Sponsor Name and Address: Smith + Nephew, Inc.
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Investigational Product(s) ENTACT◇ Septal Stapler (Next Generation)

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1. SIGNATURES

1.1 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

This page will be returned to Smith + Nephew, Inc. and a copy retained at the investigational site.

I have read the attached protocol entitled "A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT™ (Next Generation) resorbable septal staple system for septoplasty", version 2.0, dated 27Aug2020, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 21.5 of the protocol,

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith + Nephew, Inc.

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.2 COORDINATING INVESTIGATOR APPROVAL

I have read the attached protocol entitled “A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT◦ (Next Generation) resorbable septal staple system for septoplasty”, version 2.0, dated 27Aug2020 , and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.3 SPONSOR APPROVAL

	Job title	DocuSign Stamp
Head of Global Clinical Operations	Rachael Winter, Senior Director Global Clinical Operations	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 17:24:38 BST A32F12A80F1B4490986E80ACCB7471CB
Head of Global Clinical Strategy	Stephan Mangin, Clinical Strategy Director	DocuSigned by: Stephan Mangin Signer Name: Stephan Mangin Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 14:51:37 BST 77573411150E4841B3F03589FBBD3EAD
Head of Global Data Analytics	Alan Rossington, Director Biostatistics and Data Management	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 16:10:38 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative	Luca Orlandini, Vice President Medical Affairs	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 14:32:37 BST FC872951AC1C4261B85EC7A7CD09ACDC
Regulatory Representative	Piedad Pena, Manager Regulatory Affairs, Coblation, ENT	DocuSigned by: Signer Name: Piedad Pena Signing Reason: I approve this document Signing Time: 28-Aug-2020 | 13:56:32 BST 5D46F116173D4FFFA4A7648880EAC17F

2. SYNOPSIS

Title of Study:	A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT◇ (Next Generation) resorbable septal staple system for septoplasty
Study Design:	A prospective, multi-center, single arm case series
Study Type:	Observational, non- interventional, post-market clinical follow-up (PMCF) study
Study Product:	ENTACT◇ Septal Stapler Reference # | Description | Contains 601-00100* | ENTACT SEPTAL STAPLER, 3-PACK | 3 ENTACT Staplers * The ENTACT (Next Generation) Septal Stapler will launch with the same reference # number as the previous generation. Previous generation products already at customer sites will remain for consumption at launch in the US but are not part of the study. Septoplasty- The ENTACT Septal Stapler delivers implantable septal staples which are intended to connect internal tissues to aid healing and for approximation of soft tissue during nasal septal surgery.
Study Purpose:	To provide evidence to satisfy the Post-Market Clinical Follow-up (PMCF) requirements of CE Marking to market this device in Europe (data may be used to support registrations in other countries as well).
Primary Objective:	The primary objective of this study is to demonstrate clinical success of the ENTACT (Next Generation) resorbable septal staple system by examining the patient's nasal cavity at the 21 day follow-up visit.

Secondary Objective(s):	The secondary objectives are to generate performance and health economics data to support the use of ENTACT (Next Generation) resorbable septal staple.
Safety Objective(s):	Assess safety with reported complications, adverse events, adverse device effects, unanticipated serious adverse device effects, and device deficiencies.
Sample Size:	40 subjects The results of a previous clinical study on previous generations of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. Therefore based on statistical precision, the recruitment of 36 subjects would provide with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision. With the same assumption of clinical success rate and same precision target, enrolling3636 subjects in ENTACT, Next Generation will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate. To allow for a 10% drop out rate, this study will enroll 40 subjects.
Number of Study Sites:	Up to 3 sites
Targeted Global Regions:	United States (US)

Inclusion Criteria:	The patient will be eligible for the study if he or she meets all of the following inclusion criteria at the baseline screening: 1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board (IRB); 2. Clinically significant deviation of the nasal septum; 3. Willing and able to make all required study visits; 4. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).
Exclusion Criteria:	The patient will be ineligible for the study if he or she meets any of the following exclusion criteria at the baseline screening or during surgery: 1. Prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired; 2. Traditional suturing techniques is necessary; 3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent; 4. Known to be allergic to foreign body of materials of investigational product; 5. Concomitant procedures other than turbinectomy, turbinate reduction, and/or sinus surgery; 6. Pregnancy at time of the procedure; 7. Presence of infection at the site; 8. Severe drug and alcohol abusers; 9. Autoimmune disease deemed clinically significant by Principal Investigator (PI).

Study Duration:	Estimated 8 months from first study site initiation to last subject last visit. Estimated enrollment period: 6 months Follow up period: 6 weeks
Primary endpoint:	At the 21-day follow-up visit, the clinician will examine the patient's nasal cavity and will confirm: • Septum wall straight appearance (yes/no); • Complete coaptation of perichondrial flaps on septum wall (yes/no); • Absence of significant local tissue reaction at the staple site (yes/no); • Absence of hematoma swelling at the staple site (yes/no); • No need for re-intervention at the surgery site (yes/no); If all the answers to the questions above are "YES" then clinical success will be inferred (if any answer is "NO" then repair failure will be inferred).
Secondary endpoint(s):	• At the 5 and 42-day follow-up visit, the clinician will examine the patient's nasal cavity and will confirm: o Septum wall straight appearance (yes/no); o Complete coaptation of perichondrial flaps on septum wall (yes/no); o Absence of significant local tissue reaction at the staple site (yes/no); o Absence of hematoma swelling at the staple site (yes/no); o No need for re-intervention at the surgery site (yes/no).

	• Assess the following intra-operative times for full population and by sub-groups of Septoplasty only cases and Septoplasty and turbinate reduction cases:
	  ○ Total operation time for the procedure: Recorded as time between start of the procedure and when the drapes are removed from the patient, recorded in minutes.
	  ○ Time for operative closure with ENTACT Septal stapler: Recorded as time between start of closure to when the stapler was handed back to the scrub nurse, recorded in seconds.
	• Nasal Obstructions Symptom Evaluation (NOSE) score collected at pre-op and all post-operative visits;
	• Visual Analog Scale (VAS) pain collected at pre-op and all post-operative visits.

Safety Endpoint(s)	• Device-related re-intervention; • All adverse events (AEs) occurring from the time of surgery until re-intervention or study completion; • Device related AEs and serious adverse events (SAE's); • Device deficiencies (DDs).
Other exploratory endpoint(s):	• Number and type of other Smith + Nephew devices that are used with the turbinate reduction adjunct procedure.

STUDY SCHEDULE

Visit Type/name	Frequency / Time point
Screening/Pre-Operative (Visit 1)	(≤ 30 days) Within 30 days of Visit 2
Operative (Visit 2)	Day 0 - Surgery
Follow-up (Visit 3)	Day 5±2
Follow-up (Visit 4)	Day 21±7
End of Study (Visit 5)	Day 42±7

3. CONTENTS

3.1 TABLE OF CONTENTS

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3.4 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
CE	Conformité Européene
CAR	Clinical Activity Report
CER	Clinical Evidence Report
CSR	Clinical Study Report
CRF	Case Report Form(s)
CV	Curriculum Vitae
DD	Device Deficiency(ies)
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HIPAA	Health Information Portability Accountability Act
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IFU	Instructions for Use
Interventional study	A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.
IP	Investigation product
Non-interventional study	A clinical study in which the investigational medical device of interest is used in accordance with the approved instructions for use. Assigning a subject/patient to a particular therapeutic arm is not decided in advance by a protocol but falls within current practice; use of the device is clearly separated from the decision to include the patient in the study. No additional diagnostic

Abbreviation	Definition
	or monitoring procedures are used, and epidemiological methods are used to analyze the collected data.
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NOSE	Nasal Obstruction Symptom Evaluation
NR	Not Reported
PMCF	Post-Market Clinical Follow Up
PI	Principal Investigator
PP	Per-protocol Population
S+N	Smith + Nephew, Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
USADE	Unanticipated Serious Adverse Device Effect(s)
TÜV	Technischer Überwachungsverein/ Technical Inspection Association
VAS	Visual Analog Scale

4. INTRODUCTION

4.1 BACKGROUND

In addition to olfaction, one of the main functions of the nasal passage is to provide airflow.[1] Nasal airways may become obstructed, which necessitates treatment to address the blockage. Nasal airway obstruction may be caused by mucosal or structural defects resulting from trauma, idiopathic disease, or iatrogenic side effects.[1] Anatomical deformities may occur in the septum, turbinates, or nasal valve.

Septal deviation is one of the most common and prevalent problems in otorhinolaryngology.[2] A deviated septum can cause nasal obstruction and is commonly treated using septoplasty.[1-4] Nasal valve dysfunction may be associated with up to 13% of cases of nasal obstruction and is also involved in up to 95% of cases of persistent nasal obstruction after septoplasty.[1] Repairing a deviated septum can be done through a surgery called septoplasty. During surgery, the deviated cartilage and bone are removed from the septum, leaving a dead space. Septoplasty involves elevation of subperichondrial/periosteal flaps bilaterally as well as resection and/or reshaping of the deviated cartilage and/or bone.[5] The space created between the flaps during this procedure must be coapted in order to prevent septal hematoma and other complications such as abscess formation, septal perforation, or saddle-nose deformity, and separation of blood supply from the cartilage.[1]

4.1.1 Treatment Methods

Septal coaptation can be performed using various treatment methods. Nasal packing materials have been used to approximate bilateral mucoperichondrial flaps and prevent complications associated with septoplasty [6-7] as well as reduce the risk of recurrent septal deviation.[3,7] The nasal packing materials include nonabsorbable packing materials such as gauze and polyvinyl acetate sponge (Merocel; Medtronic Xomed) and absorbable materials such as Nasopore (Polyganics), and Sorbsan (Aspen Medical Europe Ltd).[2] There is no consensus in the literature

as to which material to use, or when the best time to remove the materials. In spite of the advantages, nasal packing is associated with various complications such as postoperative pain, continued bleeding[8], worsening of sleep-disordered breathing, foreign body reaction[8], and postoperative infection, which might result in toxic shock syndrome.[7] Studies have been performed which utilize a local anesthetic injection perioperatively in order to reduce postoperative pain. In a Cochrane review performed by Fujiwara[9], pain was reported to be reduced in the first 12 hours. Discomfort to the patients is one of the most important disadvantages as it leads to an increase in the length of hospital stay.[2,8] These drawbacks have led to the use of intranasal splints as an alternative to nasal packing. Septal splints increase septal stability and prevent epistaxis and synechia.[2,7] However, septal splints are also associated with increased postoperative pain and toxic shock syndrome.[10] Other methods, such as clips, clamps, and fibrin glue, were also used successfully to coapt septal mucosal flaps.[8]

Another alternative to nasal packing is suturing. Suturing helps patients to recover from anesthesia quickly and easily.[4] However, suture removal can cause pain and discomfort to the patients[4]. A systematic review conducted by Certal et al[7]. demonstrated that suturing techniques and nasal packing have a similar risk for postoperative hemorrhage, septal perforation, septal hematoma, mucosal adhesions, and location infection. However, suturing was observed to significantly decrease both postoperative pain, and headache compared to nasal packing in two systematic reviews conducted by Certal et al.[7]. Wang et al.[4] Quinn et al.[10] also conducted a systematic review and reported that suturing is associated with less postoperative pain compared to other methods of septal management such as packing and nasal splints. Although there are many advantages with suturing such as reduction in toxic shock syndrome, some of the complications and challenges associated with suturing include inability to align mucosal tears, breakage of needle and suture, visual limitations, and lateral nasal wall damage[11]. Suturing in a narrow nose can also be challenging and can take around 4 to 20 minutes.[5]

The concept of using a stapler for coaptation of the mucoperichondrial flaps, created during septoplasty, has been discussed for some time in Otolaryngology. Septoplasty is one of the

most common procedures performed in otorhinolaryngology, and many of these procedures could potentially benefit from the use of septal staples. Coaptation of mucoperichondrial flaps is necessary following septoplasty to prevent complications associated with septoplasty. The ENTACT Septal Stapler has been designed to offer an option that may facilitate this step of the septoplasty procedure. The ability to quickly accomplish this stage of the procedure may speed closure, save operating room time, and may prevent inadvertent damage to surrounding tissues in some cases.[11,5]

The ENTACT stapler initially launched in 2009 by ENTrigue Surgical Inc. before the acquisition by ArthroCare, Corporation (now S+N).

