation		8,27945
	Minimum		64,00
	Maximum		94,40
	Interquartile Range		9,40



Red line: Pooled mean ASES

Blue lines: 95% CI of pooled mean ASES

Black line: Pooled median pooled ASES

Box: Interquartile Range

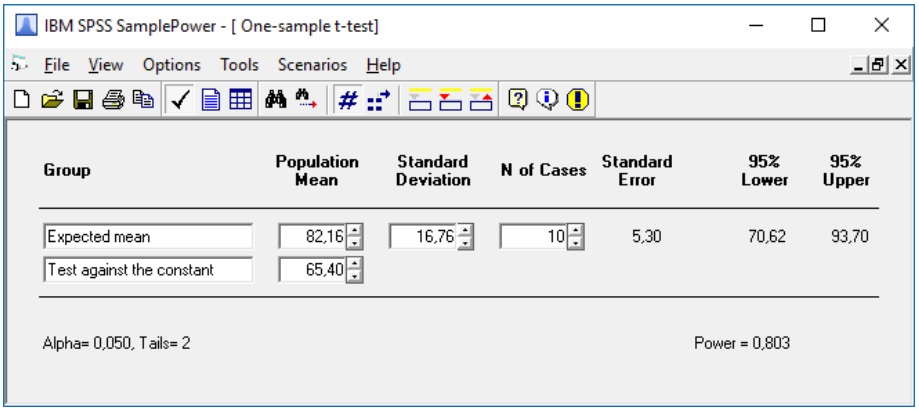
Green Line: Pooled mean ASES minus pooled std. dev. ASES (16.76)

82.16 – 16.76 **= 65.40 points**

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	2	
Path	Non-inferiority – ReUnion TSA (A) ≥ Benchmark (B, explorative meta-analysis in this document)	
Hypotheses Pair	Null (H_0)	A – B < -θ
	Alternative (H_1)	A – B ≥ -θ
Benchmark Timepoint	24 months post-operative	
Benchmark n (sources)	10	
Benchmark Mean	**82.16** (pooled mean ASES [points])	
Benchmark Std. Dev.	**16.76** (pooled std. dev. ASES [points])	
Benchmark Value Non-Inferiority Margin (-θ)	Pooled mean ASES minus pooled std. dev. ASES (16.76) 82.16 – 16.76 **= 65.40 points**	
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 82.16 points. The criterion for significance (alpha) has been set at 0.05. The test is 2-tailed, which means

<table>
<tr><td colspan="2">that effects in both directions will be interpreted. With the proposed sample size of 10 cases, the clinical investigation will have power of 80.3% to yield a statistically significant result. This computation assumes that the population from which the sample will be drawn has a mean of 82.16 points with a standard deviation of 16.76 points. The observed value will be tested against a theoretical value (constant, non-inferiority margin) of 65.40 points.</td></tr>
<tr><td colspan="2">IBM SPSS Sample Power Output – Screenshot
 

Estimated overall drop-out rate is 56% which leads to the requirement of enrolling additional 6 subjects into the clinical investigation.</td></tr>
<tr><td>Sample Size</td><td>Number of subjects to be enrolled: 16 subjects (rounded up to 20 subjects)</td></tr>
<tr><td>Overall Sample Size (multiplied by number of indications (=5)</td><td>100 subjects</td></tr>
</table>

Table 2: Sample Size Justification

In conclusion, the calculated number of subjects to be enrolled (10) plus the estimated overall drop-out rate of 56% predicts enrollment of 20 subjects per cleared indication (five) to reflect the underlying subject population adequately. As a result, an enrollment target of 100 subjects in total will be aspired.

11.2. ANALYSIS POPULATIONS

It is expected that during this clinical investigation only one population for ReUnion TSA System 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 PP Population is defined to be all subjects in the ITT Population with no major CIP violations. The CIP violations that will exclude a subject are as follows:

  - The subject does not receive the ReUnion TSA System
  - The subject does not meet all eligibility criteria
  - The subject has a protocol deviation 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.

