1. SIGNATURES

1.1 PROTOCOL SIGNATURE PAGE

This page will be returned to Smith & Nephew Inc. and a copy retained at the study site.

I have read the attached protocol entitled "A Multicenter, Post Market, Prospective Study Evaluating Safety and Efficacy of CONQUEST FN™ for the Treatment of Intracapsular Femoral Neck Fractures", version 2.0, dated 30-Nov-2018, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 20.3 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.

Role	**Name**	**Signature***	**Date Signed*** (DD-MMM-YYYY)
Principal Investigator			

1.2 SPONSOR APPROVAL

Role	Approver Name	Approver Signature
Head of Global Clinical Operations	Andy Weymann	DocuSigned by: Signer Name: Andy Weymann Signing Reason: I approve this document Signing Time: 06-Dec-2018 | 10:20 GMT 675C45EC25704A5FB20A08674419D6D8
Head of Global Clinical Strategy	Beate Hanson	DocuSigned by: Beate Hanson Signer Name: Beate Hanson Signing Reason: I approve this document Signing Time: 11-Dec-2018 | 19:18 GMT A491AB16277146CA9C8B8366F1B6BEA5
Head of Global Biostatistics & Global Data Sciences	Alan Rossington	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 12-Dec-2018 | 12:18 GMT 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Head of Global Medical Affairs	Luca Orlandini	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 11-Dec-2018 | 17:33 GMT FC872951AC1C4261B85EC7A7CD09ACDC

2. SYNOPSIS

Title of Study:	A Multicenter, Post Market, Prospective Study Evaluating Safety and Efficacy of CONQUEST FN™ for the Treatment of Intracapsular Femoral Neck Fractures
Study Design:	Prospective, single arm, multi-center study of subjects who are to be implanted with the CONQUEST FN™ Femoral Neck Fracture System for treatment of a trauma related femoral neck fracture.
Study Type:	Post-Market Clinical Follow-Up (PMCF)
Study Product:	The CONQUEST FN™ Femoral Neck Fracture System
Study Purpose:	A post-market, prospective study to evaluate the reoperation rate of displaced and nondisplaced femoral neck fractures treated with the CONQUEST FN™ system.
Primary Objective:	The primary objective of this study is to evaluate the reoperation rate for any reason of displaced and non-displaced femoral neck fractures treated with the CONQUEST FN™ Femoral Neck Fracture System at one year post-operation.
Secondary Objective(s):	The secondary objective of this study is to generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data.
Statistical Rationale:	A total minimum sample size of 90 subjects with a minimum of 45 subjects for displaced and 45 subjects for non-displaced femoral neck fractures. Since the primary and secondary endpoints are the same for all fractures, overall results will be reported as well.
Sample Size:	A minimum of 90 Subjects (minimum of 45 displaced and 45 non-displaced femoral neck fractures)
Number of Study Sites:	Approximately 10 sites
Targeted Global Regions:	United States
Inclusion Criteria:	1. The subject must provide written informed consent (reference section 7.4).

	2. The subject must be eighteen (18) years of age or older. 3. The subject must be willing and able to make all required study visits including one (1) year post-operative follow-up. 4. The subject must be able to follow instructions. 5. Subject has experienced displaced or non-displaced intracapsular femoral neck fracture and are scheduled for repair using the CONQUEST FN™ Femoral Neck Fracture System.
Exclusion Criteria:	1. Contraindications or hypersensitivity to the use of the CONQUEST FN™ Femoral Neck Fracture System or its components (316L stainless steel). 2. Subject with fracture occurring more than 7 days prior to implantation of the CONQUEST FN™ Femoral Neck System. 3. Subject has more than one fracture on target hip. 4. Subject is obese as defined by a Body Mass Index (BMI) > 40 at the time of surgery. 5. Subject, in the opinion of the Investigator, has an emotional or neurological condition that precludes cooperation and compliance with the rehabilitation regimen. 6. Therapy with another investigational agent within thirty (30) days of Screening or planned therapy with another investigational agent during the course of the study. 7. Subject has a physical condition that, in the opinion of the Investigator, would preclude adequate implant support or impede healing (e.g. blood supply impairment, insufficient bone quality or quantity, or an active, local or systemic infection). If this is identified at the time of surgery, the subject will be screen failed. 8. Subject has undergone previous surgery on the target hip. 9. Subject has severe bow of the target hip or gross distortion of the femur.

	10. Subjects who have participated previously in this clinical trial and who have healed or been withdrawn. 11. Current systemic therapy with cytotoxic drugs. 12. Subjects with a history of poor compliance with medical treatment. 13. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
Study Duration:	Approximately 30 months (18 month recruitment period, 12 month follow-up)
Primary endpoint:	Reoperation rate for any reason of displaced and non-displaced femoral neck fractures treated with the Conquest FN™ at one year post-operation.
Secondary endpoint(s):	The secondary endpoints of this study include generation of safety, performance, and health economic evidence supporting the use of the CONQUEST FN™ Femoral Neck Fracture System per the endpoints listed below: • Intraoperative complications • Radiographic outcomes including quality of fracture reduction • Construct failure past typical femoral neck fracture healing period (past 6 months) • Visual analogue scale (VAS) relating to pain at the fracture site • Quality of Life (EQ-5D-5L) • Time to return to full weight-bearing • Ambulatory status from pre-injury to study completion • Timed Up & Go • Length of hospital stay • Hospital readmissions for any reason • Device- and surgery-related adverse events • Active straight leg raise (ASLR) assessment
Safety Data	Adverse Events will be collected and 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. All events, based on these categorizations, will be reported to appropriate regulatory authorities

per ISO 14155: Clinical investigation of medical devices – Good Clinical Practice and ICH-E6.

STUDY SCHEMATIC

Schedule of events	Pre-Operative Data (Day -7 to Day 0)	Operative/ Discharge Data[1] (Day 1)	6 weeks (Day 42 ± 7 days)	3 months (Day 90 ± 7 days)	6 months (Day 180 ± 14 days)	12 months (Day 365 ± 30 days)
Informed Consent	✓					
Inclusion/Exclusion	✓					
Demographics/ Medical History	✓					
Operative Data Collection		✓				
Discharge Data Collection[1]		✓				
VAS (pain score)	✓		✓	✓	✓	✓
Timed Up & Go			✓	✓	✓	✓
EQ-5D-5L	✓		✓	✓	✓	✓
X-Ray • AP • Lateral	✓	✓	✓	✓	✓	✓
Active Straight Leg Raise			✓	✓	✓	✓
Adverse Event Assessment		✓	✓	✓	✓	✓
End of Study/Exit						✓

[1] Discharge data to be collected at time of discharge which will be dependent on subject recovery.