A summary of known and potential risks and benefits to humans of each Investigation product (IP) can be found in the Instructions for Use (IFU). Refer to the Instructions for Use (IFU).

4.2 LITERATURE SUMMARY

This section aims to provide a “state of the art” review for the indications in which ENTACT (Next Generation) resorbable septal staple system is intended to be used per **Section 4.4**. A literature search was conducted to identify recently published articles on septoplasty.

Limitations such as language or article type were imposed in some searches for publications. Limiting searches to systematic reviews, a meta-analysis was performed to obtain integrated findings from several selected studies considered to be supportive of evidence-based practices. The results of these studies are discussed in terms of their general conclusions.

This section aims to identify clinical studies or usage of the current Smith & Nephew ENTACT Septal Stapler through an extensive literature search.

In the current evaluation, the PubMed online database (MedLine component) and Embase were used to find clinical results. The medical literature was searched for an unrestricted period of

time through July 2019. The search was performed by a qualified Evidence Evaluation Specialist, in July 2019.

Four clinical studies reporting the use of ENTACT Septal Stapler in approximately 153 patients for septoplasty procedures were identified. Follow-up (FU) in these studies ranged from a minimum of one week to a maximum of 3 months.

Table 4.2-1 summarizes the study demographics from these studies.

Table 4.2-1: Study Demographics

Indication	Author, Year	Group	# of Pts	Male (n)	Mean Age (Range), Years	Mean Follow up (Range), Weeks
Open septoplasty plus turbinoplasty	Sowerby[5], 2013	ENTACT Septal Stapler	8	NR	38** (18-NR)	NR (NR-8)
Septoplasty	Sainio[12], 2019	ENTACT Septal Stapler	101	NR	NR	NR (1-12)
	Yildirim[8], 2013	ENTACT Septal Stapler	20*	NR	27** (19-34)	NR (NR-3)
	Tami[13], 2010	N/A	24	12	39.9 (20-63)	NR (NR-1)
		Total:	153		(18-63)	(1-12)

*Estimated number of patients **Mean age of the entire study population NR= Not Reported

There was one prospective randomized study[5], one prospective comparative study[8], one prospective case series[13], and one retrospective comparative study.[12]

Yildirim et al.[8] performed a comparative study that split the patients into three treatment groups; group 1 had the deviated cartilage removed or repositioned, and the mucoperiachondrial flaps closed with an ENTACT Stapler, group 2 used suture, and group 3 were treated with Merocel packing. The number of patients in each group was not specifically stated; however, as the authors mentioned the patients were split, it can be assumed that the group sizes were equal.

4.2.1 Performance

Improvement in clinical outcome scores with the ENTACT Septal Stapler are reported in **Table 4.2.1-1**.

Table 4.2.1-1. ENTACT Septal Stapler Clinical Outcome Scores

Indication	Author, Year	# of Pts	Septal Coaptation n (%)	Nasal Obstruction Symptom Evaluation (NOSE)		
				Pre-op	Post-op	Δ
Septoplasty	Sainio[12],2019	101	-	-	-	-
Open septoplasty plus turbinoplasty	Sowerby[5], 2013	8	-	12	2	10
Septoplasty	Tami[13], 2010	24	24 (100%)	-	-	-
Septoplasty	Yildirim[8], 2013	20*	-	-	-	5.7 ± 0.923
*Estimated number of patients			Δ Change from preop to postop scores			

Approximately 153 patients have undergone septoplasty using the ENTACT Septal Stapler in four studies[5,13,8,12] Sowerby et al.[5] conducted a prospective randomized study and reported a significant decrease in the mean operation time in the ENTACT Septal Stapler group compared to the quilting sutures group (28 ± 6 minutes vs. 43 ± 13 minutes respectively; p=0.014). The mean time for septal closure was also reported to be significantly lower in the ENTACT Septal Stapler group than the quilting suture group (35 ± 22 seconds vs. 420 ± 70 seconds; p<0.001).[5] In a prospective case series conducted by Tami et al.[13] the amount of time taken to apply staples from the ENTACT Septal Stapler was reported to be <60 seconds[5]. Sainio et al.[12] conducted a retrospective comparative study comparing ENTACT Septal Stapler to the non-stapler group where silicone splints, tamponade, or sutures were used during septoplasty. Sainio et al.[12] observed no significant difference in the mean operation time between the

ENTACT Stapler group and the non-stapler group (63.9 minutes vs. 64.3 minutes, respectively).[12]

A significant improvement in Nasal Obstruction Symptom Evaluation (NOSE) scores postoperatively at a 3 week follow up was also observed by Sowerby et al.[5] with an improvement of 10 and a postoperative score of 2 ($p<0.001$). NOSE scores also decreased postoperatively. However, no significant difference was observed between the groups, and the mean difference was reported to be 5.7 ± 0.923 in the ENTACT stapler group vs. 5.90 ± 0.641 in the suture group vs. 6.2 ± 0.62 in the Merocel group.[8] Nasal Obstruction Symptom Evaluation (NOSE) questionnaire assists in quantifying the severity of a patient's nasal congestion. The severity is rated on a 0-4 scale with 0 representing "no problem" and 4 representing "severe problem" in five categories, resulting in a maximum score of 20 for patients with severe obstruction. The NOSE scale was based on a max score of 20 for Sowerby et al.[5] and not reported in Yildrim et al.[8] The NOSE scale is commonly used to evaluate nasal obstruction following septoplasty.[5,19,8,16] In patients with nasal obstruction caused by septal deviation, a reduction in nasal airway obstruction following septoplasty can be used as one of the indicators of successful completion of the procedure.

Tami et al.[13] conducted a prospective, case series evaluating the performance and safety of ENTACT Septal Stapler in 24 patients and reported complete coaptation in 100% of the patients at a one week follow up.

Yildirim et al.[8] conducted a prospective, comparative study, comparing ENTACT Septal Stapler to 4/0 Pegelak (Dogsan TR) sutures, and Merocel nasal packs in patients undergoing septoplasty for deviated septum. A total of 60 patients were included in the study. Yildirim et al.[8] measured patient comfort using Visual Analog Scale (VAS) scores two days postoperative. Visual Analog Scale (VAS) scores were used to evaluate patient comfort on a scale of 0-4 with 0 representing poor and 4 representing excellent. Although postoperative VAS scores decreased,

no significant difference was observed between the groups. Postoperative (2 days) VAS scores were significantly lower in the nasal packing group compared to their preoperative VAS scores (P<0.05). The authors concluded that nasal packing had a negative impact on patient comfort compared to no packing. Mean difference in the VAS scores was reported to be 4.1 ± 0.97 in the ENTACT stapler group vs. 4.15 ±1.31 in the suture group vs. 6.4 ± 1.43 in the Merocel group.[8]

4.2.2 Safety

Complications identified in the four clinical publications are reported in **Table 4.2.2 -1**.

Table 4.2.2-1. ENTACT Septal Stapler Complications

Author, Year	# of Pts	Perforation (n)	Hematoma (n)	Edema (n)	Inflammation (n)	Infection (n)
Sainio12,2019	101	1	1	-	-	6
Sowerby[5], 2013	8	1	-	2	-	-
Tami[13], 2010	24	-	-	-	5	-
Yildirim[8], 2013	20*	-	-	-	-	-
Total	153	2	1	2	5	6

*Estimated number of patients

Device related complications were reported in three studies.[5,13,12] Perforation was reported in two studies.[5,12] Sainio et al.[12] reported perforation in 1 patient (0.99%) in the ENTACT Stapler group and a reoperation was performed in this patient. Sowerby et al.[5] reported a 1 mm postoperative perforation occurred in one patient (12.5%) due to jamming of the ENTACT Septal Stapler (2009) and stated that this can be avoided with the newer model (2010/2012) of the stapler. Perforation was in line with other outcomes reported in the State of the Art for alternative

devices for the Sainio[12] study. In Sowerby et al.[5], the authors concluded that the septal stapler can be used without an increased morbidity in comparison to suture closure or impact to subjective patient scores.

Tami et al.[13] reported that the first lot of ENTACT Septal Staplers (2009) failed to perform to design specifications and only four total staples from three staplers were implanted in one patient.

Sainio et al.[12] observed haematoma in one patient in the ENTACT Stapler group. Sainio et al.[12] reported that perforation and haematoma, which occurred at a low rate of 1% each in the study, is in agreement with the study conducted by Tami et al.[13] and stated that “ENTACT Septal Stapler is safe to use”. The complications reported in the four studies of the ENTACT stapler are performing in-line with alternative devices on the market as discussed in the State of the Art.

Some of the minor complications observed in the literature were edema, inflammation and infection. Sowerby et al.[5] conducted a prospective, randomized clinical study comparing ENTACT Septal Stapler to quilting sutures in patients undergoing septoplasty. Sowerby et al[5] observed mild edema in 2 patients in both the groups at a 3 week follow up. However, the edema resolved in 2 months. In a prospective, case series[13], mild inflammation was reported at a 1 week follow up in 21% of the patients in whom ENTACT Septal Stapler was used for approximation of mucoperichondrial flaps after septoplasty whereas no inflammation was observed in 79% of the patients. Expected rates of edema or inflammation following septoplasty were not discussed in the four publications identified. Other complications reported in the literature include bleeding,[12] and fever.[12]

Sainio et al.[12] conducted a retrospective comparative study comparing ENTACT Septal Stapler to the non-stapler group where silicone splints, tamponade, or sutures were used during septoplasty. No significant difference in the complication rate was observed between the

ENTACT Septal Stapler group (9.9%) and the subgroups such as silicone splint group (9.7%), suture group (12.7%), and the tamponade group (9.5%) in the non-stapler group.[12]

Since the ENTACT (Next Generation) Septal Stapler utilizes the same staples and a similar delivery mechanism to the previous ENTACT Septal Stapler, it is anticipated that the Next Generation device will perform the same as the previous generation device.

4.3 STUDY PURPOSE

To provide evidence to satisfy the PMCF requirements of Conformité Européene (CE) marking to market this device in Europe (data may be used to support registrations on other countries as well).

4.4 SAFETY CONSIDERATIONS

The ENTACT Septal Stapler delivers implantable septal staples that are intended to connect internal tissues to aid healing and for approximation of soft tissue during nasal surgery. Representative language of the contraindications and potential adverse effects from the ENTACT Septal Stapler can be found in the instructions for use (IFU). The ENTACT Septal Stapler are supplied sterile. The ENTACT stapler is sterilized using Gamma Irradiation.[14,15]

Potential Adverse Effects listed in the IFU include:

- Possible adverse effects include but are not limited to wound complications, including hematoma, site drainage, infection, toxic shock syndrome, and other complications that are possible with any surgery.
- When implanted, the ENTACT Staple may elicit a minimal tissue reaction characteristic of foreign body response to a substance. The tissue reaction resolves as the material is absorbed.

- Fracture or extrusion of the ENTACT Staple, with or without generation of particulate debris.

4.4.1 Tolerance limits for potential adverse effects derived from literature

Based on the state of the art data in **Table 4.2.2-1** and **Section 4.2.2** the expected tolerance limits for potential adverse effects from literature in the ENTACT Septal Stapler system are stated in **Table 4.4.1-1.**

Table 4.4.1-1. ENTACT Septal Stapler Tolerance Limits

Expected Complications (derived from literature)	Tolerance limits from literature	Tolerance limits to show no significant difference from literature* (maximum allowed)
Perforation	2/153 (1.31%)	2/40 5% (95% CI 0.6% to 16.92%)
Hematoma	1/153 (0.65%)	2/40 5% (95% CI 0.6% to 16.92%)
Edema	2/153 (1.31%)	2/40 5% (95% CI 0.6% to 16.92%)
Inflammation	5/153 (3.27%)	4/40 10% (95% CI 2.8% to 23.7%)
Infection	6/153 (3.92%)	4/40 10% (95% CI 2.8% to 23.7%)

* These numbers have been derived based on the study sample size of N=40.

Actual study adverse events occurrences will be reviewed under **Section 10.5 and Section 12** and assessed relative to the tolerance limits.

5. OBJECTIVE(S)

The primary, secondary, and safety objectives of this study are listed as follows.

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to demonstrate clinical success of the ENTACT (Next Generation) resorbable septal staple system by examining the patient's nasal cavity at the 21 day follow up visit.