11.3. ANALYSIS AND EVALUATION

11.3.1. Statistical Analysis

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

All quantitative variables, including those based on calculations (secondary elements), will be analyzed with a case summary evaluation before the detailed characteristics and parameters 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, median and mode will be analyzed. As variation parameter the standard deviation, 95% confidence interval of the mean, interquartile range and range (based on maximum and minimum) will be calculated. All quantitative variables will be assessed for normality using the Shapiro-Wilk test. For optional visualization of quantitative variables, box-and-whisker plots will be used. Additional analyses like skewness and kurtosis measures or standard errors are optional also.

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

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

11.3.2. Primary Analysis / Endpoint

The objective of the clinical investigation is to demonstrate non-inferiority (equal or better) of the ASES Shoulder Score in relationship to the officially cleared indications in comparison to respective clinical outcome data in the scientific literature.

Data collection of ASES Shoulder Score will start pre-operatively and will be collected according to schedule in Table 1. This will be repeated annually in all subjects who have the total or partial prosthesis with full or partial implant survival (including all subjects without removal of all endo-prosthesis components).

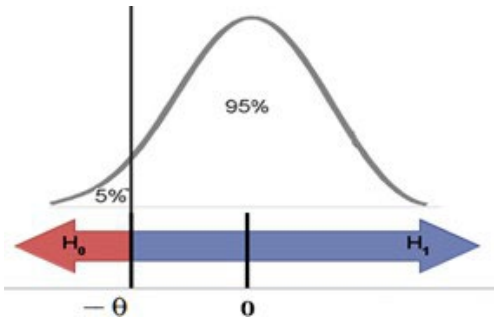
The 24 months post-operative results for subjects implanted with ReUnion TSA System will be compared to a historical group and results reported by respective clinical outcome data in the scientific literature. The benchmark sources and values will serve as the control group for the ReUnion TSA System subjects.

Higher ASES Shoulder 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 ASES Shoulder Score result means equal or more ($\geq$). 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 $-\theta$.

Hypotheses are developed to allow for a comparison of the 24 months post-operative ASES Shoulder Score effectiveness / performance between the two underlying populations. The 24 months post-operative ASES Shoulder Score 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 (H0)	A – B < -θ ReUnion TSA System – Control (Benchmark) < -θ	Central tendency of A is inferior to the central tendency of B.
Alternative (H1)	A – B ≥ -θ ReUnion TSA System – Control (Benchmark) ≥ -θ	Central tendency of A is non-inferior to the central tendency of B.



Possible Evidence (p)	**Possible Decisions**	**Possible Conclusions – ASES score**
p-value > α (0.05)	Fail to reject null hypothesis (H0)	ReUnion TSA System < Control (Benchmark) Insufficient evidence to reject the null hypothesis (H0: A - B < - θ) at the pre-determined significance level of 5%.
p-value ≤ α (0.05)	Reject null hypothesis (H1)	ReUnion TSA System ≥ Control (Benchmark) Sufficient evidence to reject the null hypothesis (H0: A - B < - θ) at the pre-determined significance level of 5%.

To test non-inferiority, the 24 months mean ASES Shoulder Score result of the ReUnion TSA System group will be compared to the mean estimate of the control group, 82.16 points.

To be able to identify an acceptable difference or zone of indifference (-θ), the pooled standard deviation of the ASES Shoulder Score result at 24 months post-operative in the control group (Benchmark) was used as lower limit (pooled standard deviation of control is 16.76 points). The lower maximum acceptable difference (-θ) is 51.87 points (mean of control - θ or 82.16 – 16.76 = 65.40 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 24 months post-operative ASES Shoulder Score results of the ReUnion TSA System against the value of 65.40 points.

11.3.3. Secondary Endpoints

The incidence of device-related AEs and implant survivorship will be assessed up to 10 years after the index procedure and monitored through collection and analyses. These analyses will be part of the annual and final reports.

