A Prospective, Multi-center, Randomized Clinical Study to Evaluate the Safety and Effectiveness of Biosure Regenesorb Interference Screw in Arthroscopic Reconstruction of Cruciate Ligaments in Chinese Patients

Protocol No.:	BIOSURE RG.SMD.PMA.2019.01
Protocol version and date:	V2.0/July 3rd, 2020
Name of investigational medical device:	Biosure Regenesorb Interference Screw
Management category of investigational medical device:	Class III medical device requiring clinical trial review and approval: Yes ☐ No☒ Similar product in China: Yes☒ No☐
Leading Site of Clinical Trial:	Peking University Third Hospital
Coordinating Investigator:	Director Gong Xi
Sponsor:	Smith & Nephew Medical (Shanghai) Limited

1 Signature

1.1 Signature Page of Protocol

This page will be returned to Smith & Nephew Medical (Shanghai) Limited and a copy will be kept in the study site.

I have read the protocol titled "A Prospective, Multi-center, Randomized Clinical Study to Evaluate the Safety and Effectiveness of Biosure Regenesorb Interference Screw in Arthroscopic Reconstruction of Cruciate Ligaments in Chinese Patients" (V2.0/July 3rd, 2020) and agree to follow all regulations described in this protocol.

I agree to fulfill the duties and responsibilities of investigators regulated in Chapter 23 of the protocol.

Without written approval of Smith & Nephew Medical (Shanghai) Limited, I agree to ensure that the confidential information contained herein won't be used for any other purpose other than the clinical study described herein.

Responsibilities	**Name**	**Signature***	**Date of Signature** (DD-MMM-YYYY)
Principal Investigator			

1.2 Coordinating investigator approval

I have read the protocol titled "A Prospective, Multi-center, Randomized Clinical Study to Evaluate the Safety and Effectiveness of Biosure Regenesorb Interference Screw in Arthroscopic Reconstruction of Cruciate Ligaments in Chinese Patients" (V2.0/July 3rd, 2020) and agree to follow all regulations described in this protocol.

Coordinating investigator approval - Name (Printed)	**Signature**	**Date of Signature** (DD-MMM-YYYY)
Gong Xi		

2 Protocol synopsis

Trial title	A Prospective, Multi-center, Randomized Clinical Study to Evaluate the Safety and Effectiveness of Biosure Regenesorb Interference Screw in Arthroscopic Reconstruction of Cruciate Ligaments in Chinese Patients
Sponsor	Smith & Nephew Medical (Shanghai) Limited
Investigational device	Biosure Regenesorb Interference Screw
Control device	BIOSURE HA Interference Screw
Trial objective	The objective of this study is to compare the safety and effectiveness of Biosure Regenesorb Interference Screw versus BIOSURE HA Interference Screw (control device) in patients requiring reconstruction of cruciate ligaments of the knee. The trial results will be used for registration of Biosure Regenesorb Interference Screw in China.
Trial design	The clinical trial is designed to be a prospective, multi-center, randomized, evaluator-blinded, parallel-controlled, non-inferiority trial.
Sample size	It is planned to include 140 subjects, 70 in the trial group and control group, respectively.
Target population	The clinical trial is carried out in patients requiring knee cruciate ligaments reconstruction.
Case selection	1. Inclusion criteria 1) Signing the Informed Consent Form (ICF) voluntarily; 2) Patients aged 18-75 years; 3) Patients clinically diagnosed with knee cruciate ligaments rupture or tear and suitable for cruciate ligaments reconstruction definitely; 4) Normal contralateral knee joint. 2. Exclusion criteria 1) Patients fail to meet the diagnosis of cruciate ligaments rupture or tear; 2) Patients with an unclosed epiphyseal plate shown on the X-ray film; 3) Patients having underwent internal fixation or reconstruction due to a knee joint fracture;

	4) Patients with obvious knee joint degeneration shown on the X-ray film; 5) Patients who cannot make a knee flexion of more than 90° during operation; 6) Patients undergoing autologous chondrocyte implantation; 7) Patients with medial meniscus or lateral meniscus completely resected; 8) Patients with significant anatomical abnormalities; 9) Pregnant or breast-feeding females or those at a child-bearing age planning to become pregnant; 10) Patients with serious osteoporosis that affects implantation of the screw; 11) Patients with a malignant tumor that causes failure to effectively fix the implant; 12) Known hypersensitivity to the implant materials; 13) Patients not suitable for operation due to obvious local or systemic infection; 14) Patients who cannot tolerate an operation due to severe malnutrition; 15) Patients with severe coagulation disorder (judged by the investigator), e.g. the hemophiliac; 16) Patients with immunodeficiency, including those who must receive immunosuppressant for a long time; 17) Patients with extensive skin diseases; 18) Obese patients having a Body Mass Index (BMI) > 35; 19) Patients who cannot cooperate in postoperative rehabilitation due to a severe mental disease or those who cannot tolerate the operation due to a cardiopulmonary disease; 20) Patients who received operation on the injured lower limb within the past year; 21) Patients who participated in any other clinical trial within the past three months; 22) Patients who cannot follow the requirements described in the study protocol; and

	23) Other patients who are considered by the investigator not suitable for this clinical study. Exclusion criteria: During the operation, if the subject was not in accordance with the diagnosis of cruciate ligament rupture or tears, or meet any of the exclusion criteria, they will be excluded from the trial.
Test duration	Expected duration of participation of each subject is around 740 days. This trial includes a 10-d screening period and a 24-month follow-up period.
Efficacy endpoints	Primary efficacy endpoint: Lysholm score at 12 Months; Secondary efficacy endpoints: ● Lysholm Score (6 Months, 24 Months) ● IKDC Score (6 Months, 12 Months, 24 Months) ● Drawer Test (6 Months, 12 Months, 24 Months) ● Lachman Test (6 Months, 12 Months, 24 Months) ● Radiological evaluation (6 Months, 12 Months, 24 Months)
Safety evaluation indicators	(1) Incidence (%) and frequency (number of events) of adverse events (AEs) related to device; (2) Incidence (%) and frequency (number of events) of adverse events; (3) Incidence (%) and frequency (number of events) of device deficiencies; (4) Reoperation rate.
Number of study sites	About 4 study sites.

Study follow-up schedule

Study procedures	Pre-operation	Intraoperative - postoperative (Day 0-5)	6 weeks after operation (± 2 weeks)	3 months after operation (± 1 month)	4.5 months after operation Telephone follow-up (± 2 weeks)	6 months after operation (± 1 month)	9 months after operation Telephone follow-up (± 2 weeks)	12 months after operation (± 2 months)	24 months after operation (± 2 months)
Days for study	-30~-1	0~5	28-56	61-121	123-150	153-213	260-287	305-426	670-790
Informed consent	√								
Inclusion/exclusion	√	√							
Demography/medical history	√								
Vital signs	√	√							
ECG	√								
Blood routine examination	√ (1)	√ (3)							
CRP	√ (1)								
Blood biochemistry	√ (1)	√ (3)							
Coagulation test	√ (1)								
Pregnancy test†	√								
Lysholm score	√ (1)					√ (8)		√ (8)	√ (8)
IKDC score	√ (1)					√ (8)		√ (8)	√ (8)
Drawer test	√ (1)					√		√	√
Lachman test	√ (1)					√		√	√
X-ray film	√ (2)	√		√ (5)		√		√	√
CT	√ (2)	√		√ (5)		√		√	√
MRI	√ 2)			√ (5)		√		√	√
Randomization	√ (7)								
Operation		√							
Telephone follow-up			√	√ (6)	√		√		
Concomitant drug (4)	√	√	√	√	√	√	√	√	√
Adverse event	√	√	√	√	√	√	√	√	√
Device Deficiency		√	√	√	√	√	√	√	√
Reoperation			√	√	√	√	√	√	√
Study	√	√	√	√	√	√	√	√	√

completion/with drawal									

(1) For preoperative lab examinations and all scores, only those within Day 1~10 before the operation are acceptable.

(2) If MRI, CT or X-ray film has been done within 30 days before the Informed Consent Form is signed, and the data are available, they can be used as the data for screening before operation.

(3) It is tested before discharge.

(4) All combination drugs associated with AEs or serious adverse events (SAEs) are reported.

(5) Imaging examination 3 months after operation is optional.

(6) Both telephone follow-up and follow-up visit to the hospital are acceptable.

(7) Subjects are randomized after signing of ICF but before anesthesia begins.

(†) If applicable, where, the pregnancy test is only suitable for females of child-bearing potential, neither premenstrual females nor sterilized or postmenopausal (i.e., 12-month amenorrhea without alternative medical reasons) females.

(8) If the subject cannot return to the site due to any public incidents or other reasons, the subject may be changed to other ways of visit (eg. Remote visit, video visit, etc) after evaluation by the investigator.

3 Contents

Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
NMPA	National Medical Products Administration
CI	Confidence Interval
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRP	C-reactive Protein
CTA	Clinical Trial Agreement
EC	Ethics Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
ITT	Intent-to-Treat Population
NDA	Non-Disclosure Agreement
PI	Principal Investigator
PP	Per-protocol Population
QA	Quality Assurance
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

4 Sponsor Information

Sponsor name:	Smith & Nephew Medical (Shanghai) Limited
Address of sponsor:	Section B, F4, General Workshop Building, No. 188, Aona Road, China (Shanghai) Pilot Free Trade Zone
Contact information of sponsor:	Brook Li Clinical Study Manager Address: No. B-E, F2, Building A, East Gate Plaza, No. 9 Dong Zhong Street, Dongcheng district, Beijing, China Post code: 100027 Tel.: 010- 6419-8395 E-mail: Brook.Li@smith-nephew.com
Project Coordinator:	Astrid Yung Associate Director, Clinical Strategy and Operations Address: No. B-E, F2, Building A, East Gate Plaza, No. 9 Dong Zhong Street, Dongcheng district, Beijing, China Post code: 100027 Tel.: 010-6419-8200 E-mail: Astrid.yung@smith-nephew.com
Related qualification documents of sponsor:	See the Qualification documents of sponsor.