3. TABLE OF CONTENTS

3.1 TABLE OF TABLES

3.2 TABLE OF FIGURES

3.3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ASLR	Active Straight Leg Raise
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
AP	Anteroposterior
CRF	Case Report Form(s)
CV	Curriculum Vitae
DevD	Device Deficiency(ies)
FAS	Full Analysis Set Population
FU	Follow-up
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intention to Treat population
MedDRA	Medical Dictionary for Regulatory Activities
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
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

Abbreviation	Definition
SAP	Statistical Analysis Plan
TUG	Timed Up and Go
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analog Scale

4. INTRODUCTION

4.1 BACKGROUND

Femoral neck fractures are major surgical challenges with high complication rates in young (<60 years), young elderly (60-70 years) and elderly adults (>70 years). Relevant literature has reported complication rates ranging from 15–64%[1,2] and 0-36%[3,4] for displaced and non-displaced femoral neck fractures, respectively. Complications typically manifest as avascular necrosis, fracture non-union with implant failure and concomitant loss of fracture reduction.[5, 6, 7] In many cases, the onset of these complications necessitates re-operation.[8] The function and anatomy of the proximal femur, including the high regional variability in local load/strain distribution, vascular supply and lack of periosteal fracture response, all contribute in making femoral neck fractures challenging to manage clinically.[9,10,11]

Conservative care for high (i.e. traumatic) or low (i.e. fragility) energy femoral neck fractures is rarely a therapeutic option, and so a higher risk surgical intervention is usually the only management choice.[12] Fixation has historically been accomplished using multiple cannulated screws or compressions hip screws with or without anti-rotation screws, which act to reduce the fracture and confer compression across the fracture site to allow healing.[13] For high-energy injuries resulting in displaced femoral neck fractures, the quality of fracture reduction is of significant importance, as poorly reduced fractures have been associated with high non-union rates and the need for repeat surgical intervention.[14] While various permutations of these fixation strategies have been utilized clinically, current data to not conclusively support the superiority of a single fixation system or approach for the treatment of intracapsular femoral neck fractures and high complication rates persist.[15,16]

The CONQUEST FN™ represents the next generation femoral neck fracture system designed to offer better intra-operative reduction control with the assurance of eliminating device failure modes. This system is dedicated to treating both non-displaced and displaced intracapsular fractures of the femoral neck. It is a dynamic locked implant system that provides multiple points

of fixed angle support with continuous compression across the fracture site, ensuring bone-on-bone contact during the fracture union process. The continuous fracture site compression and post-operative reduction maintenance is accomplished with the incorporation of telescoping compression screw technology. The novel system empowers surgeons to address the current surgical challenges and often unfavorable patient outcomes and high re-operation rate associated with the current treatment options for intracapsular femoral neck fractures.

The CONQUEST FN™ Femoral Neck Fracture System obtained 510(k) clearance from FDA on 17Mar2016. To date, it is being used in clinical practice by several institutions in the United States with approximately sixty (60) cases in which the system has been implanted. Clinical studies on the system are needed to provide evidence to assess overall safety and efficacy. A summary of known and potential risks and benefits to humans of the Study Device can be found in the Instructions for Use (IFU).

4.2 STUDY PURPOSE

A post-market, prospective study to evaluate the reoperation rate of displaced and nondisplaced femoral neck fractures treated with the CONQUEST FN™ system.Safety Considerations

Reference the current Instructions for Use (IFU) for a comprehensive list on known contraindications and safety considerations.

5. OBJECTIVE(S)

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the re-operation rate for any reason of displaced and non-displaced femoral neck fractures treated with the CONQUEST FN™ Femoral Neck Fracture System at one year post-operation.

5.2 SECONDARY OBJECTIVE(S)

The secondary objective of this study is to generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data.

6. STUDY DEVICE(S)

6.1 IDENTIFICATION

6.1.1 Study Product

Intended Use

The CONQUEST FN™ Femoral Neck Fracture System is indicated for use in displaced and non-displaced intracapsular femoral neck fractures. The present study aims to evaluate the use of CONQUEST FN™ in adults (≥ 18 years of age) who have suffered a femoral neck fracture due to trauma but are otherwise active individuals.

Device description

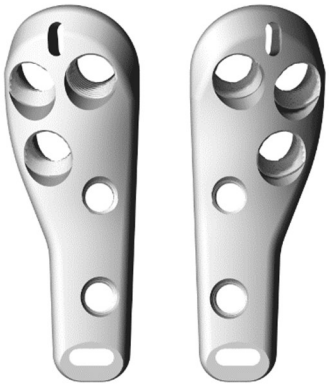
The CONQUEST FN™ is a dynamic locking plate system that includes a proximal femoral locking plate, telescoping compression screws, and reduction maintenance instrumentation. The proximal femoral locking plate is available in three sizes (left and right) (see figure 6.1.1-1), all of which are comprised of 316L Stainless Steel with a neck angle of 124 degrees and anteversion of 14 degrees. The telescoping compression screws are available in two (2) circumference sizes, 7.5mm and 8.5mm, which are also comprised of 316L Stainless Steel with lengths ranging from 75mm-130mm (5mm increments).

Manufacturer

CONQUEST FN™ is manufactured by Smith & Nephew, Inc., 1450 Brooks Road, Memphis, TN 38116.

Figure 6.1.1-1 CONQUEST FN™ Femoral Neck Fracture System (Not Actual Size)

1 Hole – 60mm length



2 Hole – 85mm length

3 Hole – 127mm length

CONQUEST FN Locking Plates 60mm Set No. 7181-1401		
Cat. No.	**Description**	**Quantity**
7580-7001L	CONQUEST FN Locking Plate 1H Left 60mm	1
7580-7001R	CONQUEST FN Locking Plate 1H Right 60mm	1
CONQUEST FN Locking Plates 85mm Set No. 7181-1401		
Cat. No.	**Description**	**Quantity**
7580-8002L	CONQUEST FN Locking Plate 2H Left 85mm	1
7580-8002R	CONQUEST FN Locking Plate 2H Right 85mm	1
CONQUEST FN™ Locking Plates 127mm Set No. 7181-1401		
Cat. No.	**Description**	**Quantity**
7580-7003L	CONQUEST FN Locking Plate 3H Left 127mm	1
7580-7003R	CONQUEST FN Locking Plate 3H Right 127mm	1

6.1.2 IP-Control and Comparator Treatment

There will be no comparator products used in this study.

6.1.3 Ancillary Products

No ancillary products are to be provided for this study.

6.2 PRODUCT USE

Refer to IFU and Surgical Technique educational brochure for full instructions.
Study center personnel with responsibilities for the medical care of subjects and/or the implantation of the study device (CONQUEST FN™) will be trained on the use and surgical techniques of CONQUEST FN™ prior to enrolling subjects in the study.

6.3 PACKAGING AND LABELING

Packaging and labelling will be prepared to meet regulatory requirements.

6.3.1 Study Device Labeling

Smith & Nephew will not supply the site with study devices due to the various size options available for use. Standard device procurement and management will be used per site processes.