Furthermore, time to (earliest) device-related AEs will be analyzed as well. For analysis of the time to the (earliest) device-related AEs as well as the time to secondary procedure (revision, removal, reoperation), the Kaplan-Meier method will be used. The time between surgery and the last available assessment will be used together with the time between date of surgery and the date of secondary procedure. Considered variables, the level of measurement and the planned analysis steps are listed in detail in the SAP.

11.3.4. 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.

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

- **ASES Total Score – Within subject changes by visit**
  The within subject score changes of the ASES Shoulder Score from visit to visit will be analyzed to help identify the changes on the subject level. This analysis will be part of the annual and final reports.

11.4. MISSING DATA / SAP DEVIATIONS

The intent is to collect as complete 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

Any deviations from the SAP will be listed in the annual or final reports.

11.5. REPORTS

11.5.1. Interim Analysis and Reports

Interim analyses will be performed on a yearly basis. The progress of the clinical investigation will be reported together with the interim results on the variable level according to the analysis plan.

The analysis of the primary endpoint will be part of the related interim / annual report when all subjects have completed the 24 months post-operative including the ASES Shoulder Score.

11.5.2. Final Analysis and Reports

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

12. Clinical Investigation Plan Deviations

A CIP deviation is a departure from the approved CIP that is not implemented or intended as a systemic change. All CIP deviations are recorded and reported to each site's IRB in accordance with the respective site's IRB policies.

13. Adverse Events

As this CIP is being carried out to satisfy the post-market requirements to support safety and efficacy/performance according to the European Medical Device Regulation (EU MDR), categorization and definition of device-related adverse events will follow the guidelines outlined in the EU MDR as "incident" reporting.

13.1. DEFINITIONS

- **An Adverse Device Effect (ADE)** is defined as any untoward or unintended response to the clinical investigation treatment; and/or a medical response which may have a causal relationship to the treatment.
- **An Incident** is defined as any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.
- **A Serious Adverse Device Effect (SADE)** is defined as any ADE that results in consequences characteristic of a SAE or might lead to the consequences if suitable action or intervention is not taken; causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening, including those events resulting in a subject's disability or permanent damage, or required intervention to prevent disability or permanent damage; results in a life-threatening illness or injury; and/or results in death (fatal).
- **A Serious Incident** is defined as any incident that directly or indirectly led, might have led or might lead to any of the following:
    - the death of a patient, user or other person;
    - the temporary or permanent serious deterioration of a patient's, user's or other person's state of health;
    - a serious public health threat
- **An Unanticipated Adverse Device Effect (UADE)** is defined as an AE not described in the informed consent, CIP or device labeling which has resulted in any of the consequences of a SAE or which might have led to any of the consequences of a SAE if suitable action had not been taken, intervention had not occurred, or if circumstances had been less opportune.

13.2. ADVERSE EVENT SEVERITY

The severity of all AEs is assessed by the Investigator utilizing the following categories:

- **Mild**: The AE is transient and easily tolerated by the subject.
- **Moderate**: The AE causes the subject discomfort and interrupts the subject's usual activities.
- **Severe**: The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening, including those events resulting in a subject's disability or permanent damage, and/or required intervention to prevent permanent disability or damage.

- **Life-Threatening**: The AE results in a life-threatening illness or injury.
- **Fatal**: The AE results in death.

13.3. RELATIONSHIP TO THE DEVICE

Only events considered possibly, probably or definitely related to the device will be captured for this clinical investigation.

13.4. ADVERSE EVENT/INCIDENT REPORTING

In the event a SADE, UADE or serious incident occurs, the Investigator is required to notify the Sponsor within 48 hours of being made aware of the event. The Investigator also is required to notify their IRB in accordance with the policies of their local laws and regulations.