In case of any change in the contact information of sponsor, it will be updated timely in the study. For the latest contact information, see the contact information of the sponsor in the investigator folder.

5 List of study sites and investigators for the multi-center clinical trial:

List of study sites and investigators should be provided in a separate document.

The study sites may be adjusted during the trial. This is an administrative change. The Sponsor will submit a written document to each study site.

6 Objective and contents of clinical trial

6.1 Trial objective

The objective of this study is to compare the safety and effectiveness of Biosure Regenesorb Interference Screw versus the control device in patients requiring repair or reconstruction of cruciate ligaments (including anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL)). The trial results will be used for registration of Biosure Regenesorb Interference Screw in China.

6.2 Study contents

This clinical trial is designed to be a prospective, multi-center, randomized, evaluator-blinded, parallel-controlled, non-inferiority trial. The primary efficacy endpoints are not inferior to the control group. The Biosure Regenesorb Interference Screw and BIOSURE HA Interference Screw are used in the trial and control groups, respectively, to evaluate the safety and effectiveness of the investigational medical device Biosure Regenesorb Interference Screw in clinical repair or reconstruction of knee cruciate ligament rupture or tear.

The subjects complying with the criteria for inclusion in this clinical trial will receive 24-month follow-up after being treated with the investigational product or the control product. The following endpoints will be recorded and evaluated: Lysholm score, IKDC score, Drawer test, Lachman test and imaging evaluation results at the follow-up visit at month 6, 12 and 24 after the operation, respectively, incidence and frequency of ADEs, AEs, and device deficiency throughout the trial and reoperation rate.

7 Background of Clinical Trial

The knee becomes one of the most injured joints due to its anatomical structure and particular function in human body. According to the statistics, there are 200,000 ACL rupture cases per year in the United States, including 100,000 requiring ACL reconstruction. An epidemiological investigation in sport injury showed that the total incidence of ACL injury is 0.47% in China. PCL injury are relatively infrequent. As reported in foreign literature, PCL injury has an incidence of 3% in the common population and account for 20% of knee ligament injury. No similar reports are found in China.

The ACL femoral attachment, located at the posterior part of the medial side of the lateral femoral

condyle, has an oval-shaped concavity, 18 mm long and 11 mm wide on average, and covers an area of 113-170 mm^2. The distal end of ACL is fan-shaped and attached to the anterior intercondyloid spine of the tibial plateau, forming an anterior-wide posterior-narrow triangle or an oval region, with an average sagittal diameter of 17 mm and a coronal diameter of 11 mm. PCL begins at the medial side of the intercondylar fossa of femur (i.e., the lateral side of medial femoral condyle) and ends at the posterior of the tibial intercondylar eminence. The therapy selection for cruciate ligament injury is affected by the natural course of ligament injury. It has currently been demonstrated in literature that patients with cruciate ligament injury will experience meniscus tear and cartilage injury and finally osteoarthritis if they re-participate in sports activities and experience recurrent joint instability. A conservative treatment will be feasible if patients are willing to change their lifestyle and reduce joint activities. Plaster fixation is a common treatment method, but it cannot thoroughly cure knee joint instability. Therefore, at present, operation is still the main therapy for cruciate ligament injury. After twenty years of development, arthroscopic cruciate ligament reconstruction has become the main therapy for cruciate ligament injury. Bone avulsion can be repaired via arthroscopic reduction + screw-fixed suture. Early arthroscopic cruciate ligament reconstruction is able to relatively better restore stability of the knee joint, maintain functions of the knee joint and reduce the incidence of secondary injury of knee cartilage and meniscus, which is a currently better choice for cruciate ligament injury.

Cruciate ligament reconstruction grafts include autografts and allotransplant. The common autografts of ligaments include ligamentum patellae, tendon of quadriceps femoris, hamstring tendon, semitendinosus tendon and gracilis tendon, etc. The most common ones are fixed bone-patellar tendon-bone (B-PT-B) and hamstring tendon (HT). Via one or two years of follow-up, some investigators found that a reliable stability was achieved for both ligamentum patellae and semitendinosus tendon with no significant difference in postoperative knee stability and that no significant difference was found in the impact on myodynamia of quadriceps femoris and rehabilitation of knee functions. It is reported in many articles that allogeneic grafts and autografts will achieve similar efficacy in cruciate ligament reconstruction as long as appropriate operations are made, such as appropriate widening of allogeneic tendon grafts and pre-tension of autografts.

Grafts can be fixed directly and indirectly. Direct fixation refers to directly squeezing the graft into the bone tunnel, while indirect fixation refers to hanging the graft into the bone tunnel. Direct fixation involves interference screws and Intrafix fixation system, etc.; while indirect fixation involves knotting on the bone bridge, Endobutton CL Ultra and Rigidfix cross pin systems, etc. Direct fixation with interference screws, the most clinically used fixation method, achieves a more stable reconstructed knee joint due to a shorter distance of the fixation point to the articular surface

as compared with indirect fixation. Interference screws can be used to fix multiple grafts mentioned above separately or in combination with other fixation methods. They can effectively fix grafts at both femoral and tibial attachments. Long-term follow-up shows that the efficacy in achieving knee joint stability doesn't vary with neither different manufacturing materials nor a single or combined use of interference screws.

Bone-tendon healing plays a critical role in surgery for repairing various injured tendons. Currently, interference screws have been widely used in clinical practice for operative fixation of the injured bone-tendon. Interference screws are often used to fix tendons in surgery for knee joint, shoulder joint and ankle joint, etc. In clinical practice, their application in knee joint ligament reconstruction is the most commonly reported and studied.

Interference screws can be classified into absorbable ones and non-absorbable ones according to the material (e.g. metal interference screws). Metal interference screws were widely used due to their high fixation strength, but currently they have been less used because their deficiencies have been gradually recognized, e.g., cutting-induced damages to grafts. In a meta-analysis study carried out by Emond, no significant differences in the postoperative knee function score and postoperative complication rate were found between metal interference screws and absorbable screws when used to fix the reconstructed cruciate ligament.

Absorbable screws have tended to replace the metal interference screws. They have the advantage of having no impact on MRI examination and providing more convenience for revision surgery while achieving similar fixation strength to metal interference screws. At present, polylactic acid is the most commonly used screw material and is degraded at different rates in different environment. Clinical effectiveness of absorbable screws has been demonstrated in many international articles. Christopher Kaeding, et al. reported that no differences in the range of motion, the level of motion and knee functions were found within 1-year follow-up between interference screws made of PPLA material (poly L-lactic acid) and those made of titanium. At the 2-year follow-up, no AEs caused by absorbable materials were found. Christian Fink, et al. reported that the absorbable screws was found in the CT scan at Month 12 to have been degraded in a 24-month study designed to compare interference screws made of polyglycolic acid/trimethylene carbonate (PGA/TMC) copolymer and those made of titanium. Yuval Arama, et al. reported PLLA-HA absorbable screws had not been completely ossified at the 5-year follow-up. Whether to be completely absorbed depends on the material of absorbable screws, bone tissue condition of patients and patient conditions in the rehabilitation period, instead of being generalized. The investigational device adopted in the study is made of PLGA, β-tricalcium phosphate and calcium sulfate, which are commonly used as the

absorbable screw material.

This study is a registration study of the imported device Biosure Regenesorb Interference Screw.

8 Characteristics, structural composition, working principle, mechanism of action and study population of the investigation product

8.1 Product characteristics

The Biosure Regenesorb Interference Screw, an absorbable screw designed with an open structure and made of biocomposite material, is used to fix ligaments, tendons, soft tissues or bone-tendon-bone grafts in knee surgery. Its manufacturing material is made of PLGA, β-TCP (β-tricalcium phosphate) and calcium sulfate. As compared with other absorbable screws made of other absorbable materials, its open structural design enables rapid bone ingrowth to make the screw integrated with bone tissue so as to promote healing. It has the following characteristics:

Bone ingrowth

- Its open structural design facilitates bone ingrowth.

Advanced materials

- In the pre-clinical study, the Biosure REGENESORB Interference Screw was replaced with bone within 24 months, but the control product BIOSURE HA Interference Screw was absorbed in a relatively longer time and might not be completely absorbed within 3~5 years.

Performance

- Excellent pullout resistance: Its fixation strength is similar to that of solid absorbable screws.
- BIOSURE Driver fully supports screws, maintains screw integrity and minimizes the possibility of breakage.

8.2 Structural composition and mechanism of action of the product

The Biosure Regenesorb Interference Screw is composed of absorbable screws and relevant instruments.