6.4 STUDY DEVICE/ ANCILLARY PRODUCTS AND STUDY SUPPLIES ACCOUNTABILITY PROCEDURES

No Study device/Ancillary Products and Study Supplies are supplied for the study and the Sponsor accountability will not be required.

6.5 SURGICAL TECHNIQUE

All study-related procedures conducted at the study site must be performed according to the recommended surgical technique described in the labeling and instructions for use (IFU).

Surgeons selected to participate in this study will be required to have completed two (2) surgeries using the CONQUEST FN™ Femoral Neck Fracture System and have written evidence of training and expertise in the study procedure.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

Subject Population

A minimum of 90 subjects (18 years of age or older) with a confirmed displaced or non-displaced intracapsular femoral neck fracture who are scheduled for repair using CONQUEST FN™ will be recruited at approximately 10 study sites in the United States. Additional sites may be added, if necessary, to meet recruitment goals. A minimum of 45 displaced and 45 non-displaced fractures are required.

7.1 INCLUSION CRITERIA

Subjects will be considered qualified for enrollment if they meet the following criteria:

1. The subject must provide written informed consent (reference section 7.4).
2. The subject must be eighteen (18) years of age or older.
3. The subject must be willing and able to make all required study visits including one (1) year post-operative follow-up.
4. The subject must be able to follow instructions.
5. Subject has experienced displaced or non-displaced intracapsular femoral neck fracture and is scheduled for repair using the CONQUEST FN™ Femoral Neck Fracture System.

7.2 EXCLUSION CRITERIA

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. Contraindications or hypersensitivity to the use of the CONQUEST FN™ Femoral Neck Fracture System or its components (e.g. stainless steel).
2. Subject with fracture occurring more than 7 days prior to implantation of the CONQUEST FN™ Femoral Neck System.
3. Subject has more than one fracture on target hip.
4. Subject is obese as defined by a Body Mass Index (BMI) > 40 at the time of surgery.

5. Subject, in the opinion of the Investigator, has an emotional or neurological condition that preludes cooperation and compliance with the rehabilitation regimen.
6. Therapy with another investigational agent within thirty (30) days of Screening or planned therapy with another investigational agent during the course of the study.
7. Subject has a physical condition that, in the opinion of the Investigator, would preclude adequate implant support or impede healing (e.g. blood supply impairment, insufficient bone quality or quantity, or an active, local or systemic infection). If this is identified at the time of surgery, the subject will be screen failed.
8. Subject has undergone previous surgery on the target hip.
9. Subject has a severe bow of the target hip or gross distortion of the femur.
10. Subjects who have participated previously in this clinical trial and who have healed or been withdrawn.
11. Current systemic therapy with cytotoxic drugs.
12. Subjects with a history of poor compliance with medical treatment.
13. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

7.3 SCREENING

Participating study sites are required to document all screened subjects. 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.

Part of the screening process will include documentation of women’s childbearing potential. If the woman is not of child bearing potential this should be documented in the medical history (e.g. surgically postmenopausal, postmenopausal [i.e. at least 1 year without menses]). For women of childbearing potential their method of birth control should be documented in the source.

7.4 INFORMED CONSENT

Before conducting any study procedures or examinations, the purpose and nature of the study will be explained to the subject in their native language. Informed Consent Forms (ICF) requiring translation from English to a subject's native language will be translated by a certified third party vendor of the Sponsor's choosing. The translated ICF will then be submitted to the site's Institutional Review Board (IRB) for review and approval prior to distributing to potential subjects. The subject will then **read**, **sign**, and **personally date** the IRB -approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent documentation will be provided to the subject and the original kept on site. Any additional requirements required by the IRB will be followed. If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible the subject shall sign and personally date the Informed Consent Form. Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the ICF, attesting that the information was accurately explained and that the informed consent was freely given.

7.5 ENROLLMENT

Enrollment in this study shall occur once the subject has successfully completed the informed consent process and successfully completed the Operative Visit (Day 1). A subject number will be assigned at the time of the Screening visit.

7.6 LOST TO FOLLOW-UP

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 prior to declaring a subject to be lost to follow-up: the subject has been contacted according to the site's policies, but no fewer than 2 documented phone contacts and 1 certified

letter without response. Copies of all attempts to reach the subjects per regular 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.

7.7 WITHDRAWAL

7.7.1 Withdrawal from Study

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, took disallowed medications)
- 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
- concurrent illness
- Adverse Events/Adverse Device Effects
- any other significant reason identified by the Investigator
- in the event any component of the original hardware is revised/exchanged

Replacement Policy

Subjects who dropout before being enrolled (i.e. during Screening) will be replaced. Subjects who drop out of the study after being enrolled, for whatever reason, will not be replaced. Any subject who drops out after randomization will not be permitted to re-enroll into the study at a later date.

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

7.7.2 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 in source documents.

7.7.3 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 multi-center, post-marketing, prospective study. Subjects will be stratified by fracture type (minimum of 45 displaced and 45 non-displaced fractures) for a minimum total of 90 enrolled subjects.

Data from eligible subjects who have provided a signed ICF will be evaluated at the pre-operative, operative/discharge, 6-weeks, 3-month, 6-month and 12-month follow-up visits.

The total study duration will include approximately 18 months for enrollment and one year of follow-up at approximately 10 sites in the United States.

8.2 ALLOCATION AND BLINDING

This study is not randomized.

8.3 STUDY ENDPOINTS

8.3.1 Primary Endpoint

The primary endpoint of this study is the re-operation rate for any reason of displaced and non-displaced femoral neck fractures treated with CONQUEST FN™ at one year post-operation.

8.3.2 Secondary Endpoints

The secondary endpoints of this study include generation of safety, performance, and health economic evidence supporting the use of the CONQUEST FN™ Femoral Neck Fracture System per the endpoints listed below:

- Intraoperative complications
- Radiographic outcomes including quality of fracture reduction
- Construct failure past typical femoral neck fracture healing period (past 6 months)
- Visual analogue scale (VAS) relating to pain at the fracture site
- Quality of Life (EQ-5D-5L)
- Time to return to full weight-bearing
- Ambulatory status from pre-injury to study completion
- Timed Up & Go
- Length of hospital stay
- Hospital readmission for any reason
- Device- and surgery-related adverse events
- Active straight leg raise (ASLR) assessment

8.3.3 Safety Endpoints

Device- and surgery-related adverse events (AE), as indicated by the Investigator.

8.3.4 Other Endpoints

The re-operation rate in older patients vs. younger patients for a given fracture type for both the displaced and non-displaced fracture types.

8.4 VISITS AND EXAMINATIONS

8.4.1 Summary

For a summary of the required procedures by visit, refer to Table 8.4.1-1: Study Procedures by Visit.