13.5. FORESEEABLE ADEs, SADEs and INCIDENTS

ADEs, SADEs and incidents which may be expected as part of the surgical intervention include:

- *Perioperative complications*
  - Malpositioning of the humeral or glenoidal component
  - Oversizing of implant components
  - Undersizing of implant components
  - Intraoperative fracture of the humerus or glenoid
  - Cement leakage, if applicable
  - Nerve injury, mild (minor motor or sensory loss, or spontaneous recovery)
  - Nerve injury, severe (significant motor or sensory loss or requiring surgical revision)
  - Vessel injury
  - Tendon injury
  - Wound complications (e.g. hematoma, wound healing disturbances)
  - Superficial infection
  - Deep infection
  - Deep vein thrombosis
  - Pulmonary embolism

- *Complications in the follow-up period*
  - Implant dislocation
  - Other subluxation or instability, symptomatic
  - Implant component dissociation, humeral head from humeral stem
  - Implant fretting or crevice corrosion
  - Implant breakage/wear, humeral or glenoidal
  - Implant loosening, humeral or glenoidal
  - Radiographic lucency, humeral or glenoidal
  - Rotator cuff tear
  - Pain related to the implant, severe
  - Late infection (e.g. hematogenous or protracted)
  - Periprosthetic fracture of the humerus or glenoid
  - Stiffness
  - Heterotopic ossification, asymptomatic or symptomatic
  - Healing disturbances of subscapularis tenotomy, if applicable
  - Non-union of lesser tuberosity osteotomy, if applicable
  - Malunion of lesser tuberosity osteotomy, if applicable

14. Reoperations

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

15. Ethics

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

This CIP and any amendments will be submitted to a properly constituted independent ethics board, in agreement with local legal prescriptions, for formal approval of the clinical investigation conduct. The decision of the ethics board concerning the conduct of the clinical investigation will be made in writing to the Investigator before commencement of this clinical investigation. Clinical investigations shall not begin until the governing regulatory authority has provided full, unconditional approval. Off-label use of the ReUnion TSA System is not permitted.

15.1. INSTITUTION REVIEW BOARD (IRB)

IRB approval will be obtained at each of the investigational sites prior to enrolling clinical investigation subjects at that site. In addition, any SAEs and UADEs that meet the reporting criteria of the IRB, will be reported to the IRB. During the clinical investigation, the Investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the clinical investigation and/or increase risk to the subjects, unless otherwise submitted by the Sponsor.

15.2. INFORMED CONSENT

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

16. Data Collection Process

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

16.1. RADIOGRAPHS

All radiographs shall be de-identified of personal health information. Radiographs will be uploaded as DICOM images into the EDC system. The radiologic analysis shall be based at minimum on an axillary lateral radiograph and an anteroposterior radiograph. Additional radiographs (e.g., 30° to 40° posterior oblique radiographs in internal and external rotation) may be used where available. For measurements, all digital radiographs shall be sized to 100%, based on the diameter of the humeral head or other suitable reference sizes.

17. Clinical Investigation Monitoring

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

18. Data Handling and Record Keeping

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

19. Reports

Analysis will be performed and interim reports will be prepared on a yearly basis. Upon the completion of all subjects' final post-operative assessment, data freeze will occur, and the final report will be prepared.