5.2 SECONDARY OBJECTIVE:

The secondary objectives are to generate performance and health economics supporting the use of ENTACT (Next Generation) resorbable septal staple.

5.3 SAFETY OBJECTIVE(S)

Assess safety with reported complications, adverse events, adverse device effects, unanticipated serious adverse device effects, and device deficiencies (DD).

5.4 CLAIMS

The proposed Marketing Claims for this study include, but are not limited to, the following:

- Approximation of septal flaps is achieved in less than a minute;
- ENTACT septal stapler saves time in the operating room compared to traditional suturing techniques.

6. INVESTIGATIONAL PRODUCT(S)

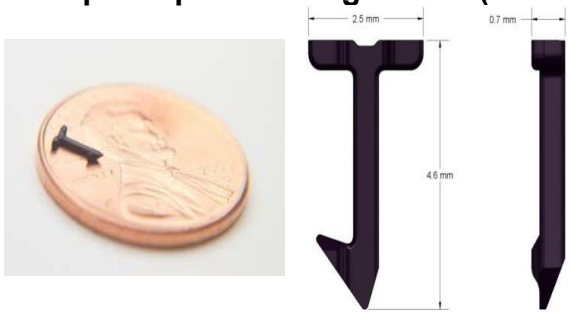
6.1 IDENTIFICATION

6.1.1 Investigation Product

The ENTACT Septal Stapler delivers implantable ENTACT septal staples which are intended to connect internal tissues to aid healing and for approximation of septal flaps of soft tissues during nasal septal surgery. The ENTACT Septal Stapler consists of resorbable fixation devices, which are delivered via a manual surgical stapler delivery system. Each sterile, single patient use device contains eight ENTACT septal staples for holding the septal tissues together during post-op healing.

The ENTACT staple is designed to resorb in about 3 to 6 weeks when used according to labeling[14,15]. The staples shown in **Figure 6.1.1-1** are made up of poly(L-lactide-co-glycolide) (PLG), which has an extensive history of use in medical applications. They are biodegradables that degrade into natural compounds found in the body and are easily eliminated through normal physiological pathways[1].

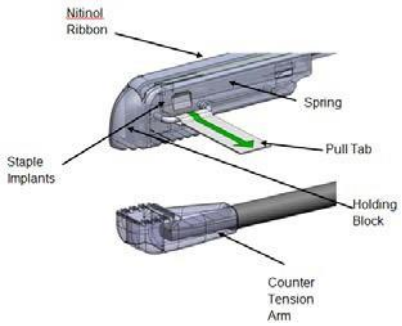
Figure 6.1.1-1 Staple Implant Configuration (2.5mm X 4.6mm X 0.7mm)



The distal tip of the ENTACT Septal Stapler mechanism shown in **Figure 6.1.1-2** displays the primary mechanical components. The preloaded implants are stacked in a holding block. The most distal implant is deployed by a Nitinol ribbon that is advanced when the trigger is pulled. Once the distal implant has exited the implant holding block, the next implant is indexed into position by the force generated by a spring.

The ENTACT Septal Stapler, with the aid of a piercing needle at the tip of the Nitinol ribbon, is designed to deploy the staple with sufficient force to penetrate the mucoperichondrial tissue, with or without cartilage reinserted. The removable tab is a safety mechanism to restrain the spring tension off the implants during storage and to prevent jamming prior to implantation.

Figure 6.1.1-2. ENTACT Septal Stapler (current design) Mechanism



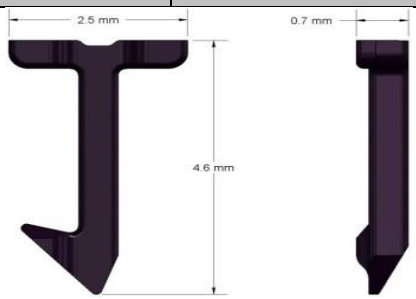
6.1.2 ENTACT Septal Stapler (Previous generations)

The ENTACT stapler originally launched in 2009 by ENTrigue Surgical Inc before the acquisition by ArthroCare (now S+N). Feedback from the market was collected, and changes to the device were implemented in 2010 and 2012. The changes were implemented to streamline the manufacturing process and improve device functionality.

6.1.3 ENTACT Septal Stapler (Next Generation)

The Next Generation device seeking CE marking utilizes the same implant as the current version of ENTACT Septal Stapler. The implant's material composition, geometry, and processing remain unchanged. The delivery system is very similar in the new device, with a few changes to the delivery part of the device in order to enhance manufacturability and reduce the cost of goods. A comparison of the current vs. new design ENTACT Septal Stapler can be found in **Table 6.1.3-1.**

Table 6.1.3-1 Comparable Device Table

	Current Design **Previous generation**	New Design **Next Generation**	Impact of Differences
Implant Design	 The ENTACT staple is ~4.6 mm long, ~2.5 mm wide and ~0.55 mm thick in the shaft middle but ~0.7 mm thick at the top and bottom tabs.		None
Implant composition	**Polymer:** L-lactide-co-glycolide **L-Lactide/Glycolide Content:** 5/95 ratio **Inherent Viscosity** 1.6 ± 0.4 dL/g **Water content:** ≤ 0.5% **D&C Violet #2:** 0 – 0.10% wt% **Monomer Content:** <5.0% total		None
Height of Distal head Width of Distal head	8.3mm 6.0mm	7.0mm 4.9mm	None, justification below
Counter tension arm material	Medical grade Polycarbonate and 17-4 Stainless steel	Ixef 1022 PARA (polyacrylamide with 50% glass fiber)	None, justification below
Implant channel material	304 Stainless steel		None
Holding block material	Medical grade Polycarbonate		None
Pins in channel material	18-8 Stainless steel	300 Series Stainless steel	None, justification below
Push ribbon material	Nitinol		None
Pull ribbon material	Nitinol		None
Sterilization	Gamma Irradiation		None

	Current Design **Previous Generation**	New Design **Next Generations**	Impact of Differences
Packaging configuration	Foil pouch, Carton		None

Indications	The ENTACT Septal Stapler delivers implantable septal staples which are intended to connect internal tissues to aid healing and for approximation of soft tissues during nasal septal surgery	None
Surgical Technique/ Deployment Methods	1. If there is no cartilage between the mucoperichondrial flaps, the staples can be delivered unilaterally. If cartilage is present, stapling the flaps bilaterally may be considered. 2. Remove protective silicone cover from the distal end of the stapler. 3. Unfold and gradually remove pull tab from the distal end of the stapler. 4. Insert the distal tip of the ENTACT Septal Stapler in the nose, one arm in each nostril. 5. Plan placement of staples, so they are spaced approximately 15 mm apart or as deemed necessary from each other. 6. Place the stapler against the mucoperichondrial flap, keeping stapler as perpendicular to the tissue surface as possible and depress handle until an audible click is heard to deploy each staple. 7. Release handle until a second audible click is heard before repositioning the distal tip of the stapler. 8. If necessary, repeat this procedure in the opposite cavity. 9. Visually inspect both nasal cavities to assure adequate approximation and sufficient penetration of the staples. 10. The device is empty when the blue indicator within the clear implant housing is against the distal tip. Firing an empty device will cause the implant guide needle to pierce and make a hole in the septum without placement of an implant. 11. When complete, dispose of stapler with any remaining staples.	None

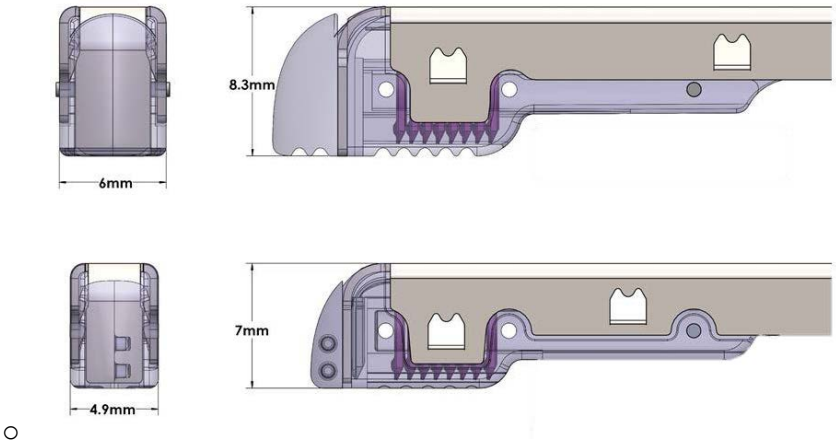
The Next Generation Smith+Nephew ENTACT Septal Stapler described in **Table 6.1.3-1** can be considered comparable to the Previous Generation of the ENTACT Septal Stapler for the following reasons:

- Clinical
  - Both devices are indicated for connecting internal tissues to aid healing and for approximation of soft tissues during nasal septal surgery.
- Technical
  - Both devices enable septal flap closure through the delivery of resorbable implants.
  - The mechanism and kinematics used to deploy the staples are the same in both devices. The principles of operation are identical.
- Biological:
  - The materials utilized in the implant, implant channel, holding block, and the push and pull ribbon are exactly the same in both devices.

Below are the identified differences between the Next and Previous Generation ENTACT Septal Stapler with a rationale for acceptance of those differences.

- Clinical:
  - None, both devices have the same intended use.
- Technical:
  - Distal head changes - the height of the distal head was reduced from 8.3mm to 7.0mm, and the width was reduced from 6.0mm to 4.9mm. The minor design changes to improve surgical access do not affect the intended use of the device.

Figure 6.1.3-1 Distal head changes from current device (top) to new device (bottom)



- Biological
  - Counter tension arm - There are no impact of differences in material for the counter tension arm as PARA has mechanical properties close to stainless steel, and is commonly used in medical devices. Smith+Nephew has conducted both biological and mechanical testing, and has objective evidence that the new device meets all the same requirements as the current device.
  - Pins in Channel - There are no impact of differences in material for the pins in channel as 18-8 stainless steel are in the 300 series stainless steel family, with different naming conventions. These designations are considered interchangeable as 300 Series stainless steels are required to contain 18% chromium and 8% nickel and 18-8 means the steel is 18% chromium and 8% nickel. Smith+Nephew has conducted both biological and mechanical testing, and has objective evidence that the new device meets all the same requirements as the current device.

The minor differences between the comparable device previous generation ENTACT Septal Stapler and Next Generation ENTACT Septal Stapler, are expected to have no impact to the safety of the devices. As these devices as considered comparable, we expect similar clinical safety and performance outcomes.

Refer to the ENTACT Septal Stapler Instructions for Use for more information.

- Do NOT place a staple where the needle path is obstructed or a collision with any object may occur.
- Do NOT use the staple on tissue which is too thick or hard (such as bone) to permit an effective tissue capture.
- Do NOT use with patients in whom radiopacity is necessary or desired since ENTACT staples are radiotransparent.
- Do NOT use in patients in whom prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired.

6.1.4 Material Specification Staple Implant

The staple implant configuration is composed of the absorbable copolymer 5% Poly-L-lactide / 95% Polyglycolide. During the molding process, a violet colorant is introduced. The D&C Violet #2 is a colorant additive (~ 0.05 wt%) to make the implants easier for the doctor to visualize upon placement in the tissue. As previously stated, the ENTACT staple used in both the current and subject devices are identical.

Table 6.1.4-1. ENTACT Septal Stapler Instrument Materials

Description	Existing Device Material (Previous Generation)	New Device Material (Next Generation)	Categorization	
			Nature of Body Contact	Contact Duration
Counter tension arm	Medical grade Polycarbonate and 17-4 Stainless steel	Ixef 1022 PARA (polyacrylamide with 50% glass fiber)		

Implant channel	304 Stainless steel		Surface contact – skin and mucosal membranes	Transient
Holding block	Medical grade Polycarbonate			
Pins in channel	18-8 Stainless steel	300 Series Stainless steel		
Push ribbon Pilot Hole ribbon	Nitinol			

6.1.5 Ancillary Product

Not applicable (NA)

6.2 PRODUCT USE

Refer to IFU for detailed information on contraindications, warnings, precautions, intended users, physician training requirements, instructions for use, and device disposal.

Sites that are familiar with the use of ENTACT Septal Stapler will be selected; no additional training is required.

6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet regulatory requirements.

6.3.1 Labeling of Investigational Product

All devices used in this study will be procured in standard commercial packaging, ordered via normal and customary Smith + Nephew procedures, and managed per study site processes.