The specifications of absorbable screws are as follows:

Product code	Description

72204389	BIOSURE REGENESORB Interference Screw, 5mm×20mm
72204390	BIOSURE REGENESORB Interference Screw, 5mm×25mm
72204391	BIOSURE REGENESORB Interference Screw, 6mm×20mm
72204392	BIOSURE REGENESORB Interference Screw, 6mm×25mm
72204393	BIOSURE REGENESORB Interference Screw, 6mm×25mm, Reverse Thread
72204394	BIOSURE REGENESORB Interference Screw, 7mm×20mm
72204395	BIOSURE REGENESORB Interference Screw, 7mm×25mm
72204396	BIOSURE REGENESORB Interference Screw, 7mm×25mm, Reverse Thread
72204397	BIOSURE REGENESORB Interference Screw, 7mm×30mm
72204398	BIOSURE REGENESORB Interference Screw, 8mm×20mm
72204399	BIOSURE REGENESORB Interference Screw, 8mm×25mm
72204400	BIOSURE REGENESORB Interference Screw, 8mm×25mm, Reverse Thread
72204401	BIOSURE REGENESORB Interference Screw, 8mm×30mm
72204402	BIOSURE REGENESORB Interference Screw, 8mm×35mm
72204403	BIOSURE REGENESORB Interference Screw, 9mm×20mm
72204404	BIOSURE REGENESORB Interference Screw, 9mm×25mm
72204405	BIOSURE REGENESORB Interference Screw, 9mm×30mm
72204406	BIOSURE REGENESORB Interference Screw, 9mm×35mm
72204407	BIOSURE REGENESORB Interference Screw, 10mm×20mm
72204408	BIOSURE REGENESORB Interference Screw, 10mm×25mm
72204409	BIOSURE REGENESORB Interference Screw, 10mm×30mm
72204410	BIOSURE REGENESORB Interference Screw, 10mm×35mm
72204411	BIOSURE REGENESORB Interference Screw, 11mm×25mm
72204412	BIOSURE REGENESORB Interference Screw, 11mm×30mm
72204413	BIOSURE REGENESORB Interference Screw, 11mm×35mm
72204414	BIOSURE REGENESORB Interference Screw, 12mm×35mm

The supporting instruments are listed as follows:

72204647	BIOSURE Driver, 5mm
72201887	BIOSURE Driver
72201201	Guide Wire, 1.2mm×18" sterile
72201889	BIOSURE Tap, 6mm
72201890	BIOSURE Tap, 7mm

72201891	BIOSURE Tap, 8mm
72201892	BIOSURE Tap, 9mm
72201893	BIOSURE Tap, 10mm

Working principle/mechanism of action:

The Biosure Regenesorb Interference Screw, an absorbable screw designed with an open structure and made of biocomposite material made of PLGA, β-TCP and calcium sulfate, is used to fix ligaments, tendons, soft tissues or bone-tendon-bone grafts in knee surgery. Its open structural design enables rapid bone ingrowth to make the screw integrated with bone tissues so as to promote healing.

8.3 Study population

The clinical trial is carried out in patients requiring knee cruciate ligaments reconstruction.

8.4 Control product

The already-marketed BIOSURE HA Interference Screw of Smith & Nephew Medical (Shanghai) Limited (hereinafter referred to as "Smith & Nephew") is selected as the control product.

The specifications and description of product used in this study are as follows:

72201768	BIOSURE HA Screw, 6mm×20mm
72201769	BIOSURE HA Screw, 6mm×25mm
72201770	BIOSURE HA Screw, 6mm×25mm, Reverse Thread
72201771	BIOSURE HA Screw, 7mm×20mm
72201772	BIOSURE HA Screw, 7mm×25mm
72201773	BIOSURE HA Screw, 7mm×25mm, Reverse Thread
72201774	BIOSURE HA Screw, 7mm×30mm
72201775	BIOSURE HA Screw, 8mm×20mm
72201776	BIOSURE HA Screw, 8mm×25mm
72201777	BIOSURE HA Screw, 8mm×25mm, Reverse Thread
72201778	BIOSURE HA Screw, 8mm×30mm
72201779	BIOSURE HA Screw, 8mm×35mm
72201780	BIOSURE HA Screw, 9mm×20mm

72201781	BIOSURE HA Screw, 9mm×25mm
72201782	BIOSURE HA Screw, 9mm×30mm
72201783	BIOSURE HA Screw, 9mm×35mm
72201784	BIOSURE HA Screw, 10mm×20mm
72201785	BIOSURE HA Screw, 10mm×25mm
72201786	BIOSURE HA Screw, 10mm×30mm
72201787	BIOSURE HA Screw, 10mm×35mm
72201788	BIOSURE HA Screw, 11mm×25mm
72201789	BIOSURE HA Screw, 11mm×30mm
72201790	BIOSURE HA Screw, 11mm×35mm
72201791	BIOSURE HA Screw, 12mm×35mm

The supporting instruments are listed as follows:

72201887	BIOSURE Driver
72201201	Guide Wire, 1.2mm×18" sterile
72201889	BIOSURE Tap, 6mm
72201890	BIOSURE Tap, 7mm
72201891	BIOSURE Tap, 8mm
72201892	BIOSURE Tap, 9mm
72201893	BIOSURE Tap, 10mm

9 Indications, contraindications and precautions of the product

9.1 Indications

The Biosure Regenesorb Interference Screw is suitable for re-attachment of ligaments, tendons, soft tissues or bone-tendon-bone grafts to treat the following indications:

Knee

- ACL repair
- PCL repair
- Extracapsular repair

  Medial collateral ligament

Lateral collateral ligament

Posterior oblique ligament

- Patellar reconstruction and tendon repair

  Antedisplacement of vastus medialis oblique

- Tendon fixation for iliotibial tract

9.2 Contraindications

- Known hypersensitive response to graft materials. If it is suspected to be sensitive to materials, a relevant test should be carried out before implantation to exclude sensitivity to materials.
- Possible reduction in the supporting force of screws and threads, e.g., insufficient number or quality of bones (including tumors and severe osteoporosis).
- Presence of infection.
- Possible limitations on activities, compliance ability or compliance willingness of patients in the healing period.
- Contraindications may be relative or absolute and must be carefully evaluated based on overall evaluation results of patients.

9.3 Warnings and precautions

- The content is sterile unless the package is opened or damaged. No re-sterilization is allowed. For single use only. Please discard any open, unused product. No use after the shelf life.
- The physician is responsible for becoming familiar with related surgical techniques before using the device.
- Please read all these instructions before use.
- The product must be stored in its original sealing bag.
- Insufficient screw insertion may cause poor screw performance.
- Incorrect drilling of the insertion site may cause screw damage or fixation failure.
- Prior to insertion, please check to ensure that the screw is completely seated onto the

BIOSURE Driver. Incorrect seating of the screw onto the BIOSURE Driver may cause screw damage.

- Incomplete seating of the screw may cause screw damage.
- The use of an unsuitable BIOSURE Driver may cause screw damage. The 5mm Biosure Regenesorb Interference Screw needs to be used with the 5mm BIOSURE Driver. All other Biosure Regenesorb Interference Screws need to be used with standard BIOSURE Driver.
- Pathological changes in soft tissues may weaken the ability to firmly fix soft tissues onto the bone.
- Do not try to implant the device into the epiphyseal plate or non-osseous tissue.
- Pathological bones (e.g., tumors, severe osteoporosis and bone immaturity) may weaken the ability to firmly fix or anchor the device.
- Hazards associated with the device reuse include, but not limited to, patient infection and/or device failure.
- Check the device before use to ensure that it is undamaged. Do not use a damaged device.
- Do not exert an excessive force onto the screws, skeletons or devices.
- Light taps are recommended for insertion of absorbable screws for the bone-tendon-bone graft.
- If the BIOSURE Driver is re-inserted into the implanted screw after being withdrawn, it shall be ensured that the BIOSURE Driver has been completely seated onto the screw before tightening the screw. Incomplete seating of the screw may cause screw damage.
- Carefully carry out aseptic processing and avoid anatomical hazards.
- Postoperative care is of great importance. The patients should be informed of limitations of the implant and precautions related to the load bearing and internal stress of the device prior to complete healing of the bone.
- After use, potential biohazards of the device need to be handled in accordance with the recognized medical specifications and applicable local and national requirements.

9.4 Potential adverse reactions

As with any surgery, this surgery will cause risks. Potential complications of such implantation surgery include, but not limited to, anesthetic complications, pain at the incision and surgical sites,

surface and deep infections, bone injury or fracture, damage to surrounding tissues or blood vessels, embolism or coagulation problems (e.g., pulmonary embolism and deep vein thrombosis), nerve injury or stroke, treatment or implantation failure and surgery or treatment related complications requiring secondary surgical intervention. The expected adverse reactions are mild inflammatory reaction, foreign body reaction, deep and superficial infections and anaphylactic reaction.

10 Overall design

10.1 Trial design

10.1.1 Study objective

This is a prospective, multi-center and randomized controlled clinical study to evaluate the safety and effectiveness of Biosure Regenesorb Interference Screw in arthroscopic repair and reconstruction of cruciate ligaments in Chinese patients.

10.1.2 Study method selection and justification

This is a prospective, randomized, multi-center clinical study designed to compare the safety and effectiveness of Biosure Regenesorb Interference Screw versus the BIOSURE HA Interference Screw in arthroscopic cruciate ligament reconstruction in Chinese subjects.

This clinical trial is a clinical trial for registration of medical device, so it is required to follow the requirements of relevant regulations issued by National Medical Products Administration (NMPA). This study is designed as a prospective, multi-center, randomized, evaluator-blinded, parallel-controlled study.

The subjects meeting the inclusion/exclusion criteria specified in the protocol will be randomized to receive implantation with the investigational product or control product. A total of 140 subjects are planned to be included in about 4 study sites. The average number of subjects should be included in each study site as mean as possible. The number of subjects included in each study site should be no more than 70 cases. The clinical follow-up evaluation will be conducted at 6, 12 and 24 months respectively after operation. The telephone follow-up should also be conducted at 6 weeks, 3, 4.5 and 9 months respectively after operation. In this study, 12-month follow-up data will be submitted for registration and 24-month follow-up will be made to observe the long-term performance and absorbability of the investigational device.

10.1.3 Measures to Reduce and Avoid Bias

10.1.3.1 Multi-center

The samples from multi-center are more representative than those from single center, the latter may lead to deviation of test results due to its systematic errors.

10.1.3.2 Blinding

To avoid the bias occurring to the research design, we appoint an independent rator in each study site, who is blinded and responsible for completing scoring at each follow-up.

10.1.3.3 Randomization/allocation

The randomization allows the patients to be given equal opportunity to be assigned to the trial group or control group, independently of investigators and/or subjective views of subjects, so that the various influencing factors tend to be distributed in a similar way, avoiding the issues of selection bias and information bias.

The subjects meeting all inclusion/exclusion criteria will be randomly allocated into any of two study groups (trial group or control group) in a ratio of 1:1 through network-based randomization system. The random number is allocated only when the subject has signed the Informed Consent Form and passes the screening test.

10.1.3.4 Parallel-controlled

This is a parallel controlled trial, in which treatment is conducted simultaneously for both the investigational group and the control group, so that potential differences influencing the outcome measures between both groups can be minimized.