Table 8.4.1-1: Study Procedures by Visit

Schedule of events	Pre-Operative Data (Day -7 to Day 0)	Operative/ Discharge Data[1] (Day 1)	6 weeks (Day 42 ± 7 days)	3 months (Day 90 ± 7 days)	6 months (Day 180 ± 14 days)	12 months (Day 365 ± 30 days)
Informed Consent	✓					
Inclusion/Exclusion	✓					
Demographics/ Medical History	✓					
Operative Data Collection		✓				
Discharge Data Collection[1]		✓				
VAS (pain score)	✓		✓	✓	✓	✓
Timed Up & Go			✓	✓	✓	✓
EQ-5D-5L	✓		✓	✓	✓	✓
X-Ray • AP • Lateral	✓	✓	✓	✓	✓	✓
Active Straight Leg Raise			✓	✓	✓	✓
Adverse Event Assessment		✓	✓	✓	✓	✓
End of Study/Exit						✓

[1] Discharge data to be collected at time of discharge which will be dependent on subject recovery.

8.4.2 Screening/Preoperative Visit

NOTE: Any subject who signs an informed consent but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects will be assigned subject numbers and their demographic information will be captured in the appropriate CRF with the reason for screen failure specified.

1. Obtain written informed consent from the subject as detailed in Section 7.4

   ----- Do not proceed until consent has been obtained -----
2. Obtain demographic information and medical history, including information on all concomitant medications/therapies and pre-injury ambulatory status.
3. Screen the subject for protocol inclusion/exclusion criteria.
4. If subject meets protocol inclusion/exclusion criteria, assign a subject number using format SS-NNN (SS = site number, NNN subject number at site). The subject number will be assigned in sequential order starting with 001. Screened subject numbers will NOT be reused by qualifying subjects.
5. Perform radiology imaging collecting both anteroposterior (AP) and lateral images of the target hip.
6. Assess level of pain from the target hip within the previous 24 hours using the Visual Analog Scale (VAS).
7. Instruct the subject to complete the health outcome questionnaire, EQ-5D-5L.
8. Instruct the subject on treatment procedures.
9. Subjects will return to the treatment facility, if applicable, for the Baseline /Operation Visit no longer than 7 days post-fracture.

8.4.3 Baseline/Operation Visit (Day 1)

NOTE: If the Investigator decides a subject should not receive the Study Device for any reason at the time of surgery, the subject will be considered a Screen Failure and the reason for non-enrollment will be clearly documented in the subject's source documents.

1. Query subject regarding any changes in general health and the use of concomitant medications.
2. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 11, adverse events and device deficiencies.
3. Perform surgery per current CONQUEST FN™ Instructions for Use (IFU).
4. Collect study-specific operative data.
5. Perform radiology imaging collecting both anteroposterior (AP) and lateral images of the target hip to ensure the CONQUEST FN™ is properly implanted.
6. Collect study-specific discharge data.
7. Instruct the subject on proper postoperative care documenting the prescribed rehabilitation plan in the subject's source document.
8. Instruct the subject on follow-up procedures, including returning to the office for Follow-up (FU) Visit 1 in 42 (± 7) days.

8.4.4 Follow-up Visits: 6 Weeks (Day 42 ± 7 days), 3 Months (Day 90 ± 7 days), 6 Months (Day 180 ± 14 days)

1. Assess level of pain from the target hip within the previous 24 hours using the VAS.
2. Instruct the subject to complete the health outcome questionnaire, EQ-5D-5L.
3. Complete active straight leg raise (ASLR) test as instructed in Section 8.5, Study Methods and Measurements.
4. Complete Timed Up and Go (TUG) test as instructed in Section 8.5, Study Methods and Measurements.

5. Query subject regarding any changes in general health, the use of concomitant medications, and ambulatory status
6. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 11, adverse events and device deficiencies.
7. Perform radiology imaging collecting both anteroposterior (AP) and lateral images of the target hip.
8. Instruct the subject on proper postoperative care documenting continued instructions in the subject's source document.
9. Instruct the subject on follow-up procedures, including returning to the office for FU Visit 2 in 90 (± 7) days and Visit 3 in 180 (± 14) days

8.4.5 Exit Visit: 12 months (Day 365 ± 30 days)

1. Assess level of pain from the target hip within the previous 24 hours using the VAS.
2. Instruct the subject to complete the health outcome questionnaire, EQ-5D-5L.
3. Complete ASLR test as instructed in Section 8.5, Study Methods and Measurements.
4. Complete TUG test as instructed in Section 8.5, Study Methods and Measurements.
5. Query subject regarding any changes in general health, the use of concomitant medications, and ambulatory status
6. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 11, adverse events and device deficiencies.
7. Perform radiology imaging collecting both AP and lateral images of the target hip.
8. Complete Exit Visit CRF

8.4.6 Unscheduled Visits

Unscheduled examinations may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the appropriate CRF.

8.4.7 Concomitant Medications and Therapies

A concomitant medication (e.g. drug, substance) and a concomitant therapy (e.g. physical therapy, TENS Unit, massage) are recorded pre-operatively and at each visit through the subject's last study visit. The subject's ambulatory status will be documented pre-operatively and at each follow-up through the last study visit.

8.4.7.1 *Concomitant Medications*

8.4.7.1.1 Excluded Concomitant Medications

There are no excluded concomitant medications for this study.

8.4.7.1.2 Recording Concomitant Medications in the CRF

Only medications related to the IP implanted and medications used to treat an AE/ADE related to the IP will be recorded in the CRF. Reference the CRF Completion Guidelines for how medications are recorded.

9.1.8 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety or use of prohibited concomitant treatments, or who are lost to follow-up. Refer to section 7.8 for further details. Where possible, a full Exit 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 7.7.1).
Any changes to medical health and/or the use of concomitant medications will be captured. If any SAE, SADE, or DevD were observed since the previous visit, they must be recorded (refer to section 11, Adverse Events and Device Deficiencies, for instructions on reporting and evaluation procedures). Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

8.4.8 Subject Pregnancy

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being used by the subject.However, if a woman becomes pregnant during

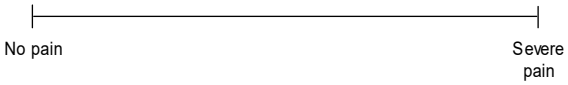
the study, S&N must be contacted immediately once the Investigator is made aware of the pregnancy. Pregnancy is not reportable as an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy.

8.5 STUDY METHODS AND MEASUREMENTS

All questionnaires should be completed prior to any other procedure at the time of the scheduled visit. The dates of all assessments should be recorded.

8.5.1 Visual Analogue Scale (VAS) for Pain

The Visual Analogue Scale is simply a line of fixed length, on which the subject marks their experience of pain with a single stroke of a pen.



At each specified visit, the subject will be asked to indicate their average level of pain from the operated hip over the prior 24 hours using a visual analog scale (VAS). The subject will record their level of pain on a 100 mm visual analog scale, similar to the one illustrated above. The scale will be marked ‘no pain’ on the left side of the scale and ‘severe pain’ at the right end of the scale. The subject will be instructed to place a vertical mark on the scale, using an ink pen.