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

The investigational product (IP) is not provided by S+N for this post-market study, and no product accountability procedures will be applied.

6.5 SURGICAL TECHNIQUE

All study-related procedures with the ENTACT Septal Stapler must be performed according to the recommended surgical technique described in the protocol or in a separate instructional document and product labeling (e.g., IFU) as applicable.

Surgeons selected to participate in this study will be familiar with using the ENTACT Septal Staples system.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

The study will consist of five visits, including screening/pre-operative, operative, and follow up visits at 5, 21, and 42 days post-surgery. The need for these visits as part of the study will be made clear in the consent form and will be fully explained at the time of recruitment.

Forty (40) individuals to be approached for participation in this study awho are receiving or seeking care for nasal septal obstructions. Subjects will be enrolled up to 3 sites across the United States.

Ethnic minorities are classed as vulnerable subjects according to International Organization for Standardization (ISO) 14155:2011; however, they will be included providing they meet other inclusion criteria, and there are informed consent documents and personnel to lead the consent process in a language that is fully understood by the potential subject.

7.2 INCLUSION CRITERIA

The patient will be eligible for the study if he or she meets all of the following inclusion criteria at the baseline screening:

1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board (IRB);
2. Clinically significant deviation of the nasal septum;
3. Willing and able to make all required study visits;
4. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).

7.3 EXCLUSION CRITERIA

The patient will be ineligible for the study if he or she meets any of the following exclusion criteria at the baseline screening or during surgery:

1. Prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired;
2. Traditional suturing techniques is necessary;
3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent;
4. Known to be allergic to foreign body of materials of investigational product;
5. Concomitant procedures other than turbinectomy, turbinate reduction and/or sinus surgery;
6. Pregnancy at time of procedure;
7. Presence of infection at the site;
8. Severe drug and alcohol abusers;
9. Autoimmune disease deemed clinically significant by Principal Investigator.

7.4 SCREENING

Subjects will be recruited for the study through the clinical practices of the Investigators.

40 individuals to be approached for participation. Subjects will be enrolled as they meet eligibility and consent to the study.

Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening and Enrollment Log. All screening activities that occur prior to consent shall be referred to as pre-screening.

Any subject that meets the definition of a Vulnerable Subject [per International Organization for Standardization (ISO) 14155:2011 Section 3.44.] should be reviewed, but not excluded from the study.

7.5 INFORMED CONSENT

Before conducting any study procedures or examinations, informed consent shall be obtained from all participants according to ISO14155 guidelines, the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. Patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written Informed Consent Form (ICF). The patients shall have sufficient opportunity to consider participation in the study. Patients will then be invited to read, sign and personally date the Institutional Review Board (IRB)-approved ICF, indicating their consent for enrollment. Additionally, the individual who obtains consent from the participant will sign and date the ICF. A copy of the signed informed consent documentation will be provided to the participant, and the original filed in the investigator site file (ISF).

In the case of vulnerable subjects, the ICF must be understood and signed by the subject's legally authorized representative (parent or legal guardian). Assent to participate in the study should be obtained for subjects ≥7 years of age and <18 years of age if allowed by local regulations. For subjects less than 7 years of age an assent will not be obtained.

In the case of minors, the ICF must be obtained by their legally designated representative. The minor shall participate in the informed consent process in a way suitable for his/her age and mental maturity. Minors will receive the study information in a way adapted to their age and mental maturity from investigators or members of the investigating team who are trained or experienced in working with children. If minors express a wish or an opinion with regards to study participation this needs to be respected by the Investigator. If during the study, the minor reaches the age of 18 years (legal competence), the informed consent shall be obtained again, before the subject can continue to participate in the clinical investigation.

Study research staff may then complete Visit 1 Initial Visit (Screening/ Pre-Operative) with the subject. If a subject refuses participation, no further information will be collected. Reason for exclusion should be noted on the Screening and Enrollment Log.

7.6 ENROLLMENT

Subjects for whom the consent process has been completed and have been treated with the study product are considered enrolled.

Subjects will be assigned a Subject ID at the time of consent.

7.7 SCREEN FAILURES

Subjects who have provided consent, completed screening, and for any reason do not meet the eligibility criteria, were not enrolled by the Investigator for any reason, or withdraw consent for any reason prior to enrollment, will be considered a consented screen failure. For these subjects, record the reason for screen failure on the Screening and Enrollment Log and complete the End of Study Case Report Form (CRF) documenting the primary reason for discontinuation. Consented screen failures will be replaced without limit by newly enrolled subjects.

7.8 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for two consecutive visits and does not return for a final visit, and study personnel are unable to contact the subject.

Some actively enrolled subjects will not return for follow-up exams on time. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts before declaring a subject to be lost to follow-up (LTFU): the subject has been contacted according to the site's policies, but no fewer than two documented phone contacts and one certified letter without response. Copies of all attempts to reach the subjects by mail or email and/or the attempts to contact the subject via other means should be documented, and that documentation should be kept with the subject's source documents at site.

7.9 WITHDRAWAL

All reasonable efforts should be made to collect 42 day postoperative data on all subjects enrolled in this study.

7.9.1 Withdrawal from Treatment

The Investigator may withdraw subjects from the study for many reasons, including but not limited to, the following:

- subject noncompliance (e.g., did not follow instructions);
- subject lost to follow-up;
- if the Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study;
- Adverse Events/Adverse Device Effects that affect the ability to evaluate the study product without bias;

- any other significant reason identified by the Investigator;
- re-intervention.

For each case, information will be obtained in the source document and the Case Report Form (CRF), detailing circumstances leading to the withdrawal.

Subjects who drop out or are withdrawn will not be re-entered into the study at a later date.

7.9.2 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the CRF and source documents.

7.9.3 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8. STUDY DESIGN

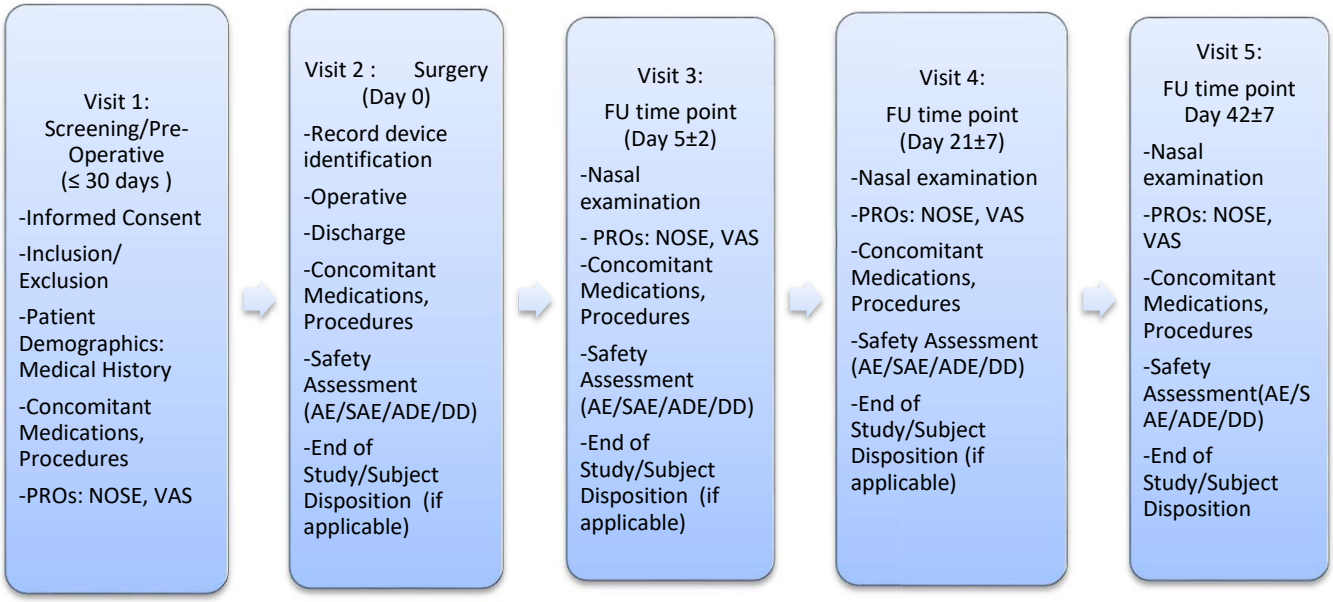
8.1 STUDY DESIGN

This is a prospective, multi-center, single arm PMCF study to evaluate the safety and performance of the ENTACT (Next Generation) resorbable staple system for septoplasty in 40 subjects. The study purpose is to provide evidence to satisfy the PMCF requirements of CE Marking to market this device in Europe (data may be used to support registrations on other countries as well).

This study will enroll at up to 3 clinical sites in the United States.

This is an open-label study with consecutive enrollment. The study will continue for 6 weeks from the date that the last subject received the study treatment to the date that the last subject completes the study as planned. Only subjects who meet the enrollment criteria as listed in **section 7** will be enrolled in the study. The study duration is an estimated 8 months from first study site initiation to last subject last visit.

Figure 8.1-1: Study Flowchart



8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

This study is not randomized. Subjects will be enrolled with the ENTACT (Next Generation) Septal Stapler system.

8.2.2 Blinding

The study is not blinded.

8.3 STUDY ENDPOINTS

8.3.1 Primary Endpoint

At the 21-day follow-up visit, the clinician will examine the patient's nasal cavity and will confirm:

- Septum wall straight appearance (yes/no);
- Complete coaptation of perichondrial flaps on septum wall (yes/no);
- Absence of significant local tissue reaction at the staple site (yes/no);
- Absence of hematoma swelling at the staple site (yes/no);
- No need for re-intervention at the surgery site (yes/no);

If all the answers to the questions above are "YES" then clinical success will be inferred (if any answer is "NO" then repair failure will be inferred).

8.3.2 Secondary Endpoints

- At the 5, and 42-day follow-up visit, the clinician will examine the patient's nasal cavity and will confirm:
    - Septum wall straight appearance (yes/no);
    - Complete coaptation of perichondrial flaps on septum wall (yes/no);

- Absence of significant local tissue reaction at the staple site (yes/no);
- Absence of hematoma swelling at the staple site (yes/no);
- No need for re-intervention at the surgery site (yes/no);

- Assess the following intra-operative times for full population and by sub-groups of Septoplasty only cases and Septoplasty and turbinate reduction cases:
  - Total operation time for the procedure: Recorded as time between start of the procedure and when the drapes are removed from the patient, recorded in minutes
  - Time for operative closure with ENTACT Septal stapler: Recorded as time between start of closure to when the stapler was handed back to the scrub nurse, recorded in seconds.
- NOSE score collected at pre-op and all post-operative visits;
- VAS pain collected at pre-op and all post-operative visits.

8.3.3 Safety Endpoints

Following are the safety endpoints for this study:

- Device-related re-intervention;
- All adverse events (AEs) occurring from the time of surgery until re-intervention or study completion;
- Device related AEs (ADEs) and serious adverse events (SAE's);
- Device deficiencies (DDs)

All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure. All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155:2011.

8.3.4 Exploratory Endpoints

Exploratory endpoints proposed, but not limited to, the following:

- Number and type of other S+N devices with the turbinate reduction adjunct procedure

8.3.5 Balanced Covariates

The inclusion/exclusion criteria will be generalizable and applicable to the widest possible subset of the population needing septoplasty. These criteria will be uniformly applied so as to enroll a cohort of subjects with similar symptoms and clinical requirements. This should maximize the applicability to as many subjects with similar baseline characteristics and help to bolster external validity.

8.3.6 Subject Attrition

Subject attrition due to reduction in sample size required for precision analysis has been accounted for in the sample size calculation so that the estimate of the Confidence Interval (CI) to be obtained will still be valid through the most efficient use of available subjects.

8.3.7 Pre-specification of Statistical Analysis

The primary outcome measure has been pre-specified as well as the type of statistical analysis to be performed to evaluate procedure success rate so as to minimize reporting bias. The precision analysis planned for the study, which includes construction of confidence intervals for the outcome summaries and a pre-defined range in which the 95% CI for the primary outcome are expected to fall within are designed to maximize the validity of the study results.

More detailed information on analyses to be carried out will be incorporated in the Statistical Analysis Plan (SAP) so as minimize any threats to external validity in order to yield clinically relevant estimates of effects and precision.