10.1.3.5 Consistency of score

The training on the consistency of the scale should be provided to the scorer of primary endpoint and secondary endpoint evaluation (such as Lysholm score, IKDC score, drawer test and lachman score) in each site, ensuring that the scorer have consistent understanding and use of the scale, thus reducing the bias between scorers.

10.1.3.6 Imaging evaluation

The imaging observation indicators are reasonable and necessary indicators for the evaluation of arthroscopic repair of soft tissues, but not included in the Lysholm score. In order to reflect the importance of imaging, imaging evaluation will be performed pre-op, 6, 12 and 24 months post-op.

10.1.3.7 Screening of subjects

In order to eliminate selection bias, the investigators will continuously screen all subjects. Subject recruitment continues until the completion of recruitment of 140 subjects. File records and enrollment registration forms for screening work must be retained and submitted to the Sponsor as needed.

10.1.3.8 Investigator training

Prior to the clinical trial, the Clinical Research Associate, 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 patient 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 released during the clinical trial, thus to minimize the interferential factors.

10.1.3.9 Clinical trial audit

The monitoring plan is established. The Clinical Research Associate is selected and appointed by the sponsor to conduct a regular on-site monitoring visit of trial center, making sure that all contents in the trial protocol are strictly followed. The source data are verified to ensure it is consistent with the electronic case report form (eCRF).

10.1.4 Selection of subjects

10.1.4.1 Inclusion criteria

Subjects must meet all of the inclusion criteria:

(1) Signing the Informed Consent Form (ICF) voluntarily;

(2) Patients aged 18-75 years;

(3) Patients clinically diagnosed with knee cruciate ligaments rupture or tear and suitable for cruciate ligaments reconstruction definitely;

(4) Normal contralateral knee joint.

10.1.4.2 Exclusion criteria

Subjects with any of the following characteristics must be excluded from participation in the study:

(1) Patients not complying with the diagnosis criteria for cruciate ligaments rupture or tear;

(2) Patients with an unclosed epiphyseal plate shown on the X-ray film;

(3) Patients having underwent internal fixation or reconstruction due to a knee joint fracture;

(4) Patients with obvious knee joint degeneration shown on the X-ray film;

(5) Patients who cannot make a knee flexion of not less than 90° during operation;

(6) Patients undergoing autologous chondrocyte implantation;

(7) Patients with medial meniscus or lateral meniscus completely resected;

(8) Patients with significant anatomical abnormalities;

(9) Pregnant or breast-feeding females or those at a child-bearing age planning to become pregnant;

(10) Patients with serious osteoporosis that affects screw implantation;

(11) Patients with a malignant tumor that causes failure to effectively fix the implant;

(12) Known hypersensitivity to the implant materials;

(13) Patients not suitable for operation due to obvious local or systemic infection;

(14) Patients who cannot tolerate an operation due to severe malnutrition;

(15) Patients with severe coagulation disorder (judged by the investigator), e.g. the hemophiliac;

(16) Patients with immunodeficiency, including those who must receive immunosuppressant for a long time;

(17) Patients with extensive skin diseases;

(18) Obese patients having a Body Mass Index (BMI) > 35;

(19) Patients who cannot cooperate in postoperative rehabilitation due to a severe mental disease or those who cannot tolerate the operation due to a cardiopulmonary disease;

(20) Patients who received operation on the injured lower limb within the past 1 year;

(21) Patients who participated in any other clinical trial within the past three months;

(22) Patients who cannot follow the requirements described in the study protocol; and

(23) Other patients who are considered by the investigator not suitable for this clinical study.

10.1.4.3 Exclusion criteria

During the operation, if subjects are found not to comply with the diagnosis criteria for cruciate ligaments rupture or tear or found to comply with the exclusion criteria, they will be excluded from the trial.

10.1.4.4 Criteria and procedures for withdrawal/termination of study

Participation in the study is voluntary and subjects may drop out at any time point in the study. Any subjects who have not completed the study should make every effort to complete the final evaluation. The reason for withdrawal must be recorded in the original document and the corresponding case report form (CRF). After the subject withdraws from the study, there is no need to replace him/her or continue follow-up.

Investigators may also choose subjects to withdraw from the study for reasons including but not limited to:

- Serious Adverse Event
- Investigators decide subjects to withdraw for safety reasons.
- The subjects do not accept the investigational device implantation during the operation
- The subjects do not comply with follow-up
- Subjects are lost to follow-up

When investigators decide subjects to withdraw, the relevant reasons should be recorded in the

original document and the corresponding case report form (CRF).

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to other parties (investigator, Ethics Committee, Sponsor and regulatory authorities). If the study is prematurely terminated or suspended, the investigator will promptly inform the Ethics Committee and the GCP office and will provide the reason(s) for the termination or suspension. Circumstances that may need termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would induce stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and approved by the Sponsor and Ethics Committee.

10.1.4.5 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 (2) consecutive visits or does not return for a final visit, and study personnel is 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: 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.

10.1.4.6 Time of enrollment

The study enrollment can be started only after the Ethics Committee has approved and signed a clinical trial agreement at each site. Before the enrollment, the relevant procedures and requirements should be completed according to the regulations of relevant departments. The competitive enrollment is taken in the study with a preliminarily estimated time of 12 months. The enrollment time can be adjusted according to the actual situation.

Subjects who have completed the informed consent form and have been assigned a random number are considered to be enrolled.

10.1.4.7 Duration of the trial

The enrollment of subjects is planned to last for about 12 months. The primary endpoint of study is Lysholm score at 12 months after operation. Considering the need of bone tissue ingrowth and patient functional recovery, the follow-up of this study should last throughout 12 months after operation. In this trial, a summary of 12-month follow-up data will be reported to NMPA, and 24-month follow-up data will be observed. The specific duration will be adjusted according to the actual situation.

10.1.4.8 Expected duration of participation of each subject

The duration of participation of each subject in the clinical trial is about 12 months with long-term observation for 24 months, the data of which may be adjusted according to the visit window specified in the protocol due to the specific circumstances.

10.1.4.9 Number of subjects

Number of subjects required for the entire clinical trial is about 140. 70 subjects each in the investigational group and control group. For the number of subjects, see the chapter of sample size calculation.

10.1.5 Efficacy evaluation method

10.1.5.1 Primary efficacy endpoints

The primary study endpoint is the Lysholm score at Month 12 after operation.

The Lysholm score, a knee scoring system created by Lysholm and Gillqui in 1982 and revised in 1985, has been applied in many international literature articles, and its reliability, effectiveness and sensitivity have been demonstrated in international literature. The Lysholm score is a scoring scale the most commonly used before and after arthroscopic knee surgery. A preliminary assessment can be made for the level of motion of patients with different intensity. The scale evaluates functions of patients based on 8 items: limp, support, interlocking, pain, instability, swelling, stair climbing and squatting. The total Lysholm score is 0-100. Pain and instability account for a higher proportion in this score. The knee functions of patients are considered excellent when the score is 95-100, good when 84-94, fair when 65-83 and poor when less than 65. The measurement takes about 3-5 min. The Lysholm score emphasizes the patient's subjective perception of symptoms and grade dysfunction in combination with the score and the level of daily activity. Studies have shown that the scale is the most reliable for patients undergoing cruciate ligament reconstruction and the difference in score is more significant when it is used to evaluate patients who self-limit activities.

10.1.5.2 Secondary efficacy endpoints

- Lysholm Score (Month 6, Month 24)
- International Knee Documentation Committee (IKDC) score (at months 6, 12 and 24)

The scoring scale was proposed in 2000 after being repeatedly revised by major sports medicine and medical organizations in Europe and America. The scale is composed of a knee evaluation form (10 items) and a knee ligament examination form (8 items), involving joint pain, sport level and ability of daily activities. The total score is 0-100. The IKDC scale is for evaluating the symptoms, functions and physical activities of the knee joint, helping compare different knee diseases.

- Drawer Test (Month 6, Month 12, Month 24)

Anterior drawer test: It is used for ACL examination. The patient should be supine with the knees flexed to 90 degrees and the feet flat on table and keep relaxed. The examiner sits on the examination table against the patient feet for fixation, grasps the tibia of the knee and draws the shank forward. The patient will be diagnosed with forward straight instability if the tibia is forward displaced 5 mm more than the uninjured side.

Posterior drawer test: It is used for PCL examination. The patient should be supine with the knees flexed to 90 degrees. The examiner places both hands behind the knee joint, with the thumbs on the extensor aspect. The proximal end of shank is repeatedly drawn backward. The posterior displacement of the tibia along the femur suggests partial or complete CL rupture.

- Lachman Test (Month 6, Month 12, Month 24)

The Lachman test is carried out at injured and uninjured sides simultaneously. The patient should be supine with the knees flexed to 20-30 degrees and the injured limb slightly rotated outward. The examiner stands beside the injured side, immobilizes the lower end of the femur with one hand, and presses the posterior side of the upper end of the tibia forward (Lachman test) or backward (reverse Lachman test). A positive test result is got. Positive results suggest ACL or PCL injury.

- Imaging evaluation (Month 6, Month 12, Month 24)

Take X-ray films, CT images and MRI images of the knee before operation, intraoperative - post-operative (Day 0-5) (only X-ray films and CT images), 6, 12, 24 months after operation, respectively. Observe bone ingrowth and bone absorption, etc. All imaging observations are to be reported on the CRF.

Other imaging films taken are at the discretion of the individual Investigator.

Although imaging evaluation will be performed at each site by the investigator, all imaging examination data will be stored in electronic DICOM format at the site until they are no longer needed in case further evaluation by an independent centralized reviewer is requested by NMPA. All imaging examination data must be modified in order to protect subjects' identity if they are sent to Smith & Nephew, or designee, for independent review. If independent review is required, it will be done by a board certified radiologist selected by the Sponsor based on experience in orthopaedics and joint replacement imaging.

10.1.6 Safety evaluation method

10.1.6.1 Description of safety parameters

No formal hypothesis testing is performed for safety analysis. Descriptive statistics will be used to summarize safety events.