The Investigator, or designee, will measure the distance (in millimeters) from the left end of the VAS scale to the vertical line drawn by the subject. This value will be entered in the subject’s CRF as a measure of the pain associated with the operated hip.

8.5.2 EQ-5D-5L

The EuroQol EQ-5D-5L is a standardized instrument for use as a measurement of health outcome. It consists of a descriptive system with 5 dimensions (mobility, self-care, usual

activities, pain/discomfort and anxiety/depression), which are each assigned five levels (no problems, slight problems, moderate problems, severe problems and extreme problems), as well as, a Visual Analogue Scale where subjects indicate a numerical value from 1-100 where 0 is the worst imaginable health state and 100 is the best imaginable health state.

The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state.

8.5.3Timed Up and Go (TUG)

The Timed Up and Go Test assesses mobility, balance, walking ability, and fall risk in adults by measuring time, in seconds, that it takes the individual to stand from a chair, walk a distance of 10 feet, walk back to the chair, and sit down. The subject will perform the test in their everyday footwear with their walking aid (cane, walker), if applicable.[17] The site will follow the guidelines provided by the Centers for Disease Control and Prevention recording the results on the form provided by the Sponsor.[18]

8.5.4 Assessment of Quality of Fracture Reduction

The quality of the final fracture reduction will be defined using the criteria described by Upadhyay et el.[14] Appropriate reduction will be defined as the principal compressive trabeculae measuring >160° in the AP view and <5° of posterior angulation in the lateral view. If reduction is acceptable in both views, it will be classified as grade I. Grade II will be indicative of one plane of malreduction, and grade III will be indicative of malreduction in both radiographic views.

Pre-operative radiographs will be reviewed and classified as displaced (e.g. Garden III & IV) or non-displaced (e.g. Garden I & II) femoral neck fractures by the Investigator at each site. Quality of fracture reduction will also be assessed post-operatively by the Investigator at each site.

8.4.5 Active Straight Leg Raise (ASLR) Assessment

The ALSR assessment provides information about the ability of load transfer and motor control strategies in the lumbo/pelvic/hip complex. ASLR will be performed with the subject in a relaxed supine position with legs straight and feet apart. Subjects will be instructed to raise their operated leg 20cm above the examination table without bending the knee and without pelvic movement relative to the trunk. A score will be provided by the subject for the operated limb on a six-point Likert scale (0 = not difficult at all, 1 = minimally difficult; 2 = somewhat able to do, 3 = fairly difficult, 4 = very difficult, 5 = unable to do).

9. STATISTICAL DESIGN

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan. The SAP will be more detailed and account for all analyses. All analyses will be conducted with statistical software SAS Version 9.4 or later.

9.1 GENERAL

The subject data will be described and summarised using the baseline demographic and medical variables, which include, but are not limited to, age, gender, ethnicity, medical and medication history, diagnostic factors as well as study process variables (e.g. AE and withdrawal(s)). Summary statistics will be given according to the nature of the variable, continuous or categorical. For continuous variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be presented, while for categorical variables the number of observations, frequency, and percentages will be reported.

Primary, secondary, and exploratory outcome variables and derived variables will also be summarised accordingly. Parametric statistical tests will be used if the data are normally distributed and corresponding non-parametric tests will be considered if the data are not. Where necessary, suitable regression techniques will be used to adjust for confounding variables since the study is non-randomised. The results will be reported at 5% significance level and where appropriate 95% confidence intervals will be given.

9.2 ANALYSIS POPULATIONS

- Intention to Treat population (ITT), including all subjects randomized into the study.
- Full analysis set population (FAS), following Intention to Treat principle including all subjects who were randomized into the study and attended at least one post-baseline assessment
- Safety Population (SAF), including all subjects who have received the IP or the control devices.
- Per-Protocol Population (PP), including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria.

Statistical analysis will be performed using each of the patient populations as follows. Analysis of the primary, secondary and exploratory efficacy objectives will be performed separately using both the Full Analysis Set and the Per Protocol Population. All safety analyses will utilize the Safety Population.

9.3 BASELINE DATA

The subjects will be described and summarised using the baseline demographic and medical variables, which include, but are not limited to, age, gender, ethnicity, medical and medication history, diagnostic factors. Summary statistics will be given according to the nature of the variable, continuous or categorical. For continuous variables, the number of observations, mean, standard deviation, median, minimum, and maximum will be presented, while for categorical variables the number of observations, frequency, and percentages will be reported. A complete accountability report, along with the explanation for lost-to-follow-up, death, revision, and withdrawn subjects will be provided with the methods being detailed in the SAP.

9.4 EFFICACY ANALYSIS

The study is non-comparative and non-randomized, single cohort, post-marketing, multicenter prospective study to evaluate the clinical outcomes of the CONQUEST FN™ Femoral Neck Fracture System. A minimum total of 90 subjects will be enrolled in the study, which includes a 5% estimate for subjects lost to follow-up at 1 year.

9.4.1 Analysis of Primary Endpoint

A two-sided confidence interval will be provided for the proportion of re-operation (i.e. re-operation rate) for any reason of displaced and non-displaced femoral neck fractures treated with CONQUEST FN™ at one-year post-operation.

9.4.2 Analysis of Secondary Endpoint(s)

The rate or mean of the following outcomes at 1 year post-operation will be reported:

- Intraoperative complications
- Radiographic outcomes including quality of fracture reduction
- Construct failure past typical femoral neck fracture healing period (past 6 months)
- Visual analogue scale (VAS) relating to pain at the fracture site
- Quality of Life (EQ-5D-5L)
- Time to return to full weight-bearing
- Ambulatory status from pre-injury to study completion
- Timed Up & Go
- Length of hospital stay
- Hospital readmission for any reason
- Device and surgery related adverse events
- Active straight leg raise (ASLR) assessment

9.4.3 Analysis of Other Endpoint(s)

Provide the re-operation rate in older patients vs. younger patients for both the displaced and non-displaced fracture types.

9.5 SAFETY ANALYSES

All safety analyses will be conducted using the safety population. The number of incidences and number of subjects reporting all adverse events will be summarized both overall and by

seriousness, severity, relationship to study device and outcome. Incidences and number of subjects reporting device deficiencies will also be summarized. Further summaries of safety data may be described in the SAP.

9.6 INTERIM ANALYSES

Once the last subject passes 6 Months, an interim analysis composed of summarizing the outcome and safety data will be performed. Additional unscheduled interim analyses may be performed during the conduct of this study to support requests from regulatory authorities and scientific publications.