20. Completion of the Clinical Investigation

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

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

21. Essential Documents

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

22. Publication Policy

Refer to the clinical investigation agreement for the publication policy

23. References

1. Cuff DJ, Pupello DR, Santoni BG, Clark RE, Frankle MA. Reverse Shoulder Arthroplasty for the Treatment of Rotator Cuff Deficiency: A Concise Follow-up, at a Minimum of 10 Years, of Previous Reports. J Bone Joint Surg Am. 2017 Nov 15; 99(22):1895-1899.
2. Irlenbusch U, Blatter G, Gebhardt K, Pap G, Zenz P. Prospective study of double-eccentric hemi shoulder arthroplasty in different aetiologies: midterm results. Int Orthop. 2011 Jul;35(7):1015-23.
3. Flurin PH, Marczuk Y, Janout M, Wright TW, Zuckerman J, Roche CP. Comparison of outcomes using anatomic and reverse total shoulder arthroplasty. Bull Hosp Jt Dis (2013). 2013;71 Suppl 2:101-7.
4. Press CM, O'Connor DP, Elkousy HA, Gartsman GM, Edwards TB. Glenoid perforation does not affect the short-term outcomes of pegged all-polyethylene implants in total shoulder arthroplasty. J Shoulder Elbow Surg. 2014 Aug;23(8):1203-7.
5. Hsu JE, Namdari S, Baron M, Kuntz AF, Abboud JA, Huffman GR, Williams GR, Glaser DL. Glenoid perforation with pegged components during total shoulder arthroplasty. Orthopedics. 2014 Jun;37(6):e587- 91.
6. Kiet TK, Feeley BT, Naimark M, Gajiu T, Hall SL, Chung TT, Ma CB. Outcomes after shoulder replacement: comparison between reverse and anatomic total shoulder arthroplasty. J Shoulder Elbow Surg. 2015 Feb;24(2):179-85.
7. Steen BM, Cabezas AF, Santoni BG, Hussey MM, Cusick MC, Kumar AG, Frankle MA. Outcome and value of reverse shoulder arthroplasty for treatment of glenohumeral osteoarthritis: a matched cohort. J Shoulder Elbow Surg. 2015 Mar 11. pii: S1058-2746(15)00043-9.
8. Gulotta LV, Chambers KL, Warren RF, Dines DM, Craig EV. No Differences in Early Results of a Hybrid Glenoid Compared With a Pegged Implant. Clin Orthop Relat Res. 2015 Sep 9.
9. Petri M, Euler SA, Dornan GJ, Greenspoon JA, Horan MP, Katthagen JC, Millett PJ. Predictors for satisfaction after anatomic total shoulder arthroplasty for idiopathic glenohumeral osteoarthritis. Arch Orthop Trauma Surg. 2016 Jun;136(6):755-62.
10. Schoch B, Werthel JD, Cofield R, Sanchez-Sotelo J, Sperling JW. Shoulder arthroplasty for chondrolysis. J Shoulder Elbow Surg. 2016 Sep;25(9):1470-6. doi: 10.1016/j.jse.2016.01.005. Epub 2016 Mar 30.
11. Alentorn-Geli E, Assenmacher AT, Sperling JW, Cofield RH, Sánchez-Sotelo J. Plication of the posterior capsule for intraoperative posterior instability during anatomic total shoulder arthroplasty. J Shoulder Elbow Surg. 2017 Jun;26(6):982-989.

24. Clinical Investigation Plan Signature Page

ReUnion TSA System

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

Signature of Investigator	Date of Signature
Name of Investigator (Printed)	

25. Document Version History

Version	Effective Date	Description	Revised/Created by
1	12Oct2018	Initial version	Lindsay Mattfolk

Certificate Of Completion

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Status: Completed
Subject: Please DocuSign: 12OCT2018_ReUnion TSA_Protocol Development.pdf
Source Envelope:
Document Pages: 23
Signatures: 4
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
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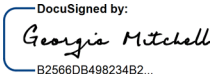
Georgia Mitchell georgia.mitchell@stryker.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: B2566DB4-9823-4B21-8287-8F1BD6240617 Using IP Address: 69.141.177.192 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/15/2018 8:32:26 AM Viewed: 10/15/2018 8:57:39 AM Signed: 10/15/2018 8:59:20 AM
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Helmut Mueckter helmut.mueckter@stryker.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: C24B3BDD-5E94-46ED-8398-FBC9B3EE30A7 Using IP Address: 165.225.80.49 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Ich habe dieses Dokument geprüft	Sent: 10/15/2018 8:32:26 AM Viewed: 10/15/2018 8:54:08 AM Signed: 10/15/2018 8:55:02 AM
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Jemin Dedania jemin.dedania@stryker.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 5B8D8CF9-5DB1-4E5E-A800-D11CDCAB128D Using IP Address: 69.74.233.66 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/15/2018 8:32:27 AM Viewed: 10/16/2018 6:56:52 AM Signed: 10/16/2018 6:57:29 AM
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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will

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