10.1.6.2 Safety evaluation contents

Safety evaluation includes the following contents:

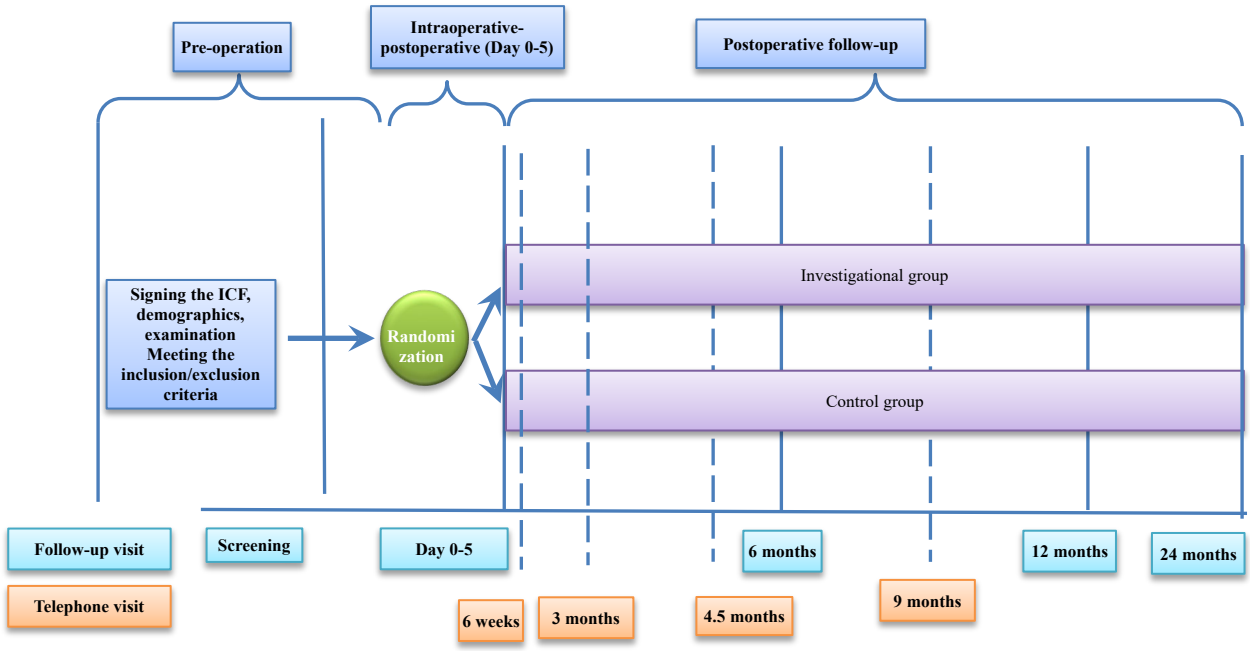
- Incidence (%) and frequency (number of events) of AEs related to device;
- Incidence (%) and frequency (number of events) of adverse events;

- Incidence (%) and frequency (number of events) of device deficiencies;
- Reoperation rate.

10.2 Study procedures

10.2.1 Study flowchart

Figure 10.2.1Schematic diagram of study design



10.2.2 Study procedures

10.2.2.1 Evaluation before enrollment in the study

Prior to initiating any study-related activities on a subject, sites must first perform the following pre-study activities:

- Informed consent must be obtained from each subject entering the study using the EC-approved consent form. Informed consent must be obtained prior to any study activity.
- Inclusion and exclusion criteria will be carefully reviewed to verify subject eligibility.
- All combination drugs associated with AEs or SAEs are recorded after the subject signs the ICF.
- The subject enrollment time is the moment when the device is implanted.

10.2.2.2 Pre-operative study activities

Prior to the operation, the following information must be collected:

- Demographics include:
    - Age at surgery (calculated from date of birth)
    - Gender (male/female)
    - Occupation
    - Height (in cm) and body weight (in kg)
    - Body mass index (BMI)
- Vital signs: pulse, blood pressure, respiration and body temperature
- Physical examination status
- Medical history will be obtained and will include:
    - Previous medical history (HEENT, respiratory, gastrointestinal, hematological, cardiovascular, endocrine/metabolic, musculoskeletal, immunological, neurological, genitourinary, prior surgery, others)
    - Tobacco use and alcohol intake (tobacco use: never used, past use, current use; alcohol intake)
    - Closure of epiphyseal plate
    - Current medical history of knee diseases: time of knee injury, cause of knee injury, conditions of the studied knee side (left/right) and the contralateral knee joint, cause of CL rupture or tear, other combined knee injury, knee degeneration and whether or not to totally excise the medial or lateral meniscus
    - Previous surgeries on the affected knee joint (For surgery history, fracture fixation, arthroscopy, ligament surgery, autologous cell transplantation or other surgery, please specify)
    - Safety events
    - All combination drugs associated with AEs or SAEs are recorded.

In addition, subjects will be evaluated clinically pre-operatively using:

- Lysholm Score
- IKDC Score
- Drawer test

- Lachman test
- Lab evaluation (blood routine, C-reactive protein (CRP), blood biochemistry and coagulation function)
- Pregnancy test
- ECG
- Imaging evaluation
    - X-ray film
    - MRI
    - CT

10.2.2.3 Intraoperative-postoperative (Day 0-5) evaluation

- Inclusion and exclusion criteria will be reviewed against to verify subject eligibility.
- Vital signs
- Collection of information on the operative procedure for each subject including:
    - Surgical time (time from entering and leaving the operating room, from skin open to skin close)
- Use of absorbable screws (specifications, number), femoral screws and tibial screws.
    - Labels of the device components used are to be adhered to the Operative medical record page.
    - Treatment of associated other injuries
- Collection of information on discharge including:
    - Admission date
    - Discharge date
- Lab evaluation (blood routine, blood biochemistry; and examination before discharge)
- Imaging evaluation after the operation
    - X-ray film

- CT

- Safety events
- Device deficiency
- All combination drugs associated with AEs or SAEs are recorded.

10.2.2.4 Surgical operation training

The investigators must make a professional judgment based on indications, surgical techniques and medical history of patients to select the appropriate size of screws, bone tunnels and BIOSURE Driver.

Generally, arthroscopy is carried out via anteromedial and anterolateral incisions in the surgery. Remove residual ACL/PCL tissues and perform arthroplasty with a minimally invasive incision. The tibial and femoral tunnels are drilled and then fixed with or without absorbable screws for grafts.

The patient is in supine position, and undergoes routine anesthesia and disinfection. Adopt the conventional approach. Prepare the graft: The investigator selects a homologous tissue as the graft based on conditions of the patient. Under the arthroscopic monitoring, find the femoral attachment of CL, select an appropriate BIOSURE Driver based on the graft diameter and complete the preparation of femoral tunnel. Find the tibial attachment of CL, select an appropriate BIOSURE Driver based on the graft diameter and complete the preparation of tibial tunnel. Insert the prepared graft into the bone tunnel at both ends, and insert the 1.2 mm Smith & Nephew guide wire when the graft is inserted at an appropriate position. Select appropriate absorbable screws based on bone tunnel length and graft diameter.

Note: When BTB is used as a graft, it is recommended to prepare an insertion point using BIOSURE Driver of an appropriate size + 1.2 mm guide wire. The BIOSURE Driver 1 mm bigger than the screw is required when the bone is relatively rigid. Do not use the Biosure Regenesorb Interference Screw with reverse thread when BTB is used as a graft.

Completely install the screw onto the BIOSURE Driver until the laser mark indicates that the screw is installed to the specified length. Tension the graft with a suitable force, and insert the absorbable screw to the appropriate depth to ensure that the graft has been sufficiently anchored in the bone tunnel. Ensure that the BIOSURE Driver is always parallel to the bone tunnel. Remove the BIOSURE Driver and the guide wire. The operation is completed.

If device replacement/repair is required in the initial operation, the investigators will need to replace/repair the device according to the conventional medical device replacement/repair method (e.g., other safe fixation methods).

10.2.2.5 Study activities of follow-up visit post-op

Subjects should return to hospital for follow-up visit at 6 weeks, 12 months and 24 months postoperatively and evaluated clinically using the following endpoints, and the follow-up information should be record in the medical record. Please refer to Study Visit Schedule for the acceptable follow-up windows.

(1) 6, 12, 24 months after the operation

- Lysholm Score
- IKDC Score
- Drawer test
- Lachman test
- Knee joint condition: whether to require a re-operation, whether to experience tear or rupture again.
- Collect and record any AE since last visit.
- Device Deficiency
- All combination drugs associated with AEs or SAEs are recorded.
- Imaging evaluation
    - X-ray film
    - MRI
    - CT

10.2.2.6 Telephone follow-up post-op

Telephone follow-up will be performed at 6 weeks, 3, 4.5 and 9 months after the operation to ensure that the subject is not lost to follow-up between two visits, and to collect adverse events in time. The subject may choose to receive an imaging examination during his/her follow-up visit to the

hospital 3 months after the operation. The follow-up information should be recorded in the medical record of the subject. Please refer to Study Visit Schedule for the acceptable follow-up windows.

Collect and record any AE since last visit and necessity for re-operation.

At one week prior to each follow up visit after the operation, the Clinical Research Coordinator will call the subject to confirm the appointment. During the contact with the subject, if any change of subject contact information is observed, e.g. address, phone number, then the corresponding contact information in the subject's medical file should be updated as well.

10.2.2.7 Unscheduled Visits

All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF.、

10.2.2.8 Laboratory examinations

The laboratory examinations required to be performed include:

- Blood routine examination: Haemoglobin, Platelet count, WBC count, neutrophil count, erythrocyte sedimentation rate
- Coagulation examination: Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB)
- Biochemical examination: Urea or urea nitrogen, creatinine, AST (SGOT), ALT (SGPT), blood glucose
- C-reactive Protein
- Pregnancy test: females at a child-bearing age only

10.2.2.9 Imaging examination

Take X-ray films, CT images and MRI images of the knee joint pre-operation, intraoperative-postoperative (Day 0-5) (X-ray film and CT image), 6- and 12- month follow-up after operation, respectively. All imaging observations are to be reported on the CRF. Postoperative device-related and surgical adverse events are to be reported.