8.4 METHODS USED TO MINIMIZE BIAS AND MAXIMIZE VALIDITY

8.4.1 Multi-center

The samples from multi-center are more representative than those from single center, and the latter may lead to deviation of study results due to its systematic errors. The required number of cases can be enrolled in a shorter period, and the samples are more representative and the results are more generalizable.

In this study, subjects will be enrolled at multiple sites, utilizing up to 3 US sites. This will reduce the effect of observer bias that might arise at any one investigational site as well as maximize the diversity of subjects treated.

8.4.2 Screening of Subjects

In order to eliminate selection bias, the Investigators will continuously screen all subjects. Subject recruitment continues until the completion of subject recruitment.

8.4.3 Investigator Training

Prior to the clinical trial, the clinical research associate (CRA), coordinating with the persons in charge of the study sites, will train the Investigators on the study protocol, making sure they are familiar with the use of investigational medical device, and implement subject enrollment strictly in accordance with the inclusion criteria and exclusion criteria, conduct relevant examinations according to the protocol requirements, also master all new device-related information found during the clinical trial, thus to minimize the interferential factors. The follow-up exams will be delegated to Investigators not involved in the procedure to reduce potential bias by the surgeon.

8.4.4 Clinical Trial Monitoring

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study. The monitor is selected and appointed by the Sponsor to conduct a regular on-site monitoring visit, making sure that all contents in the study protocol are strictly followed. The

source documents are inspected to ensure consistent contents with the CRF. Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Smith+Nephew standard operating procedures (SOPs) and the Clinical Monitoring Plan.

9. STUDY PROCEDURES

9.1 VISITS AND EXAMINATIONS

None of the listed activities are undertaken by Sponsor personnel.

Table 9.1.1-1: Study Procedures by Visit

Schedule of Events	Patient screening and surgery		Post-operative patient visits		
	Screening/Pre-Operative ≤ 30 days	Surgery Day 0	FU time point Day 5±2	FU time point Day 21±7	FU time point Day 42±7
Informed Consent	X	-	-	-	-
Inclusion/Exclusion	X	-	-	-	-
Demographics: Medical History	X	-	-	-	-
Operative data (Intra-operative delivery success, intra-operative time to deploy staples to complete septoplasty)	-	X	-	-	-
Discharge data	-	X	-	-	-
Visual assessment of nasal cavity	-	-	X	X	X
NOSE score	X	-	X	X	X
Visual Analog Scale	X	-	X	X	X
Concomitant Medications, Procedures	X	X	X	X	X
Safety assessment (AE/SAE/ADE/DD)	-	X	X	X	X

End of Study/Subject disposition	-	*	*	*	x

*As needed
Post-operative visits:
(1) Day 5±2 covers the true “fixation” period for initial healing
(2) Day 21±7 covers the standard of care for patient follow-up
(3) Day 42±7 covers the clinical follow-up duration associated with the lifetime of the device
Notes:
Subjects who have undergone a re-intervention procedure of the implant will be considered terminated from the study from the date of the re-intervention. Study related data will not be collected following the date of the re-intervention.
All concomitant medications/ procedures including any associated with an AE, SAE or SADE will be recorded.

9.1.1 Screening/Preoperative Visit (Visit 1)

Below are the procedures that will be done at the Screening/Preoperative visit.

NOTE: Any subject who signs an informed consent/assent but fails to meet the required entry criteria is considered to be a consented Screen Failure.

1. Obtain written informed consent from the subject as detailed in **Section 7.5**

   ----- Do not proceed until consent has been obtained -----

2. Obtain demographic information and medical history, including information on all concomitant medications/therapies.
3. Screen the subject for protocol inclusion/exclusion criteria.
4. Assign the subject a Subject ID.
5. Complete Screening and Enrollment Log.
6. Complete NOSE score assessment and VAS pain score.

7. Subjects will be instructed to return for the Operation Visit (Procedure) as scheduled by the site.

9.1.2 Treatment/Operation Visit (Visit 2)

1. Query subject regarding any changes in general health and the use of concomitant medications.
2. Commence treatment/operation.
3. Confirm eligibility criteria
4. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in **Section 12,** adverse events and device deficiencies. Also record concomitant medications/therapies used to treat AEs.
5. Record Intra-operative delivery success, total operation time and Intra-operative time for operative closure with ENTACT septal stapler.
6. Record device identification information for the stapler (e.g., Unique Device Identifier, Lot Number, Serial Number, Catalogue Number) and the number of staples used.
7. Instruct the subject on proper postoperative care/procedures, including any contraindicated treatments/medication(s).
8. Instruct the subject on follow-up procedures, including returning the treatment facility in 5 days (± 2) days for follow-up visit.
9. Complete Operation and Discharge Visit CRFs.
10. If applicable, complete an End of Study CRF.

9.1.3 Follow-up Visit (Visit 3) Day 5 (± 2 days)

1. Query subject regarding any changes in general health and the use of concomitant medications.
2. Record assessment of nasal cavity.

3.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in **Section 12**, adverse events and device deficiencies. Also record concomitant medications/therapies used to treat AEs.
4.	Complete NOSE score assessment and VAS pain score.
5.	Instruct the subject on follow-up procedures, including returning the treatment facility at 21 days post-operative (± 7) days for follow-up visit.
6.	If applicable, complete an End of Study CRF.

9.1.4 Follow-up Visit (Visit 4) Day 21 (± 7 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record assessment of nasal cavity.
3.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in **Section 12**, adverse events and device deficiencies. Also record concomitant medications/therapies used to treat AEs.
4.	Complete NOSE score assessment and VAS pain score.
5.	Instruct the subject on follow-up procedures, including returning the treatment facility at 42 days post-operative (± 7) days for follow-up visit.
6.	If applicable, complete an End of Study CRF.

9.1.5 End if Study (Visit 5) Day 42 (± 7 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record assessment of nasal cavity.

3.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in **Section 12**, adverse events and device deficiencies. Also record concomitant medications/therapies used to treat AEs.
4.	Complete NOSE score assessment and VAS pain score.
5.	Complete an End of Study CRF.

Subjects may be provided participant stipends as agreed upon by Sponsor and the site, and as allowed by the site's standard operating procedures/regulations and IRB. Stipend amounts may cover costs associated with the study participant to complete follow-up visits, but cannot be coercive.

9.1.6 Concomitant Medications and Therapies

Concomitant medications and concomitant procedures are recorded at any time from enrollment into the study through the subject's last study visit.

Any concomitant medications/ procedures associated with an AE, SAE or SADE will be recorded.

9.1.7 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety, who are lost to follow-up, or who have missed 2 study visits. Where possible, a full End of Study Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (**see Section 7.9**).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition. Medical care will not be provided to the

subject after the clinical investigation is completed, other than the standard care provided by the site, which is not considered a study visit(s).

9.1.8 Subject Pregnancy

Women of child-bearing potential are not excluded from the study. However, if a woman becomes pregnant during the study, S+N must be contacted immediately once the investigator is made aware of the pregnancy and a decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis.

9.2 STUDY METHODS AND MEASUREMENTS

9.2.1 Nasal Obstruction Symptom Evaluation (NOSE) scale

The Nasal Obstruction Symptom Evaluation (NOSE)[16,21] scale is a patient reported outcome (PRO) instrument that will be administered to capture subject perception of the degree of nasal airway patency. The Nose Scale will be completed at Screening, Day 5, Day 21 and Day 42.

The NOSE scale is a validated instrument, which was developed by the American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) [16,21], and has been used in several clinical trials. The scale is brief, easy to complete, and is an important tool for pre- and post-intervention evaluation of symptoms in subjects with nasal obstruction. The NOSE Scale[21] allows subjects to quantify their symptoms based on the severity of obstruction.

Subjects will be asked, “Since your last follow up visit, how much of a problem were the following conditions for you?” Specifically, subjects will be asked to rate their perceptions on the Likert scale with respect to the following characteristics:

- Nasal congestion or stuffiness
- Nasal blockage or obstruction

- Trouble breathing through my nose
- Trouble sleeping
- Unable to get enough air through my nose during exercise or exertion

Participants will rate their responses using a Likert scale with response options 0, 1, 2, 3 or 4, as follows:

(0) Not a Problem
(1) Very Mild Problem
(2) Moderate Problem
(3) Fairly Bad Problem
(4) Severe Problem

9.2.2 Visual Analog Scale

A Visual Analog Scale (VAS)[18] is a patient-reported outcome instrument that will be used to capture subjects' degree of pain and in the area where ENTACT resorbable staples were implanted. The Visual Analog Scale (VAS) for pain is a continuous scale completed by the subject who is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the subject's mark, providing a range of scores from 0–100. For pain intensity, the scale is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 [100-mm scale]). The VAS will be completed at Screening, Day 5, Day 21, and Day 42.

10. STATISTICAL DESIGN

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The SAP will contain more specific details of the statistical analyses that will be carried out as well as provide information on any changes or deviations from the projected analyses in this protocol. The

Clinical Study Report (CSR) will also highlight changes made to the analyses specified in the protocol.

10.1 GENERAL

Smith+Nephew's Global Biostatistics group or designee will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted. Point estimates and their corresponding 95% two-sided confidence intervals will be generated where appropriate. Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum, and maximum values. All analyses will be performed in SAS 9.4 (or later).

10.2 ANALYSIS POPULATIONS

The following analysis populations will be used for this study:

- Safety population (SAF): This includes all patients who have received the study device.
- Full Analysis Set (FAS): This includes all patients who were recruited into the study and have at least one post-baseline visit.
- Per-Protocol (PP) population: This includes all subjects in the FAS who have no significant protocol deviations and who meet all the inclusion/exclusion criteria.

Statistical analysis will be performed using each of the patient populations as follows: Analysis of the primary and secondary endpoints will be performed separately using both the FAS and PP populations. All safety analyses will utilize the SAF population.

10.3 BASELINE DATA

Data to be summarized at baseline includes but is not limited to all collected demographic variable such as age, gender, primary diagnosis, height, weight, Body-Mass-Index and medical history. The baseline variables will be used to describe the outcome data where necessary.

10.4 EFFICACY ANALYSIS

10.4.1 Analysis of Primary Endpoint

Data will be collected on whether the septum wall appearance and need for re-intervention at the surgery site are due to the device or the procedure. Only those that are device-related will contribute to the primary endpoint analyses, in line with the primary objective of this study. A binary variable will be defined as follows; one if all five of the following criteria are true and 0 if at least one of the criteria is false:

- Septum wall straight appearance
- Complete coaptation of perichondrial flaps on septum wall
- Absence of significant local tissue reaction at the staple site
- Absence of hematoma swelling at the staple site
- No need for re-intervention at the surgery site

Clinical success will be inferred for a patient if their binary variable is 1. Clinical success will be reported as a count and percentage with a 95% CI using Clopper-Pearson Exact methodology. A logistic model will be used to evaluate the adjusted and unadjusted models for the primary outcome variable. The variables considered important and to be included in the final model are age and BMI. All other baseline and medical factors collected at baseline will be evaluated for

importance in adjusted models and only those statistically significant in an unadjusted model will be considered in the final model.

This analysis will be carried out using the FAS as the primary analysis population and the PP population using for sensitivity analysis.

10.4.2 Analysis of Secondary Endpoints

Nasal cavity assessments at day 5 and day 42 will be summarized and presented as count and percentage of each criterion.

Successful staple deployment at the operative visit will be summarized by count and percentage. A 95% exact confidence interval for a single proportion will be presented for successful staple deployment using the Clopper-Pearson method. The number of staples used and whether the stapler misfired will also be presented.

Total operating room time will be calculated and summarized using descriptive statistics and will be presented descriptively by septoplasty only cases as well as septoplasty and turbinate reduction cases.

Intra-operative time to deploy staples to complete septoplasty, calculated as time between start of closure to when the stapler was handed back to the scrub nurse, will be summarized and presented descriptively by septoplasty only cases as well as septoplasty and turbinate reduction cases.

NOSE score will be calculated and summary statistics will be presented by visit. Change in NOSE score from the pre-operative visit to each post-operative visit will also be presented and an ANOVA model will be used to assess statistical significance.

The VAS Pain score will be summarized by visit. Change in VAS Pain score from the pre-operative visit to each post-operative visit will also be presented and an ANOVA model will be used to assess statistical significance.

10.4.3 Analysis of Other Endpoints

- Number and type of other S+N devices that are used with the turbinate reduction adjunct procedure.