10. SAMPLE SIZE JUSTIFICATION

Precision Analysis was used to assess the overall proportion of re-operation rate for any reason of displaced and non-displaced femoral neck fractures treated with the CONQUEST FN™ Femoral Neck Fracture System at one-year post-operation. Assuming a 5% lost to follow-up rate after the first year, a minimum of 90 subjects will be enrolled (based on the inclusion/exclusion criteria) in order to complete 80 evaluable subjects. The 90 subjects will be enrolled to allow a minimum of 45 subjects with each of the following indications to be recruited: displaced or non-displaced femoral neck fractures. For the displaced group this number of subjects is sufficient to estimate the proportion of success rate to within 12% by use of the two-sided 95% confidence interval (assuming an overall success rate of 87%). And for the non-displaced group this number of subjects is sufficient to estimate the proportion of success rate to within 10% use of the two-sided 95% confidence interval (assuming an overall success rate of 93%).

11. ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 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 (see reference within the table).

Table 12.1-1: Categories of Adverse Event

	NOT DEVICE-RELATED	DEVICE- OR PROCEDURE-RELATED	
NON-SERIOUS	ADVERSE EVENT (AE) (SEE 12.1.1)	ADVERSE DEVICE EFFECT (ADE) (SEE 12.1.2)	
SERIOUS	SERIOUS ADVERSE EVENT (SAE) (SEE 12.1.3)	SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)	
		ANTICIPATED	**UNANTICIPATED**
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE) (SEE 12.1.4)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE) (SEE 12.1.4)

11.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence temporally associated with the use of a study device, whether or not considered causally related to that study device.

AE is used both to refer to AE which are non-serious non-study device or procedure-related 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.[19]

11.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the Investigator, is related to the study device or the procedure.

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

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

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

11.1.3 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 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. [19]

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above. [19]

11.1.4 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.[19]

Note 1 to entry: 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. [19]

11.1.5 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.

11.1.6 Device Deficiency

A Device Deficiency (DevD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DevD includes malfunctions, use errors and inadequate labelling. [19]

11.2 REPORTING PROCEDURES

AE of any kind and DevD 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,

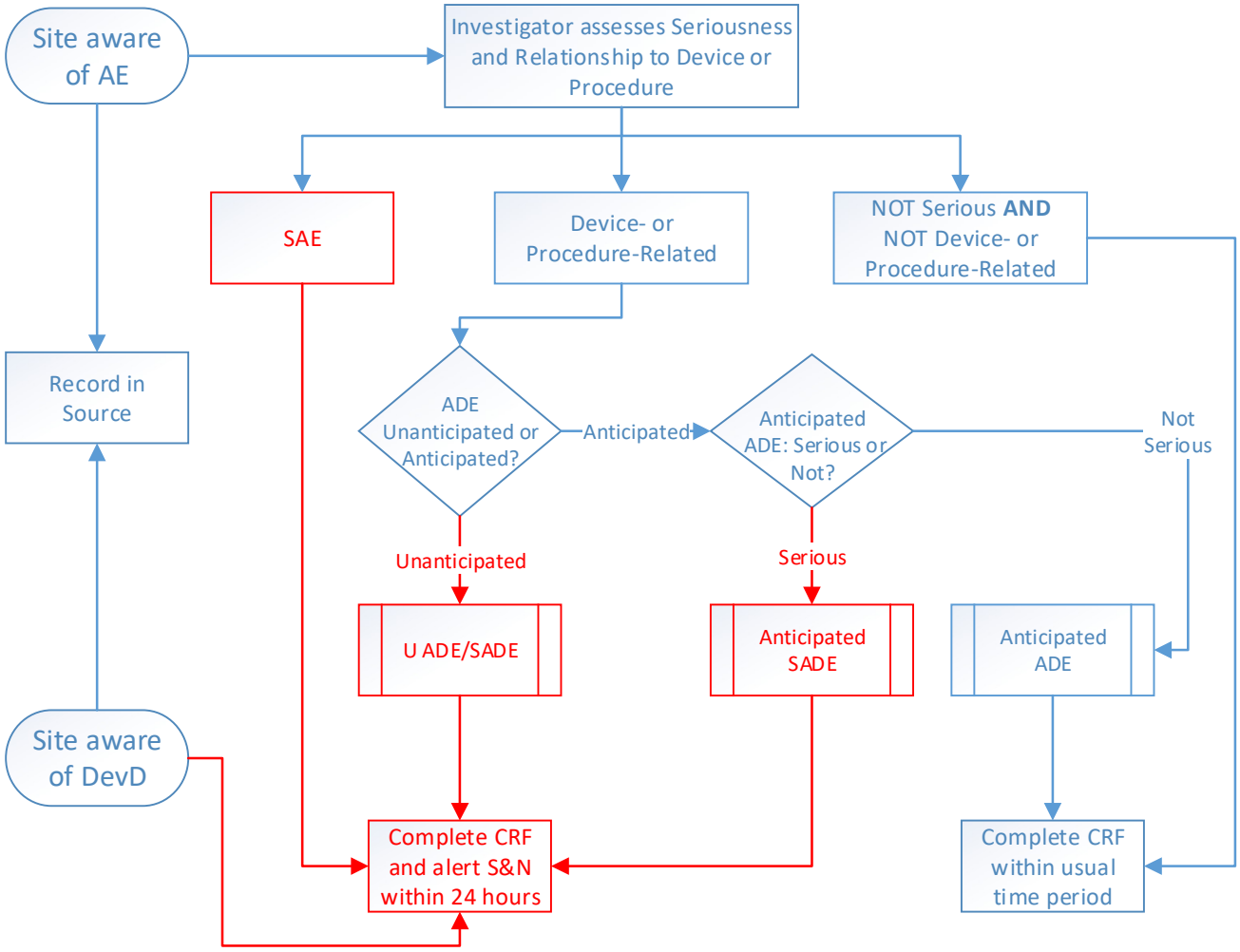
seriousness, and severity. ADE, SAE, and DevD will be entered into the CRF and reported to the Sponsor within 24 hours of the investigator being informed about the event (Figure 12.2-1). For ADE and DevD, details of the product/procedure related to the event will be included and where applicable, pictures 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 within 24 hours of the information being available to the investigator.

All adverse events, including SAE and ADE, 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/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.

Figure 11.2-1: Evaluation and Reporting of AE and DevD



11.3 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 in order 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 within the CRF.

11.3.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S&N study device and are ongoing at 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 study device and are ongoing at 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.

12. INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 20.3 of this protocol.

13. 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, with GCP regulations, and with applicable regulatory requirements.

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

13.1 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.

13.2 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 approval.

13.3 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.

13.4 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.

14. PROTOCOL AMENDMENTS

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

15. CONFIDENTIALITY OF THE STUDY

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

16. STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; ISO 14155: Clinical investigation of medical devices – Good Clinical Practice; ICH-E6, and the US regulatory authority.

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.

17. END OF STUDY

The end of study is defined as the date of the last subject, last visit. No additional care for subjects will be provided under the protocol once their participation in the study has ended.

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.