Mainly observe bone ingrowth into screw of the absorbable screw after implantation.

X-ray films, CT images and MRI images are taken during the postoperative 24-month follow-up to mainly observe absorption of the absorbable screw after implantation. All imaging observations are reported in CRF.

The specific imaging evaluation requirements will be provided in a separate document to radiologists for evaluation of examination results.

10.2.2.10 Activity limitations

The patients need to self-limit their activities and bear acceptable loads within 6 months after operation. Rehabilitation is recommended 2 weeks after operation until to 3 months. Moderate activities are allowed 4 months after operation. Vigorous exercise is only recommended 6 months after operation.

10.2.3 Device operation specifications

All study-related arthroscopic surgery procedures will be operated according to the surgical technique described in the specifications and IFU.

The physicians participating in this study must skillfully master the arthroscopic surgery procedures for soft tissue repair. In addition, before the investigational device is implanted, all physicians participating in this study must be appropriately trained in the surgical technique and device use.

10.3 Monitoring plan

This study will be monitored by the Sponsor or qualified personnel designated by the Sponsor. The monitor can be employees of the Sponsor, can also come from the contract research organization (the Sponsor's agent). The Sponsor or Sponsor's agent will monitor according to the monitoring frequency and the monitoring contents specified in the monitoring plan.

The Sponsor, Sponsor's agent, EC and regulatory authorities can directly access the source documents, so as to verify and evaluate the clinical data submitted by the investigator to the Sponsor through the CRF.

The investigator is responsible for obtaining and maintaining the integrity of the subject health information (original document) recorded in the medical record. The source data includes all original record information and certified copies of the original records (including clinical findings,

observations, or other activities used for study reconstruction and evaluation in clinical study).

Prior to the implementation of the clinical agreement, the Sponsor performs qualification evaluation visits to each study site to ensure that all investigators have received the corresponding training and that their personnel, facilities and resources are sufficient to carry out this study.

Before starting this study, the investigator must ensure that the following activities are completed and provide documentary records to the Sponsor.

10.3.1 Non-Disclosure Agreement

A Non-Disclosure Agreement (NDA) must be fully executed with the site and the Sponsor and any other appropriate parties.

10.3.2 Clinical Trial Agreement

A CTA must be fully executed by the site and the Sponsor and any other appropriate parties. Prior to initiation of the study, all investigators who will participate in the study need to be authorized by the principal investigator (PI), and the authorization outlines the responsibilities associated with the study. Unauthorized investigators are not allowed to participate in the study.

10.3.3 Ethical Approval

The protocol and informed consent materials must be approved by the EC at each institution. Copies of EC approval documents must be provided to the study Sponsor.

10.3.4 Documentation of Qualifications

A current, signed, dated CV and a current medical license for the principal Investigator and sub-Investigators must be submitted to the Sponsor prior to the study and in case of any update.

10.3.5 Monitoring visit by Sponsor

A site initiation visit will be performed by the Sponsor following the completion of the CTA negotiation and documented EC approval to provide training to the site on the specifics of the study and its conduct. The site must have written approval from the Sponsor before beginning enrollment.

The Sponsor may perform interim monitoring visits on a regular basis according to a schedule determined by the Sponsor. During these visits, the monitor will verify:

- Signed and dated informed consent forms
- Informed consent process occurred and is documented appropriately
- All inclusion/exclusion criteria were met
- Source documentation is complete and available
- Data on CRFs is verified by the source documentation
- Compliance with the protocol
- The reporting of adverse events occurred as required
- All required study documentation is complete and available

A monitoring visit will be performed by the Sponsor after the study closed to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review the investigator files to ensure required documentation 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 EC reporting requirements.

11 Data Management

Investigators will be provided with eCRFs based on the electronic data acquisition and management system to collect the data obtained during this study. The eCRFs include fields to record from source documentation specific information relative to the schedule of events. The investigator will complete a complete eCRF after each subject is included. The investigator will submit the completed PDF version of eCRF to the Sponsor.

Data quality procedures are designed to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed, and that complications or adverse events are immediately identified and addressed until closure.

The Sponsor and study sites will promptly review all faxed eCRFs and accompanying documentation to identify inconsistent or missing data and device-related complications. Problems with these data will be addressed via online data queries. Investigators will resolve the queries or provide the Sponsor with information regarding the reasons for not resolving the query and an

expected resolution date.

To ensure the confidentiality of data, Smith & Nephew, Inc., the leading site and the authorizer will maintain a secure study database that maintains the confidentiality of study data.

Data quality is the basis for evaluating the clinical study results. Standardized data management helps to obtain true, accurate, complete and reliable high-quality data.

Clinical data management personnel should develop data management plan based on clinical trial protocol, specify and record data management tasks for the clinical trial, including personnel, roles, job contents, operation procedures, etc. in a detailed and comprehensive manner. The data management plan should be completed after the trial protocol is finalized and before the first subject is enrolled, which can be implemented only after the approval is obtained. Data management plans need to be updated and revised in time according to actual operations.

Each step of data management needs to establish and follow the corresponding standard operating procedures.

The design of the eCRF should guarantee the collection of all data which is specified in the trial protocol and meets the needs of statistical analysis. eCRF completion guidelines should be developed and training for investigators and CRC should be provided.

In the data management plan, a clear data flow should be established. The investigators should cooperate with the CRC to complete all eCRFs after the end of visit and respond after receiving the online data query, or provide information to the Sponsor to indicate the reason why the query has not been resolved and expected resolved date.

The data management department should formulate a detailed data verification plan before data verification, and define the data verification contents, methods and verification requirements.

Medical coding is the process of matching the descriptions of adverse events, medical diagnoses, concomitant medication, previous medication, previous medical history, etc. collected from the CRF with the terms in the standard dictionary. If medical coding is used, the coding process, coding tools, coding dictionaries and versions, as well as the relevant standard documents for performing the coding should be detailedly described in the data management plan.

The process of the database locking, the person in charge and the SOP file executed should be detailedly described in the data management plan.

When the database is locked, the unlocking and re-locking of the database should be specified in advance and the conditions and processes should be described in detail.

The trial data, the time of input/import into the database, the inputer, the data audit trail and the document formed in the data management process all need to be completely saved. The data formed in the data management process usually includes but is not limited to: clinical trial data, external data, database metadata information, laboratory test reference range, logical test and derived data change control list, electronic data query table, and program code, etc.. The files formed in the data management process usually includes but is not limited to: data management plan, blank eCRF, eCRF completion guide, PDF file of completed eCRF, annotated CRF, database design description, database entry description, data verification plan, data quality control verification report, etc.

The trial data, management files, media, archiving methods and time limits that need to be archived should be specified in the data management plan.

The data management department needs to determine the data as well as the quality control items, quality control methods (such as quality control frequency, sample selection method and sample size), quality requirements, qualification criteria and remedial measures for failure to meet the expected quality standards, etc. of data management operation process.

For data management work during and after the study, data manager should write data management report, summarize data management process, and present data management implementation procedures, SOP and management quality using qualitative and quantitative parameters.

The contents related to the data management implementation process, SOP and management quality should be fully and detailedly described in the data management report, including participating institutions/departments and responsibilities, major time nodes, CRF and database design, data verification and clean-up, medical coding, external data management, data quality assurance, data transfer records at key nodes, version change records of key documents and deviations from data management plan.

To ensure the confidentiality of data, the data management department will maintain the security of the study database and protect the confidentiality of study data.

12 Statistical considerations

12.1 Statistical design, method and analysis procedure

12.1.1 Statistical analysis principles

The statistical software SAS 9.4 or above is used for statistical analysis. The sample size is calculated using PASS 13. Adopt the trial results for endpoint analysis. FAS and PPS are used to

analyze primary and secondary outcomes while SS is used to analyze safety indicators.

Unless otherwise specified, all significance tests and hypothesis tests use a two-sided test at a significance level of 5%. When appropriate, the obtained p value will be cited and the two-sided 95% confidence interval will be generated. All p values will be rounded to three decimal places. In all tables, the p values less than 0.001 will be expressed as "<0.001".

Continuous variables will be summarized using summary statistics such as mean, standard deviation, median, minimum, maximum, lower quartile (Q1) and upper quartile (Q3), etc. Classified and ordinal variables are summarized using frequency and percentage.

For comparison of general conditions in two groups, an appropriate method will be adopted based on the indicator type to carry out analysis. Continuous indicators in two groups will be evaluated using a two-sample t-test (if data is normally distributed) or the Wilcoxon rank-sum test (if data is non-normally distributed). Classified data will be analyzed using a chi-square test or the Fisher's Exact Test (if the chi-square test is not applicable), and ranked data using the Wilcoxon rank-sum test or CMH test.

12.1.2 Completion and Demographic Analysis

Baseline Data

Demography and medical variables at baseline (including but not limited to, age, gender, race, medical history, medication history and disease diagnosis) will be used to describe subjects and summarize subject information. Summary statistics will be given based on the nature of variables (continuous or classified variables). For continuous variables, the number of observations, mean, standard deviation, median, minimum and maximum will be reported. For classified variables, the number of observations, frequency and percentage will be reported.

A detailed list of different data set sizes in each group, case distribution of each site, total dropout rate comparison and reasons for not completing the study, should be provided. The demographic characteristics (age, height, vital signs, etc.), the medical history and the medication history of the patients are described, and comparison of the age, height, body weight, etc. between the two groups will be conducted to measure the comparability between the two groups. The outcome data can be accepted and reported only when the baseline of two groups is balanced; otherwise, the outcome data needs to be corrected and then can be reported.

12.1.3 Primary efficacy endpoints

Primary efficacy evaluation will be based on Full Analysis Set (FAS) and Per-Protocol Set (PPS). For the statistical description and inference of the data, the applicable descriptive endpoints and hypothesis testing methods will be selected based on the characteristics of the data.