10.5 SAFETY ANALYSES

All safety endpoints will be summarized using the safety population.

Adverse Events

The number of subjects reporting: adverse events, serious adverse events, severe adverse events, device-related adverse events, serious device-related adverse events, unanticipated adverse events, and serious unanticipated adverse events will be summarized. In addition, for each adverse event, the following will be summarized: severity, the relationship to the investigational device, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

Device deficiencies

The number of device deficiencies and the number of patients reporting a device deficiency will be summarised.

Additional summaries of safety endpoints, if applicable, will be described in the SAP.

10.6 INTERIM ANALYSES

There are no formal interim analyses planned for this study, however Clinical Activity Reports (CAR) may be produced to faciliate the publication of the results for scientific conferences and publications. Additional adhoc analyses may occur as needed (e.g. for abstracts or publications).

11. SAMPLE SIZE JUSTIFICATION

The results of a previous clinical study[17] on an earlier generation of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. The ICH E9 guidance states that power should be greater than or equal to 80%.[24] Therefore based on statistical precision, the recruitment of 36 subjects would provide us with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision.

With the same assumption of clinical success rate and same precision target, enrolling 36 subjects in ENTACT (Next Generation) will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate. To allow for a 10% drop out rate, this study will enrol 40 subjects.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of adverse events are shown in **table 12.1-1**. The definitions for each of these categories are given in the subsequent sections.

Table 12.1-1: Categories of Adverse Event

	NOT DEVICE-RELATED	DEVICE- OR PROCEDURE-RELATED	
NON-SERIOUS	ADVERSE EVENT (AE)	ADVERSE DEVICE EFFECT (ADE)	
SERIOUS	SERIOUS ADVERSE EVENT (SAE)	SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)	
		ANTICIPATED	**UNANTICIPATED**
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease of untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not causally related to the IP/Ancillary Product.

Note 1: This definition includes events related to the IP, comparator or ancillary products.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the IP

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events and as an umbrella term referring to adverse events of all classifications.

An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the investigator, is related to the use of the IP.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in **section 12.1.3 and 12.1.4** are met.

12.1.3 Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, in the view of either the Investigator or the Sponsor, it:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1) a life-threatening illness or injury, or

- 2) a permanent impairment of a body structure or a body function, or
- 3) in-patient or prolonged hospitalization, or
- 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

- c) led to foetal distress, foetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report (see Section 4.4 for details).

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. DD includes malfunctions, use errors, and inadequate labeling.

12.2 AE CODING DICTIONARY

Coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical signs, symptoms, and conditions

12.3 REPORTING PROCEDURES

AE of any kind and DD will be recorded in the applicable CRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, if applicable, seriousness, and severity. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee **(see figure 12.3-1 and Figure 12.3-2):**

- ADE and DD – without unreasonable delay
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)

For ADE and DD, details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to S+N unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the CRF according to the timescales above.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The investigator will inform the IRB/ Independent Ethics Committee (IEC) of adverse events according to the IRB/IEC requirements.

Depending on the nature of the adverse event, S+N may request copies of the subject's medical records, Imaging, Operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by S+N and should be forwarded as soon as it becomes available. In certain cases, S+N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the Investigator Site File (ISF) Sponsor Contact Information Sheet to report SAE, unanticipated ADE and SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of AE

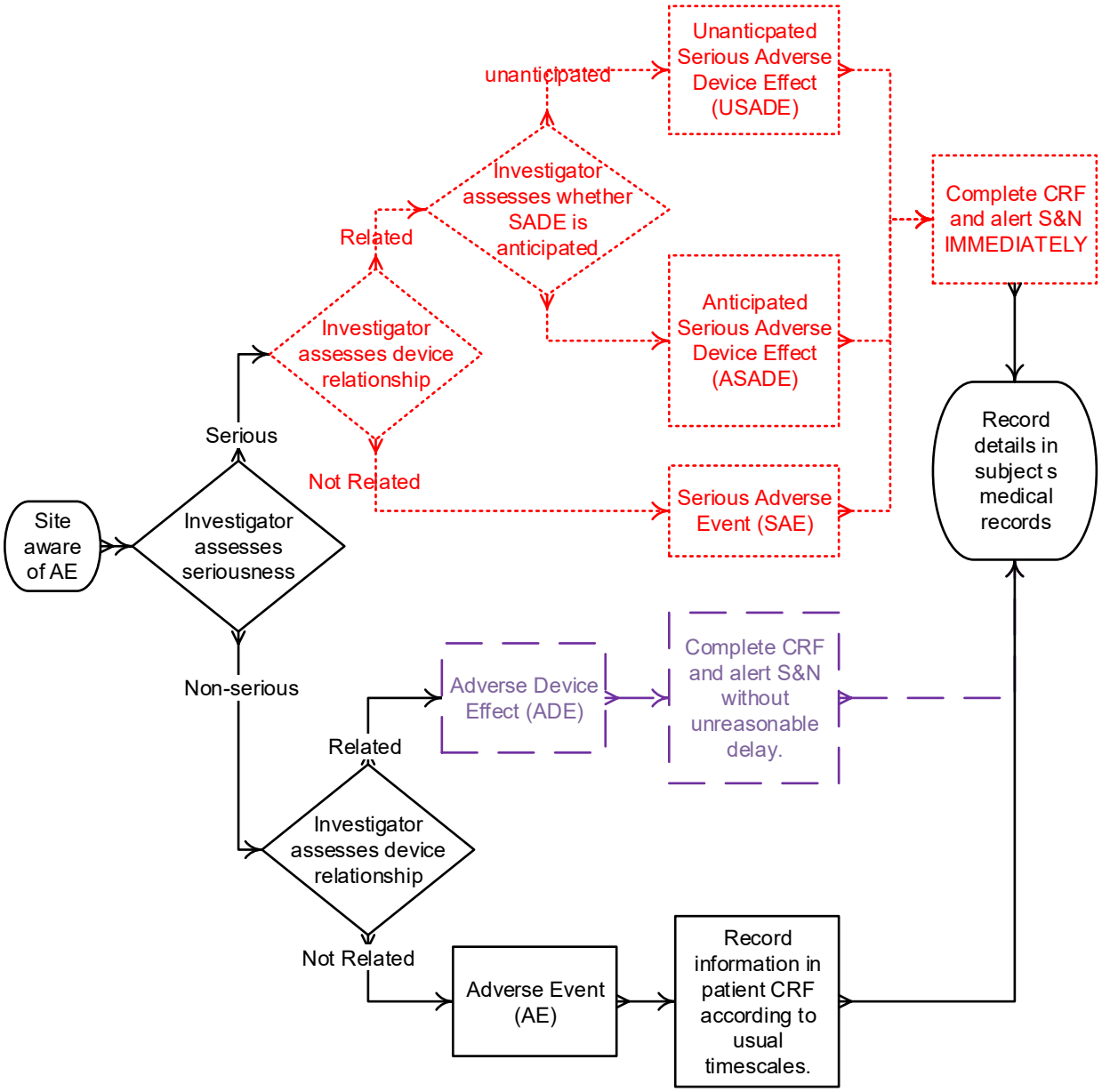
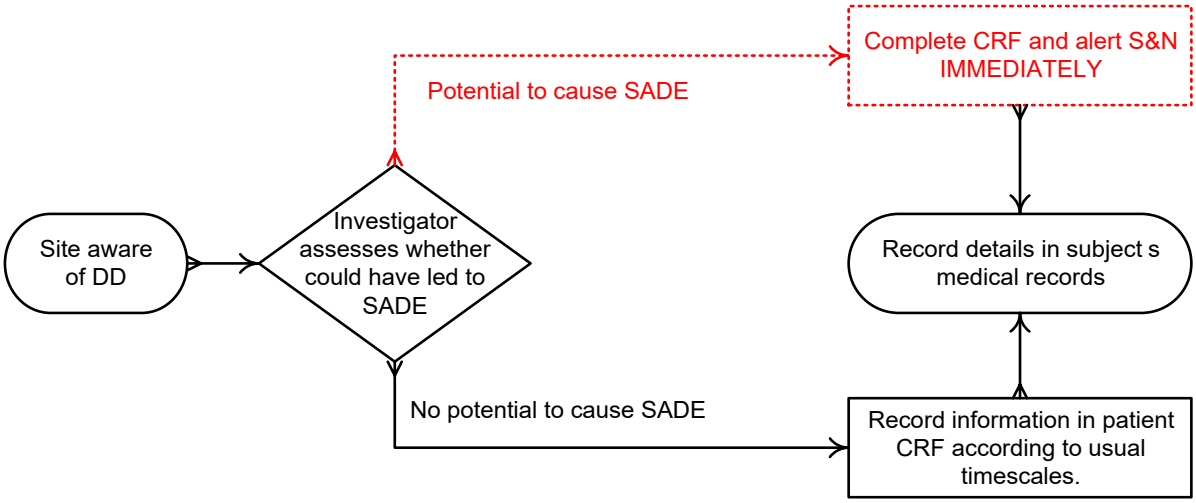


Figure 12.3-2: Evaluation and Reporting of Device Deficiencies



12.4 UNBLINDING OF INVESTIGATIONAL PRODUCT

Not Applicable

12.5 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

Any additional data must be documented and available to the Sponsor, who will determine whether the data need to be documented in the CRF, and as required, the Clinical Study Report.

12.5.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S&N IP and are ongoing at the end of subject's participation: The event should be followed until it is either resolved or until the event has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or S&N IP and are ongoing at the end of subject's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

13. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP) and all applicable regulatory requirements as outlined in **Appendix 21.5** of this protocol.

In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study, and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved

protocol and amendment(s), if applicable, with GCP regulations, and with applicable regulatory requirements.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

14.1 SITE QUALIFICATION VISIT

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities, and resources to adequately conduct the study.

14.2 SITE INITIATION VISIT

A site initiation visit to provide training on the specifics of the study, site obligations, and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor following the execution of the CTA and documented IRB/IEC approval.

14.3 SPONSOR AUDITS AND REGULATORY INSPECTION

Quality Assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

14.4 CLOSE-OUT VISIT

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory

requirements regarding records retention and IRB/IEC reporting requirements. When no subjects have been included, a remove close-out visit may be conducted.

15. PROTOCOL AMENDMENTS

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/IEC. Protocol amendments need to be approved by the IRB/IEC and Regulatory Authority(ies) according to the applicable requirements prior to implementation at the site.

16. CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement (CTA).

17. STATEMENTS OF COMPLIANCE

The investigation was conducted in compliance with applicable requirements in the protection of human subjects' regulations in 21 CFR part 50, Good Clinical Practices, the institutional review board's regulations in 21 CFR part 56. In compliance with the Food and Drug Administration Amendments Act of 2007 (FDAAA), this study will be listed in www.clinicaltrials.gov.

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; and ISO 14155: Clinical investigation of medical devices – Good Clinical Practice[20, 22].

This clinical study will not commence until the required approval/favorable opinion from the IRB or regulatory authority has been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith+Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to

operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

18. END OF STUDY

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor.

The end of study CRF needs to be completed for any subject that does not complete the study, to document the reason for termination.

The entire study may be terminated if deemed necessary by the Sponsor (e.g. the product is determined to not be safe). Sites may be terminated for reasons that include, but are not limited to non-compliance to the protocol, ethical violations, or inability to recruit subjects.

19. PUBLICATION POLICY

19.1 PUBLICATION OF STUDY DATA

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

19.2 DATA SHARING

Smith+Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith+Nephew, therefore, supports the data sharing requirements of

The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017[26]. In accordance, Smith+Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to the sponsor. To gain access, data requestors will need to sign a data access agreement.

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21. APPENDICES

21.1 PROTOCOL AMENDMENT

21.1.1 General Purpose

It was requested by the notified body TUV, which stands for (Technischer Überwachungsverein, English translation: Technical Inspection Association), to update the protocol based on the feedback provided by the TUV reviewer. The following amendments were made to correct and clarify the protocol. This study will start subject enrollment with Protocol Version 2.0.

21.1.2 Rationale

The rationale for the changes are as follows:

Rationale 1: Per the TUV review, the inclusion criteria are stricter than those mentioned in the IFU (e.g., age 18 and older). Removed age inclusion to allow the standard of care data to be collected for this study per the recommendations of the TUV. In addition, **Section 7.5** was updated to include vulnerable populations and minors informed consent language.