Reasonable efforts should be made to retain enrolled subjects for the 12-month post-operative follow-up of this study. A study termination CRF will need to be completed for any subject that does not complete the study and reason for termination must be documented.

18. PUBLICATION POLICY

18.1 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.

18.2 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. In accordance, Smith & Nephew will consider requests to share individual (deidentified) 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 9 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 datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.[20]

19. REFERENCES

1. Kenan, S., et al., Long Term Outcomes Following Reduction and Fixation of Displaced Subcapital Hip Fractures in the Young Elderly. IMAJ, 2015. 17: p. 341;345

2. Han, S., et al., Risk stratification for avascular necrosis of the femoral head after internal fixation of femoral neck fractures by post3operative bone SPECT/CT. Nucl Med Mol Imaging, 2017. 51: p.49;57.

3. Farooq, M.A., et al., Intracapsular fractures of the femoral neck in younger patients. Ir J Med Sci, 2005. 174(4): p. 42;5.

4. Campenfeldt, P., et al., Good functional outcome but not regained health related quality of life in the majority of 20369 years old patients with femoral neck fracture treated with internal fixation: A prospective 23 year follow-up study of 182 patients. Injury, 2017. 48(12): p. 2744;2753.

5. Sprague, S., et al., Young femoral neck fractures: are we measuring outcomes that matter? Injury, 2015. 46(3): p. 507;14.

6. Griffin, J., et al., What is the impact of age on reoperation rates for femoral neck fractures treated with internal fixation and hemiarthroplasty? A comparison of hip fracture outcomes in the very elderly population. J Orthop, 2016. 13(1): p. 33;9.

7. Kenan, S., et al., Long3Term Outcomes Following Reduction and Fixation of Displaced Subcapital Hip Fractures in the Young Elderly. IMAJ, 2015. 17: p. 341;345

8. Slobogean, G.P., et al., Complications following young femoral neck fractures. Injury, 2015. 46(3): p. 484;91.

9. Lotz, J.C., E.J. Cheal, and W.C. Hayes, Stress Distributions within the Proximal Femur during Gait and Falls: Implications for Osteoporotic Fracture. Osteoporosis Int, 1995. 5: p. 252;261.

10. Nawathe, S., et al., Cortical and trabecular load sharing in the human femoral neck. J Biomech, 2015. 48(5): p. 816;22.

11. Yuan, H.F., et al., Predictive value of single photon emission computerized tomography and computerized tomography in osteonecrosis after femoral neck fracture: a prospective study. Int Orthop, 2015. 39(7): p. 1417;22.

12. Goudie, E., A. Duckworth, and T. White, Hip fractures in young adults. Orthopaedics and Trauma, 2017. 31(2): p. 76;85.

13. Slobogean, G.P., et al., Management of young femoral neck fractures: is there a consensus? Injury, 2015. 46(3): p. 435;40.

14. Upadhyay A. , et al., Delayed internal fixation of fractures of the neck of the femur in young adults: A PROSPECTIVE, RANDOMISED STUDY COMPARING CLOSED AND OPEN REDUCTION. J Bone Joint Surg [Br] 2004. 86:B(7): p. 1035;1040.

15. Bhandari M, et al., Optimal Internal Fixation for Femoral Neck Fractures: Multiple Screws or Sliding Hip Screws? J Orthop Trauma, 2009. 23(6): p. 403;407.

16. Hoshino, C.M. and R.V. O'Toole, Fixed angle devices versus multiple cancellous screws: what does the evidence tell us? Injury, 2015. 46(3): p. 474;7.

17. Lysack, C. L., Household and Neighborhood Safety, Mobility. *Handbook of Assessment in Clinical Gerontology*. p. 619-646**.**

18. Center for Disease Control and Prevention: Stopping Elderly Accidents, Deaths, & Injuries. https://www.cdc.gov/steadi

19. ISO 14155:2011 Clinical investigation of medical devices for human subjects – good clinical practice.

20. Taichman, DB, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors. Ann Intern Med. 2017. 6th June. doi:10.7326/M17-1028

20. APPENDICES

20.1 PROTOCOL AMENDMENT

Section	Current Text 04Jun2018 Version 1	Revised Text 30Nov2018 Version 2.0
2. Synopsis – Secondary Objective	To generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data.	The secondary objective of this study is to generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data.
2. Synopsis – Statistical Rationale	A total sample size of 90 subjects with a minimum of 45 subjects for displaced and non-displaced femoral neck fractures. Since the primary and secondary endpoints are the same for all fractures, overall results will be reported as well.	A total minimum sample size of 90 subjects with a minimum of 45 subjects for displaced and 45 subjects for non-displaced femoral neck fractures. Since the primary and secondary endpoints are the same for all fractures, overall results will be reported as well.
2. Synopsis – Inclusion Criteria	1. Provide IRB approved informed consent, which will consist of reading, signing, and dating the informed consent document after the Investigator, sub-Investigator, or other designated study staff member has explained the study procedures, risks, and contact information.	1. The subject must provide written informed consent (reference section 7.4).
2. Synopsis – Exclusion Criteria	N/A - Inadvertently left this exclusion criteria out of this section.	3. Subject has more than one fracture on target hip.

2. Synopsis – Exclusion Criteria	5. Therapy with another investigational agent within thirty (30) days of Screening.	6. Therapy with another investigational agent within thirty (30) days of Screening or or planned therapy with another investigational agent during the course of the study.
2. Synopsis – Exclusion Criteria	N/A - Inadvertently left this exclusion criteria out of this section.	12. Subjects with a history of poor compliance with medical treatment.
2. Synopsis – Secondary endpoint(s)	• Intraoperative complications • Radiographic outcomes including quality of fracture reduction • Construct failure past typical femoral neck fracture healing period (past 6 months) • Pain (VAS) • EQ-5D-5L • Time to return to full weight-bearing • Ambulatory status from pre-injury to study completion • Timed Up & Go • Length of hospital stay • Readmissions for any reason • Device- and surgery-related adverse events • Active straight leg raise (ASLR) assessment	The secondary endpoints of this study include generation of safety, performance, and health economic evidence supporting the use of the CONQUEST FN™ Femoral Neck Fracture System per the endpoints listed below: • Intraoperative complications • Radiographic outcomes including quality of fracture reduction • Construct failure past typical femoral neck fracture healing period (past 6 months) • Visual analogue scale (VAS) relating to pain at the fracture site • Quality of Life (EQ-5D-5L) • Time to return to full weight-bearing • Ambulatory status from pre-injury to study completion • Timed Up & Go • Length of hospital stay • Hospital readmissions for any reason