The primary efficacy endpoint of this study is Lysholm score at 12 months after operation. The non-inferiority testing is performed for efficiency of primary efficacy endpoint, and the test hypothesis is as follows:

Invalid hypothesis: H0: $\mu1-\mu2 \leq -\delta$

Alternative hypothesis: H1: $\mu1-\mu2 > -\delta$,

where, $\mu1$ and $\mu2$ are the Lysholm scores in the investigational group and control group, respectively. δ is a non-inferiority critical value. At $\alpha=0.025$ (one-sided test), the hypothesis test is carried out using a two-sided t-test. A non-inferiority test is carried out on the Lysholm scores in the investigational group and control group. The 95% confidence interval between the two groups is calculated.

12.1.4 Secondary efficacy endpoints

The secondary efficacy evaluation is based on Full Analysis Set (FAS) and Per-Protocol Set (PPS).

Summary statistics of all other secondary variables will be given based on the nature of variables (continuous or classified variables). For continuous variables, the number of observations, mean, standard deviation, median, minimum and maximum will be reported. For classified variables, the number of observations, frequency and percentage will be reported.

12.2 Calculation of sample size

12.2.1 Total Sample Size

The primary efficacy endpoint of this study is the Lysholm score at 12 months after operation; the trial is designed as a non-inferiority trial. Accroding to references, the non-inferiority margin is set as 5 in this study. Assuming that the variance in both the investigational group and control group is 9, the difference between two groups is 0, the significance level is set to $\alpha=0.025$ (one-tailed), power $1-\beta=0.80$, the calculation formula of sample size is analyzed by referring to the non-inferiority of quantitative indicator:

$$n_T = n_C = \frac{2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 \sigma^2}{(D-\Delta)^2}$$

In which, σ is the standard deviation; D is the mean difference between two groups, which is expected to be detected, D=uT-uC; Δ is the non-inferiority margin. At least 51 subjects should be included in each group in order to achieve 80% power, 102 in total. In consideration of 20% drop-out rate, 64 subjects are planned to be included in each group, 128 subjects in total; 12 subjects are planned to be added to increase the success rate of trial, 140 subjects in total and 70 in each group.

The estimation of sample size is completed by using PASS13.

12.2.2 Number of Subjects with Each Disease in Clinical Trial and Reason for Determination

In this trial protocol, it is strictly required that patients should be enrolled in compliance with the inclusion/exclusion criteria. It can be considered that all the patients have the same type of disease, and are not further divided.

12.2.3 In multi-center clinical trial, minimum and maximum number of subjects in each clinical trial institution and justification

This trial will be carried out at the same time in a number of clinical study sites. In principle, the number of subjects enrolled in each site will be distributed as evenly as possible to ensure adequate site representation. However, considering the feasibility and progress of the enrollment, the number of subjects enrolled will be adjusted according to the actual situation to ensure that the enrollment scale at each site is relatively balanced, and that the final enrollment scale for a specific site should not exceed 50% of the total number of cases.

12.3 Significance level and power of the clinical trial

The statistical significance level takes the one-tailed significance level of α=0.025, 80% power (1-β).

12.4 Expected drop-out rate

Expected drop-out rate is not more than 20%.

12.5 Criteria for acceptability/unacceptability of clinical trial result

Primary efficacy endpoint (the Lysholm score at 12 months after operation): If the lower limit of 95% CI for the efficacy difference between two groups is greater than the non-inferiority margin, it is considered that the investigational product is non-inferior to the control product, the statistical hypothesis is valid and the result of clinical trial is qualified; otherwise, the hypothesis is invalid, and the result of clinical trial is unacceptable.

12.6 Criteria and reason for terminating the trial based on the statistical consideration

This trial does not include interim analysis and does not terminate the trial according to statistical reasons.

12.7 Statistical Method of All Data, Together with the Handling Method of Missing, Unused and Wrong Data (Including Discontinuation and Withdrawal) and Unreasonable Data

The statistical analysis plan is developed before the trial. The statistical analysis programming and logic test programming are conducted according to the statistical analysis plan after database locking, then the simulation database test is conducted and the statistical analysis plan is issued according to the results.

The Last Observation Carried Forward (LOCF) is used for imputation for missing data of primary efficacy endpoint. The handling of the outliers is to inquire the investigator about the unreasonable data and determine how to resolve the queries which are given by the data manager.

12.8 Reporting Procedure of Deviation from Original Statistical Plan

In the event of an "incomplete implementation of the statistical analysis plan", the change procedure should be applied in advance, such as changes in the statistical plan should be truthfully recorded in the statistical analysis plan, including changed position, change reasons, change time and other revision records.

12.9 Selection criteria and justification of subjects included in the analysis

12.9.1 Full Analysis Set (FAS)

Full Analysis Set (FAS): According to the basic principle of Intention To Treat (ITT), all subjects who are randomized in the trial and have at least one effectiveness evaluation are included in the Full Analysis Set. The Last Observation Carried Forward (LOCF) is used for analysis when the primary efficacy endpoint is missing.

12.9.2 Per-protocol Set (PPS)

Per Protocol Set (PPS): it refers to a set of subjects that complete the trial, excluding those with serious protocol violation.

12.9.3 Safety Data Set (SAS)

Safety Analysis Set (SS): Refers to all subjects who are randomly assigned to use the investigational device and have at least one baseline safety evaluation.

13 Feasibility analysis

13.1 Possibility analysis on success

Smith & Nephew is a leading enterprise in the domestic arthroscope industry and has a complete R&D, production and quality control (QC) system. The Biosure Regenesorb Interference Screw and similar products developed by Smith & Nephew have been marketed and used in foreign countries. Post-marketing supervision results show that no unexpected AEs and SAEs have been reported, demonstrating their safety and effectiveness.

The material and design of the investigational product in this trail meet the technical requirements of national registration and testing, the product has passed the testing of Quality Supervision and Inspection Center for Medical Devices successfully, and all the performance indicators are qualified.

The design of this clinical study protocol is in accordance with *Guidance for Clinical Trial Design of Medical Devices*, and is repeatedly discussed and demonstrated by clinical experts, clinical study sites, statisticians and internal experts of Smith & Nephew.

The clinical sites that undertake this trial have complete instruments, equipment and technical resources, and have passed the national certification for qualifications of clinical study sites. The investigators are outstanding academic leaders in the field of domestic sports medicine, with rich experience in clinical study, and can guarantee the smooth progress of clinical study.

13.2 Possibility analysis on failure

In the previous studies, most of the subjects were older patients. During the early follow-up of the trial, due to the limitation of functional recovery of patients after surgery, there was a phenomenon of loss to follow-up. In view of this problem, according to the *Guidance for Clinical Trial Design of Medical Devices*, the follow-up time is arranged scientifically, which not only ensures that the early recovery data of patients can be collected completely in the study, but also fully considers the convenience of patients' actions. In order to avoid the loss to follow-up of patients, in the informed process, the study team will fully emphasize the necessity for follow-up and the importance of protocol compliance with the patient, allowing the patient to fully understand the study procedures, arrange telephone follow-up at 4.5 months and 9 months, and ensure the integrity of the adverse event collection of patients during the trial, at the same time repeatedly confirm and remind the follow-up arrangements of patients in advance, and give compensation for the transportation cost from an ethical perspective.

Rating scale is a subjective evaluation index; in order to ensure consistency, each site should specify the fixed raters, who are given consistency training according to scoring criteria.

The grasp of inclusion and exclusion criteria is the key to the success of the trial. The sites and the Sponsor will provide sufficient training and the portable reminder cards for the investigators at the start of the trial. After the first patient is enrolled in each site, the inspector of Sponsor will arrange a visit to the study site to ensure that the understanding of the study sites for the inclusion and exclusion criteria as well as the grasp of the study sites for the process are in line with the protocol requirements.

14 Quality control of clinical trial

The quality assurance (QA) process is designed in each link of this study to ensure that the study is carried out according to the protocol, ensure that the complete and accurate data is submitted to the Sponsor in time, and ensure that complications or adverse events are immediately discovered and handled until the end of the trial. The investigators and study sites will provide direct access right to the original documents and study records for the audit of the Sponsor, the representative of Sponsor, EC and other regulatory authorities.

14.1 Study Monitoring

Clinical study monitoring is an important means to ensure the quality of clinical study.

This study will be monitored by the Sponsor or by qualified personnel designated by the Sponsor. Qualified personnel may be employees of the Sponsor, or may be from a contract research organization (the agent of Sponsor). The Sponsor will monitor according to the monitoring frequency and the monitoring contents specified in the monitoring plan. The monitoring contents include and are not limited to the following aspects.

The Sponsor, the agent of Sponsor, EC and regulatory authorities can directly access the source documents, so as to verify and evaluate the clinical data submitted by the investigator to the Sponsor through the CRF.

The investigator is responsible for obtaining and maintaining complete health information of subjects recorded in the medical records (original documents). The raw data includes all original record information and certified copies of the original records (including clinical findings, observations, or other activities used for study reconstruction and evaluation in clinical study).

Prior to the implementation of the clinical agreement, the Sponsor performs qualification evaluation visits to each study site to ensure that all investigators have received the corresponding training and that their personnel, facilities and resources are sufficient to carry out this study.

Details can be found in the section of "Monitoring Plan" of this trial.

14.2 Audit of Sponsor

The objective of audit is to ensure the quality of the clinical trial project, ensure that the risk of the trial is controllable and evaluate whether the implementation of the trial is strictly in accordance with the trial protocol and the standard operating procedure of the Sponsor; audit also check whether all study guidelines and quality standards are implemented, promptly discover any careless mistake and errors, ensure the authenticity and reliability of clinical data, and data traceability, and promote the investigators, monitors, CRC to perform their work better, put forward meaningful suggestions for the trial, and guide the project to carry out better.