Rationale 2: Per the TUV review, the exclusion criteria exceeded those in the IFU (e.g., diabetes, pregnancy, previous septoplasty, smokers, etc.). Removed diabetes, previous septoplasty, and smokers as an exclusion criteria to allow the standard of care data to be collected for this study per the recommendations of the TUV. Clarification provided regarding pregnancy to pregnant at time of procedure. Pregnant women, fetuses, and neonates are often considered vulnerable and protected by ISO and additional regulations. Any elective surgeries such as a septoplasty are off-limits during pregnancy. Although work done to the nose has nothing to do with the womb, the sedation and medication will be harmful to the growing fetus. Subjects are allowed to continue participation in the trial if they do become pregnant after the procedure. The additional tests included in the study schematic do not pose a risk to the subject or the fetus.

Rationale 3: TUV requested further clarification regarding the sample size. As the sample size was not clear, explaining why an 80% power confidence is acceptable. Per ICH, E9 guidance states that power should be greater than or equal to 80%. 80% is a widely used industry standard. Thirty-six subjects would provide us with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations, to within ±11% precision. To allow for a 10% drop out rate, this study will enroll 40 subjects.

Rationale 4: TUV expressed concerns regarding the potential bias of the surgeon with follow up exams. Therefore a statement was added in **Section 8.4.3;** the follow-up exams will be delegated by the Investigators not involved in the procedure to reduce potential bias by the surgeon.

Rationale 5: **Sections 4.2, 4.2.2, and 4.4.1** were added and updated to provide ENTACT staple system safety data collected from literature. Tolerance limits for potential adverse effects were derived from **Section 4.2.2.**

Rationale 6: Administrative changes, removing duplicate words, and adding citations.

21.1.3 Effect on Study Status

Not applicable; this amendment is to be in effect and implemented prior to subject enrollment

21.1.4 Details

Section	Current Text 24/APR/2020 Version 1.0	Revised Text 27/AUG/2020 Version 2.0
Heading	Version 1.0, Date 24Apr2020 original protocol	Version 2.0 Date 27Aug2020
1.1 Protocol Signature Page	I have read the attached protocol entitled “A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT™ (Next Generation) resorbable	I have read the attached protocol entitled “A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT™ (Next Generation) resorbable septal staple system for septoplasty”, version 2.0, dated 27Aug2020 , and agree to abide by all provisions set forth herein.

	septal staple system for septoplasty", version 1.0, dated 24Apr2020, and agree to abide by all provisions set forth herein. I agree to comply with the Investigator's Obligations stipulated in Section 21.2 of the protocol,	I agree to comply with the Investigator's Obligations stipulated in Section 21.5 of the protocol,
1.2 Coordinating Investigator Approval	I have read the attached protocol entitled "A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT™ (Next Generation) resorbable septal staple system for septoplasty", version 1.0, dated 24Apr2020, and agree to abide by all provisions set forth therein.	I have read the attached protocol entitled "A prospective, multi-center, single arm PMCF study to evaluate the safety and performance of ENTACT™ (Next Generation) resorbable septal staple system for septoplasty", version 2.0, dated 27Aug2020 , and agree to abide by all provisions set forth therein.
1.3 Sponsor Approval	Head of Global Biostatistics	Head of Global Data Analytics
2. Synopsis Sample size	Minimum of 30 and maximum of 40 subjects The results of a previous clinical study on previous generations of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. Therefore based on statistical precision, the recruitment of 36 subjects would provide with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision.	40 subjects The results of a previous clinical study on previous generations of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. Therefore based on statistical precision, the recruitment of 36 subjects would provide with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision. With the same assumption of clinical success rate and same precision target, enrolling 36 subjects in ENTACT, Next Generation will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate. To allow for a 10% drop out rate, this study will enrol 40 subjects.

	The study will aim to enroll a minimum of 30 subjects and a maximum of 40 subjects. With the same assumption of clinical success rate and same precision target, enrolling between 30 and 40 subjects in ENTACT Next Generation will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate.	
2. Synopsis Inclusion criteria	The patient will be eligible for the study if he or she meets all of the following inclusion criteria at the baseline screening: 1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board (IRB); 2. Male or female, aged 18 years and older with a clinically significant deviation of the nasal septum; 3. Willing and able to make all required study visits; 4. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).	The patient will be eligible for the study if he or she meets all of the following inclusion criteria at the baseline screening: 1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board (IRB); 2. Clinically significant deviation of the nasal septum; 3. Willing and able to make all required study visits; 4. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).
2. Synopsis Exclusion Criteria	The patient will be ineligible for the study if he or she meets any of the following exclusion criteria at the baseline screening or during surgery: 1. Prolonged tissue approximation beyond that needed for normal	The patient will be ineligible for the study if he or she meets any of the following exclusion criteria at the baseline screening or during surgery: 1. Prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired; 2. Traditional suturing techniques is necessary; 3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent;

	tissue closure is necessary or desired; 2. Traditional suturing techniques is necessary; 3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent; 4. Known to be allergic to foreign body of materials of investigational product; 5. Concomitant procedures other than turbinectomy, turbinate reduction, and/or sinus surgery; 5. Uncontrolled diabetes; 6. Pregnancy; 7. Previous septoplasty; 8. Presence of infection at the site; 9. Smokers and severe drug and alcohol abusers; 10. Autoimmune disease deemed clinically significant by Principal Investigator (PI).	4. Known to be allergic to foreign body of materials of investigational product; 5. Concomitant procedures other than turbinectomy, turbinate reduction, and/or sinus surgery; 6. Pregnancy at time of procedure; 7. Presence of infection at the site; 8. Severe drug and alcohol abusers; 9. Autoimmune disease deemed clinically significant by Principal Investigator (PI).
3. Table of Contents and through protocol	Original sections and page numbers	Updated sections and page numbers
4.2 Literature summary		This section aims to provide a “state of the art” review for the indications in which ENTACT (Next Generation) resorbable septal staple system is intended to be used per **Section 4.4**. A literature search was conducted to identify recently published articles on septoplasty. Limitations such as language or article type were imposed in some searches for publications. Limiting searches to systematic reviews, and meta-analysis was performed to obtain integrated

findings from several selected studies considered to be supportive of evidence-based practices. The results of these studies are discussed in terms of their general conclusions.

This report aims to identify clinical studies or usage of the current Smith & Nephew ENTACT Septal Stapler through an extensive literature search.

In the current evaluation, the PubMed online database (MedLine component) and Embase was used to find clinical results. The medical literature was searched for an unrestricted period of time through July 2019. The search was performed by a qualified Evidence Evaluation Specialist, in July, 2019.

4.2.2 Safety

Complications identified in the four clinical publications are reported in **Table 4.2.2 -1**.

Table 4.2.2-1. ENTACT Septal Stapler Complications

Table 4.2.2 - 1. ENTACT Septal Stapler Complications

Author, Year	# of Pts	Perforation (n)	Hematoma (n)	Edema (n)	Inflammation (n)	Infection (n)
Sainio[12] 2019	101	1	1	-	-	6
Sowerby[5], 2013	8	1	-	2	-	-
Tami[13], 2010	24	-	-	-	5	-
Yildirim[3], 2013	20*	-	-	-	-	-
Total	153	2	1	2	5	6

*Estimated number of patients

Device related complications were reported in three studies.[5,13,12] Perforation was reported in two studies.[5,12] Sainio et al.[12] reported perforation in 1 patient (0.99%) in the ENTACT Stapler group and a reoperation was performed in this patient. Sowerby et al.[5] reported a 1 mm postoperative perforation occurred in one patient (12.5%) due to jamming of the ENTACT Septal Stapler (2009) and stated that this can be avoided with the newer model (2010/2012) of the stapler. Perforation was in line with other outcomes reported in the State of the Art for alternative devices for the Sainio[12] study. In Sowerby et al.[5], the authors concluded that the septal stapler can be used without an increased morbidity in comparison to suture closure or impact to subjective patient scores.

Tami et al[13] reported that the first lot of ENTACT Septal Staplers (2009) failed to perform to design specifications and only four total staples from three staplers were implanted in one patient.

Sainio et al.[12] observed haematoma in one patient in the ENTACT Stapler group. Sainio et al.[12] reported that perforation and haematoma, which occurred at a low rate of 1% each in the study, is in agreement with the study conducted by Tami et al.[13] and

stated that “ENTACT Septal Stapler is safe to use”. The complications reported in the four studies of the ENTACT stapler are performing in-line with alternative devices on the market as discussed in the State of the Art.

Some of the minor complications observed in the literature were edema, inflammation and infection. Sowerby et al.[5] conducted a prospective, randomized clinical study comparing ENTACT Septal Stapler to quilting sutures in patients undergoing septoplasty. Sowerby et al.[5] observed mild edema in 2 patients in both the groups at a 3 week follow up. However, the edema resolved in 2 months. In a prospective, case series[13], mild inflammation was reported at a 1 week follow up in 21% of the patients in whom ENTACT Septal Stapler was used for approximation of mucoperichondrial flaps after septoplasty whereas no inflammation was observed in 79% of the patients. Expected rates of edema or inflammation following septoplasty were not discussed in the four publications identified. Other complications reported in the literature include bleeding,[12] and fever.[12]

Sainio et al.[12] conducted a retrospective comparative study comparing ENTACT Septal Stapler to the non-stapler group where silicone splints, tamponade, or sutures were used during septoplasty. No significant difference in the complication rate was observed between the ENTACT Septal Stapler group (9.9%) and the subgroups such as silicone splint group (9.7%), suture group (12.7%), and the tamponade group (9.5%) in the non-stapler group.[12]

Since the ENTACT (Next Generation) Septal Stapler utilizes the same staples and a similar delivery mechanism to the previous ENTACT Septal Stapler, it is anticipated that the Next Generation device will perform the same as the previous generation device.

4.4.1 Tolerance limits for potential adverse effects derived from literature		Based on the state of the art data in **Table 4.2.2-1** and **Section 4.2.2** the expected tolerance limits for potential adverse effects from literature in the ENTACT Septal Stapler are the stated in **Table 4.4.1-1** **Table 4.4.1-1. ENTACT Septal Stapler Tolerance Limits** Expected Complications (derived from literature) / Tolerance limits from literature / Tolerance limits to show no significant difference from literature* (maximum allowed) Perforation / 2/153 (1.31%) / 2/40 5% (95% CI 0.6% to 16.92%) Hematoma / 1/153 (0.65%) / 2/40 5% (95% CI 0.6% to 16.92%) Edema / 2/153 (1.31%) / 2/40 5% (95% CI 0.6% to 16.92%) Inflammation / 5/153 (3.27%) / 4/40 10% (95% CI 2.8% to 23.7%) Infection / 6/153 (3.92%) / 4/40 10% (95% CI 2.8% to 23.7%) * These numbers have been derived based on the study sample size of N=40. Actual study adverse events occurrences will be reviewed under **Section 10.5 and Section 12** and assessed relative to the tolerance limits. Actual study adverse events occurrences will be reviewed under **Section 10.5** and **Section 12** and assessed relative to the tolerance limits.
5.4 Claims	• Increased distance between both the distal ends for accommodating broader range of anatomies; • Overall, approximately 30% reduction in the distal arm volume for improved posterior access.	Removed claims- data not collected in this study
7.1 Subject Population	A minimum of 30 and maximum of 40 individuals to be approached for participation in this study and will include adult patients (ages 18 and over) who are receiving or seeking care for nasal septal obstructions. Subjects will be enrolled up to 3 sites across the United States.	Forty (40) individuals to be approached for participation in this study who are receiving or seeking care for nasal septal obstructions. Subjects will be enrolled up to 3 sites across the United States.
7.2 Inclusion Criteria	1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with	1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board (IRB); 2. clinically significant deviation of the nasal septum; 3. Willing and able to make all required study visits;

	governing Institutional Review Board (IRB); 2. Male or female, aged 18 years and older with a clinically significant deviation of 3. the nasal septum; 4. Willing and able to make all required study visits; 5. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).	4. Able to read and understand the approved informed consent form and patient reported outcome assessments (written and oral).
7.3 Exclusion Criteria	1. Prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired; 2. Traditional suturing techniques is necessary; 3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent; 4. Known to be allergic to foreign body of materials of investigational product; 5. Concomitant procedures other than turbinectomy, turbinate reduction and/or sinus 6. surgery; 7. Uncontrolled diabetes; 8. Pregnancy; 9. Previous septoplasty; 10. Presence of infection at the site; 11. Smokers and severe drug and alcohol abusers; 12. Autoimmune disease deemed clinically significant by Principal Investigator.	1. Prolonged tissue approximation beyond that needed for normal tissue closure is necessary or desired; 2. Traditional suturing techniques is necessary; 3. Radiopacity is necessary or desired since ENTACT septal staples are radiotransparent; 4. Known to be allergic to foreign body of materials of investigational product; 5. Concomitant procedures other than turbinectomy, turbinate reduction and/or sinus surgery; 6. Pregnancy at time of procedure; 7. Presence of infection at the site; 8. Severe drug and alcohol abusers; 9. Autoimmune disease deemed clinically significant by Principal Investigator.