		• Device- and surgery-related adverse events • Active straight leg raise (ASLR) assessment
2. Synopsis – Study Schematic	Pre-Operative Data	Pre-Operative Data (Day -7 to Day 0)
3.3 List of Abbreviations	N/A - Inadvertently left out of table	FU - Follow-up
3.3 List of Abbreviations	N/A - Inadvertently left out of table	TUG – Timed Up and Go
4.2 Study Purpose	The purpose of this study is to evaluate the re-operation rate for any reason of the CONQUEST FN™ Femoral Neck Fracture System one year post operation.	A post-market, prospective study to evaluate the reoperation rate of displaced and nondisplaced femoral neck fractures treated with the CONQUEST FN™ system.
5.2 Secondary Objective(s)	The secondary objective of this study is to generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data	The secondary objective of this study is to generate safety and performance evidence for the CONQUEST FN™ Femoral Neck Fracture System via the collection of functional outcomes, quality of life, and safety data including the following: 1. Intraoperative complications 2. Radiographic outcomes including quality of fracture reduction

		3. Construct failure past typical femoral neck fracture healing period (past 6 months) 4. Pain (VAS) 5. EQ-5D-5L 6. Time to return to full weight-bearing 7. Ambulatory status from pre-injury to study completion 8. Timed Up & Go 9. Length of hospital stay 10. Readmissions for any reason 11. Device and surgery related adverse events 12. Active straight leg raise (ASLR)
6.5 Surgical Technique	All study-related procedures conducted at the investigational site must be performed according to the recommended surgical technique described in the labeling and instructions for use (IFU).	All study-related procedures conducted at the study site must be performed according to the recommended surgical technique described in the labeling and instructions for use (IFU).

6.5 Surgial Technique	Surgeons selected to participate in this study will be required to have completed three (3) surgeries using the CONQUEST FN™ Femoral Neck Fracture System and have written evidence of training and expertise in the study procedure.	Surgeons selected to participate in this study will be required to have completed two (2) surgeries using the CONQUEST FN™ Femoral Neck Fracture System and have written evidence of training and expertise in the study procedure.
Subject Enrollment and Withdrawal – Subject Population	Approximately 90 subjects (18 years of age or older) with a confirmed displaced or non-displaced intracapsular femoral neck fracture who are scheduled for repair using CONQUEST FN™ will be recruited at approximately 10 investigational centers in the United States. Additional sites may be added, if necessary, to meet recruitment goals. A minimum of 45 displaced and 45 non-displaced fractures are required.	A minimum of 90 subjects (18 years of age or older) with a confirmed displaced or non-displaced intracapsular femoral neck fracture who are scheduled for repair using CONQUEST FN™ will be recruited at approximately 10 study sites in the United States. Additional sites may be added, if necessary, to meet recruitment goals. A minimum of 45 displaced and 45 non-displaced fractures are required.
7.1 Inclusion Criteria	1. The subject must provide written informed consent (reference section 7.5).	1. The subject must provide written informed consent (reference section 7.4).
7.2 Exclusion Criteria	6. Therapy with another investigational agent within thirty	6. Therapy with another investigational agent within thirty

	(30) days of Screening or during the course of the study.	(30) days of Screening or planned therapy with another investigational agent during the course of the study
7.2 Exclusion Criteria	7. Subject has a physical condition that, in the opinion of the Investigator, would preclude adequate implant support or impede healing (e.g. blood supply impairment, insufficient bone quality or quantity, or an active, local or systemic infection).	7. Subject has a physical condition that, in the opinion of the Investigator, would preclude adequate implant support or impede healing (e.g. blood supply impairment, insufficient bone quality or quantity, or an active, local or systemic infection). If this is identified at the time of surgery, the subject will be screen failed.
7.2 Exclusion Criteria	N/A - Inadvertently left this exclusion criteria out of this section.	11. Current systemic therapy with cytotoxic drugs.
7.5 Enrollment	A subject ID will be assigned at the time of the Screening visit.	A subject number will be assigned at the time of the Screening visit.
8.1 Study Design	Subjects will be stratified by fracture type (45 displaced and 45 non-displaced fractures) for a total of approximately 90 enrolled subjects.	Subjects will be stratified by fracture type (minimum of 45 displaced and 45 non-displaced fractures) for a minimum total of 90 enrolled subjects.
Table 8.4.1-1 Study Procedures by Visit	Pre-Operative Data	Pre-Operative Data (Day -7 to Day 0)
8.4.2 Screening/Preoperative Visit	N/A - Inadvertently left this out of this section.	5. Perform radiology imaging collecting both anteroposterior (AP) and lateral images of the target hip.
8.4.3 Baseline/Operation Visit (Day 1)	N/A - Inadvertently left this out of this section.	3. Perform surgery per CONQUEST FN™ surgical technique guide.

8.4.3 Baseline/Operation Visit (Day 1)	N/A - Inadvertently left this out of this section.	5. Perform radiology imaging collecting both anteroposterior (AP) and lateral images of the target hip to ensure the CONQUEST FN™ is properly implanted.
8.4.4 Follow-up Visits	Number 5 listed twice. Previously numbers 1-8	Renumbered to remove duplicate numbering. Now numbered 1-9
8.4.5 Exit Visit	Exit Visit (Day 365 ± 30 days)	8.4.5 Exit Visit: 12 months (Day 365 ± 30 days)
8.4.7 Concomitant Medications and Therapies	A concomitant medication (e.g. drug, substance) and a concomitant therapy (e.g. physical therapy, TENS Unit, massage) are recorded at any time from enrolment into the study through the subject's last study visit.	A concomitant medication (e.g. drug, substance) and a concomitant therapy (e.g. physical therapy, TENS Unit, massage) are recorded pre-operatively and at each visit through the subject's last study visit.
8.4.8 Subject Pregnancy	Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being used by the subject as outlined in the protocol's inclusion criteria.	Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being used by the subject.
9.4 Efficacy Analysis	A total of 90 subjects will be enrolled in the study, which includes a 5% estimate for subjects lost to follow-up at 1 year.	A minimum total of 90 subjects will be enrolled in the study, which includes a 5% estimate for subjects lost to follow-up at 1 year.
10. Sample Size Justification	Assuming a 5% lost to follow-up rate after the first year, 90 subjects will be enrolled (based on the inclusion/exclusion criteria) in order to complete 80	Assuming a 5% lost to follow-up rate after the first year, a minimum of 90 subjects will be enrolled (based on the inclusion/exclusion criteria) in order to complete 80 evaluable subjects. The 90 subjects will be

	evaluable subjects. The 90 subjects will be enrolled to allow a minimum of 40 subjects with each of the following indications to be recruited: displaced or non-displaced femoral neck fractures	enrolled to allow a minimum of 45 subjects with each of the following indications to be recruited: displaced or non-displaced femoral neck fractures
12. Investigator Obligations	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.	Removed.
Entire document	Spelling errors	Corrected all spelling errors

20.2 INSTRUCTIONS FOR USE

Refer to Instructions for Use (IFU) supplied by the Sponsor.

20.3 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155)

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:

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)

ii. The informed consent form consists of an information form and informed consent signature form. These two forms can either be combined in one document or separated into two documents

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, foetus 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 acknowledgement 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. 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.