7.4 Screening	A minimum of 30 and a maximum of 40 individuals to be approached for participation. Subjects will be enrolled as they meet eligibility and consent to the study.	40 individuals to be approached for participation. Subjects will be enrolled as they meet eligibility and consent to the study.
7.5 Informed Consent	Before conducting any study procedures or examinations, informed consent shall be obtained from all participants according to ISO14155 guidelines. Patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written Informed Consent Form (ICF). The patients shall have sufficient opportunity to consider participation in the study. Patients will then be invited to read, sign and personally date the Institutional Review Board (IRB)-approved ICF, indicating their consent for enrollment. Additionally, the individual who obtains consent from the participant will sign and date the ICF. A copy of the signed informed consent documentation will be provided to the participant, and the original filed in the investigator site file (ISF). Once the subjects has consented, the PI or delegated.	Before conducting any study procedures or examinations, informed consent shall be obtained from all participants according to ISO14155 guidelines the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. Patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written Informed Consent Form (ICF). The patients shall have sufficient opportunity to consider participation in the study. Patients will then be invited to read, sign and personally date the Institutional Review Board (IRB)-approved ICF, indicating their consent for enrollment. Additionally, the individual who obtains consent from the participant will sign and date the ICF. A copy of the signed informed consent documentation will be provided to the participant, and the original filed in the investigator site file (ISF). In the case of vulnerable subjects, the ICF must be understood and signed by the subject's legally authorized representative (parent or legal guardian). Assent to participate in the study should be obtained for subjects ≥7 years of age and <18 years of age if allowed by local regulations. For subjects less than 7 years of age an assent will not be obtained. In the case of minors, the ICF must be obtained by their legally designated representative. The minor shall participate in the informed consent process in a way suitable for his/her age and mental maturity. Minors will receive the study information in a way adapted to their age and mental maturity from investigators or members of the investigating team who are trained or experienced in working with children. If minors express a wish or an opinion with regards to study participation this needs to be respected by the Investigator. If during the study, the minor reaches the age of 18 years (legal competence), the informed consent shall be obtained again, before the subject can continue to participate in the clinical investigation.
8.1 Study Design	This is a prospective, multi-center, single arm PMCF study to evaluate the safety and	This is a prospective, multi-center, single arm PMCF study to evaluate the safety and performance of the ENTACT (Next Generation) resorbable staple system for septoplasty in 40

	performance of the ENTACT (Next Generation) resorbable staple system for septoplasty in a minimum of 30 and maximum of 40 subjects. The study purpose is to provide evidence to satisfy the PMCF requirements of CE Marking to market this device in Europe (data may be used to support registrations on other countries as well).	subjects. The study purpose is to provide evidence to satisfy the PMCF requirements of CE Marking to market this device in Europe (data may be used to support registrations on other countries as well).
8.3.3 Safety Endpoints	• Device-related re-intervention; • All adverse events (AEs) occurring from the time of surgery until re-interention or study completion;	• Device-related re-intervention; • All adverse events (AEs) occurring from the time of surgery until re-intervention or study completion;
8.4.2 Screening of Subjects	In order to eliminate selection bias, the Investigators will continuously screen all subjects. Subject recruitment continues until the completion of recruitment subject recruitment.	In order to eliminate selection bias, the Investigators will continuously screen all subjects. Subject recruitment continues until the completion of subject recruitment.
8.4.3 Investigator Training	Prior to the clinical trial, the clinical research associate (CRA), coordinating with the persons in charge of the study sites, will train the Investigators on the study protocol, making sure they are familiar with the use of investigational medical device, and implement subject enrollment strictly in accordance with the inclusion criteria and exclusion criteria, conduct relevant examinations according to the protocol requirements, also master all new device-related information found	Prior to the clinical trial, the clinical research associate (CRA), coordinating with the persons in charge of the study sites, will train the Investigators on the study protocol, making sure they are familiar with the use of investigational medical device, and implement subject enrollment strictly in accordance with the inclusion criteria and exclusion criteria, conduct relevant examinations according to the protocol requirements, also master all new device-related information found during the clinical trial, thus to minimize the interferential factors. The follow-up exams will be delegated by the Investigators not involved in the procedure to reduce potential bias by the surgeon.

	during the clinical trial, thus to minimize the interferential factors.	
11.0 Samples Size Justification	The results of a previous clinical study17 on an earlier generation of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. Therefore based on statistical precision, the recruitment of 36 subjects would provide us with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision. The study will aim to enrol a minimum of 30 subjects and a maximum of 40 subjects. With the same assumption of clinical success rate and same precision target, enrolling between 30 and 40 subjects in ENTACT (Next Generation) will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate.	The results of a previous clinical study[17] on an earlier generation of the study device found that 92% of subjects had successful fixation of tissue after one week. It is assumed that the study device will perform at least as well as the 92% found previously. The ICH E9 guidance states that power should be greater than or equal to 80%.[24] Therefore based on statistical precision, the recruitment of 36 subjects would provide us with at least 80% probability of obtaining a 2-sided 95% confidence interval, around the estimate proportion of successful fixations of tissue, to within ±11% precision. With the same assumption of clinical success rate and same precision target, enrolling 36 subjects in ENTACT (Next Generation) will provide probabilities between 78.4% and 90.3% of obtaining the 2-sided 95% confidence interval of the success rate. To allow for a 10% drop out rate, this study will enrol 40 subjects.
20.0 References		Addition of references 20-23

21.1.5 Approval/Notification

It will be necessary to obtain IRB/EC approval prior to implementation of any change in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the IRB/EC of the study site by the Investigator.

21.2 INSTRUCTIONS FOR USE

Refer to the Instruction for Use supplied with this protocol

21.3 EQUIPMENT AND SPECIAL INSTRUCTIONS

Not Applicable

21.4 ADDITIONAL INFORMATION

Not applicable

21.5 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2011)

1. General:
    a. The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.
2. Qualification of the PI. The PI shall:
    a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,
    b. be experienced in the field of application and trained in the use of the investigational device under consideration,
    c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
    d. be knowledgeable with the method of obtaining informed consent.

3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
    a. has the required number of eligible subjects needed within the agreed recruitment period, and
    b. has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.
4. Communication with the IEC. The PI shall:
    a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
    b. comply with the requirements described in 4.5 of ISO 14155:2011.
        i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: the Protocol; IB or equivalent; informed consent form and any other written information provided to subjects; procedures for recruiting subjects and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.
        ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.
        iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:
            1. SAEs
            2. Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of deviations made to protect the rights, safety, and well-being of human subjects under emergency circumstances.
            3. Progress reports, including safety summary and deviations
            4. Amendments to any documents already approved by the IEC.

5. If applicable, notifications of suspension or premature termination
6. If applicable, justification and request for resuming the clinical investigation after suspension.
7. Clinical investigation report or summary.

iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:

1. Approval/favorable opinion of amendments
2. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
3. Approval for resumption of a suspended clinical investigation if applicable.

c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:

a. General:

i. Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)

b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These

requirements also apply with respect to informed consent obtained from a subject's legally authorized representative:

i. Ensure that the PI or his/her authorized designee conducts the informed consent process
ii. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
iii. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
iv. Not waive or appear to waive the subject's legal rights
v. Use native non-technical language that is understandable to the subject
vi. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
viii. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
ix. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

c. Special circumstances for informed consent (the following provisions are subject to national regulations):

i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.
ii. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable

to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.

iii. Emergency treatments:

1. For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.
2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

e. Information provided to the subject. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
   iv. Alternative procedures
   v. Confidentiality
   vi. Compensation
   vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
   viii. Information on the role of Sponsor's representative in the clinical investigation
   ix. Contact persons
   x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the subject's continued participation shall be made available to the subject.
   xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation
   xii. Termination procedures

f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
   ii. A statement declaring that refusal of participation incurs no penalty for the subject
   iii. A statement declaring that discontinuation at any time incurs no penalty for the subject
   iv. A statement with regard to the possible consequences of withdrawal

v. An acknowledgment of the information provided and confirmation that all the subject's questions were answered

vi. A statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation

vii. A statement confirming that the subject or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.

g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

h. Ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and

i. Ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:

a. indicate his/her acceptance of the protocol in writing,

b. conduct the clinical investigation in compliance with the protocol,

c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,

d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,

e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,

f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,

g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,
h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
k. maintain the device accountability records,
l. allow and support the Sponsor to perform monitoring and auditing activities,
m. be accessible to the monitor and respond to questions during monitoring visits,
n. allow and support regulatory authorities and the IEC when performing auditing activities,
o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
p. review and sign the clinical investigation report, as applicable.

7. Medical care of subjects. The Principal Investigator shall

a. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
b. inform the subject of the nature and possible cause of any adverse events experienced,
c. provide the subject with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the subject,
d. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
e. provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for

emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,

f. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,

g. if appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),

h. inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and

i. make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

8. Safety reporting. The Principal Investigator shall:

a. record every adverse event and observed device deficiency, together with an assessment,

b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,

c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,

d. report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and

e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

Certificate Of Completion

Envelope Id: 930EB5F1D9B4464AA0CAEE5AC314BAB9
Status: Completed
Subject: Please DocuSign: 2020 08.27 ENTACT Study Protocol Version 2.0 Clean Version pdf.pdf
Source Envelope:
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7135 Goodlett Farms
Cordova, TN 38016
esvanhnelly.podany@smith-nephew.com
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Signer Events	Signature	Timestamp
Alan Rossington alan.rossington@smith-nephew.com Clinical Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 556E7DBF-CA8A-4287-A7EE-3EE9B5B3ABFD Using IP Address: 216.222.214.6 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Aug-2020 | 20:38 Resent: 28-Aug-2020 | 11:30 Viewed: 28-Aug-2020 | 16:08 Signed: 28-Aug-2020 | 16:10
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Luca Orlandini Luca.Orlandini@smith-nephew.com Clinical Sr. Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: FC872951-AC1C-4261-B85E-C7A7CD09ACDC Using IP Address: 216.222.214.6 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Aug-2020 | 20:38 Resent: 28-Aug-2020 | 11:30 Viewed: 28-Aug-2020 | 14:29 Signed: 28-Aug-2020 | 14:32
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Signer Events	Signature	Timestamp
Piedad Pena Piedad.Pena@smith-nephew.com Regulatory Manager 2 Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 5D46F116-173D-4FFF-A4A7-648880EAC17F Using IP Address: 216.222.219.1 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Aug-2020 | 20:38 Resent: 28-Aug-2020 | 11:30 Viewed: 28-Aug-2020 | 13:55 Signed: 28-Aug-2020 | 13:56
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Rachael Winter Rachael.Winter@smith-nephew.com Clinical Sr. Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: A32F12A8-0F1B-4490-986E-80ACCB7471CB Using IP Address: 194.207.232.40 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Aug-2020 | 20:38 Resent: 28-Aug-2020 | 11:30 Viewed: 28-Aug-2020 | 17:24 Signed: 28-Aug-2020 | 17:24
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Stephan Mangin Stephan.Mangin@smith-nephew.com Clinical Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 77573411-150E-4841-B3F0-3589FBBD3EAD Using IP Address: 136.49.123.247 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 27-Aug-2020 | 20:38 Resent: 28-Aug-2020 | 11:30 Viewed: 28-Aug-2020 | 14:50 Signed: 28-Aug-2020 | 14:51
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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

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Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	28-Aug-2020 | 11:30
Certified Delivered	Security Checked	28-Aug-2020 | 17:24
Signing Complete	Security Checked	28-Aug-2020 | 17:24
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