Participation in the study means acceptance of an audit to the study site, and is independent of the monitoring follow-up, so as to assess the compliance with the protocol, guidelines and regulations. The auditor designated by the quality control department or his/her representative will be responsible for such visits. The Sponsor has the right to require the sites with poor trial quality to perform rectification.

14.3 Laboratory Quality Control

The laboratories of each study site should establish a unified standard for laboratory test indicators, standard operating procedures and quality control procedures. For the laboratory test items, the national legal measurement units must be adopted, the items of the test reports must be complete (including date, test items, test results and their normal ranges). Special test item(s) must be tested by a special person.

15 Ethical issues and informed consent of clinical trial

15.1 Ethical Considerations and Ethical Approval

This clinical study must follow the Declaration of Helsinki, and should be carried out according to the clinical study standards and regulations related to medical devices issued by International conference on Harmonization (ICH) and China.

Investigators are responsible for obtaining written and dated approval from an Ethics Committee (EC) prior to enrolling subjects. This approval should include the protocol, the informed consent form, subject recruitment materials, advertising or any written information that will be provided to subjects.

Investigators are responsible for maintaining EC approval throughout the study by submitting progress reports (continuing review reports) at least annually and more often if requested by the EC.

Withdrawal of EC Approval: The Investigator shall report to the Sponsor within 5 working days if, for any reason, the EC withdraws approval to conduct the investigation. The report will include a complete description of the reason(s) for which approval was withdrawn.

Progress Reports: The Investigator is required to submit annual progress reports to the study Sponsor and to the reviewing EC. Reports must include the number of subjects, a summary of all follow-up evaluations, a summary of all adverse events, protocol deviations and a general description of the study progress.

Final Report: The Investigator will submit a final report to the Sponsor and to the EC within 3 months of completion of the study, termination of the study or termination of that Investigator's participation in the study.

Other Reports: Upon request of the Sponsor, NMPA or the EC, the Investigator shall provide

accurate, complete and current information.

Additional documents that require the Investigator obtain written and dated EC approval during the course of the study include:

- Protocol amendments (should not be implemented prior to EC approval)
- Informed consent form revisions (Sponsor reserves the right to review all revised informed consent forms prior to submission as they relate to the Sponsor's obligations)
- Protocol deviation report
- Adverse events described in Section 16 of this protocol
- All other documents as required by the EC

15.2 Informed consent

Investigators are responsible for obtaining and documenting the voluntary informed consent of the study subjects prior to conducting any study-related assessments per International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

In obtaining informed consent, Investigators must adhere to GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to beginning the study, the Investigator must obtain written and dated EC approval of the informed consent form. The informed consent form and any other written information provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's continued consent. All revised informed consent forms must have written and dated EC approval in advance of use.

The communications with the subject regarding informed consent process (initial and subsequent) will be documented in the medical record. Subjects should receive a copy of the initial signed and dated informed consent form (in the local language) prior to the subjects' participation in the study and any revised informed consent forms during the duration of the study.

Use of device without Informed Consent: No subject may be treated with a study device without prior Informed Consent. Such treatment constitutes a violation of NMPA regulations. The Investigator shall submit a report indicating the circumstances for the occurrence to Smith & Nephew and to the reviewing EC within five working days after the use occurs.

16 Adverse Event Reporting and Complaint

16.1 Definition

An adverse event is defined as any untoward medical occurrence in a clinical investigation in which a subject is administered a study device and which does not necessarily have a causal relationship with the device. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study device, whether or not related to the study device.

Any events that occur newly or deteriorate in severity and frequency as compared with baseline conditions, or abnormal results found in the process of diagnosis, including abnormal laboratory findings, are included herein.

Note: The Sponsor collects the information on adverse events when the subjects sign the informed consent form.

The following are specific definitions of adverse events:

AE Adverse event - any untoward medical occurrence in a subject, regardless if there is a relationship between the AE and the device.

SAE Serious Adverse Event - an adverse event that:

A Serious Adverse Event is any AE that results in a death or a serious deterioration in the health of the subject during the clinical trial, including a life-threatening illness or injury, a permanent impairment of a body structure or a body function, in-patient hospitalization or prolongation of existing hospitalization, medical or surgical intervention to prevent permanent impairment of a body structure or a body function; or results in fetal distress, foetal death or congenital abnormality, congenital anomaly, etc.

ADE Adverse Device Effect – any untoward and unintended response to a medical device (This definition includes any event that is a result of a user error).

SADE Serious Adverse Device Effect – An adverse effect that has resulted in any of the consequences characteristic of a serious adverse event

UADE Unanticipated Adverse Device Effect - An “unanticipated adverse device effect” (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with this device which was not previously identified in nature, severity, or

degree of incidence in the application of the device.

USADE Unanticipated Serious Adverse Device Effect - Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

ASADE Anticipated Serious Adverse Device Effect - A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

DD Device Deficiency - An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance; Device deficiencies include malfunctions, use errors, and inadequate labeling.

16.2 Treatment for Adverse Events

In the event of an adverse event, the Investigator and/or other professional personnel in attendance will provide whatever appropriate therapy for the event. Under all circumstances, a suspected adverse event relating to the study device should be provided the adequate medical treatment.

16.3 Reporting of adverse events

16.3.1 Investigator Adverse Event Reporting

All AEs will be categorized according to the investigator's clinical judgment as mild, moderate or serious based on the following definitions:

Mild: The subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.

Moderate: The subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or well-being and may require medical intervention and/or close follow-up.

Serious: The adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

Reporting of adverse events to regulatory authorities will be undertaken according to the provisions of NMPA and guidances.

For all UADEs, SAEs, USADEs, SADEs and device deficiencies which may lead to a SAE, that occur during the course of the clinical study, once the investigator knows, he/she must take appropriate treatment measures for the subjects and report to the Sponsor and the study site of hospital immediately.

The administrative department of medical device clinical trials shall send written reports to corresponding EC, the food and drug administration of the concerned province or autonomous region or municipality directly under the central government, and the competent authority of health and family planning within 24h. Regarding adverse events of death, study sites and investigators should provide all required data to the corresponding Ethics Committees and Sponsor.

Details of all adverse events or device deficiency must be recorded on the adverse event/device deficiency forms provided and faxed/e-mailed to the contact of Sponsor where possible at the time of reporting. Please keep the fax report or print an email as a record of the time limit. The contact details are shown in the Section "1. Sponsor Information" of the protocol.

The Investigator must submit a detailed report that will identify the description of symptoms, classification of the event, date of onset, severity, treatment, and outcome. Supporting medical records may be obtained as an adjunct to an adverse event report and placed in the subject's study file.

During the clinical study, all serious and non-serious adverse events should be followed up to determine the final outcome.

All SAEs, which haven't been resolved at the end of the study or when the subjects withdraw prematurely from the study, must be followed up until one of the followings is achieved:

- The event is resolved
- Achieve stable state
- Reasonable explanation is provided
- Lost to follow-up or death
- The event restores to the baseline level (if the baseline value is available)
- When it is impossible to obtain more information (the patient or medical staff refuses to provide more information, and there is evidence showing that the patient is still lost to follow-up after the medical staff tries his/her best)

Once a subject has completed the study, the investigator should follow up for outcomes on all AEs

classified as possibly/definitely related to the investigational product and all serious adverse events until a final outcome can be determined or the end of the whole study (last subject last visit), whichever comes first.

During the subject's participation in the trial, any event that caused hospitalization or prolonged hospitalization must be reported as a serious adverse event, unless because of:

- Hospitalization for social reasons rather than adverse events
- Surgery or operation that has been planned prior to participation in the trial (must be recorded in the original medical record and CRF)

16.3.2 Sponsor Adverse Event Reporting

For the serious adverse events and the device deficiencies that may cause serious adverse events, Smith & Nephew should report to the food and drug administration and the competent authority of health and family planning at the same level where the device is registered within 5 workdays after being informed. Smith & Nephew should also inform other study sites and investigators that participate in the trial, and timely inform the Ethics Committee of such study site through its administrative department for clinical trial of medical device.

16.3.3 Causal relationship between AEs and the device and its evaluation criteria

The AE is set to be related to the device in case of being "extremely probably related", "definitely related" and "probably related"; in case of other classification, the AE is set to unrelated to the device.

Classification	Description
Definitely un-related	The AE is identified as a result of a concomitant disease or the effects of another device/drug and is not related to the investigational product.
Probably un-related	The AE is more probably caused by other reasons and will not be improved or its prognosis is difficult to be judged after device withdrawal. Its recurrence is not found or difficult to be judged after device reuse.
Probably related	The occurrence of the AE meets the reasonable time sequence upon device use. The AE may be caused by the device or other reasons. It is improved

	after device withdrawal.
Extremely probably related	The occurrence of the AE meets the reasonable time sequence upon device use. The AE is more reasonably attributed to the used device than other reasons. It is improved after device withdrawal.
Definitely related	The occurrence of the AE meets the reasonable time sequence upon device use. The AE is more reasonably attributed to the used device than other reasons. The AE mode is consistent with the previously known mode caused by the device. The AE is improved after device withdrawal but appears after device reuse.

16.3.4 Causal relationship between AEs and surgery and its evaluation criteria

The AE is set to be related to the operation in case of being "extremely probably related", "definitely related" and "probably related"; in case of other classification, the AE is set to unrelated to the operation.

Classification	Description
Definitely un-related	The AE is identified as a result of a concomitant disease or the effects of another device/drug and is not related to the operation.
Probably un-related	The AE is more probably caused by other reasons and will not be improved or its prognosis is difficult to be judged in case of no operation/upon operation. Its recurrence is not found or difficult to be judged in case of operation.
Probably related	The occurrence of the AE meets the reasonable time sequence of operation. The AE may be caused by the operation or other reasons. It is improved upon operation completion.
Extremely probably related	The occurrence of the AE meets the reasonable time sequence of operation. The AE is more reasonably attributed to the operation than other reasons. It is improved upon operation completion.
Definitely related	The occurrence of the AE meets the reasonable time sequence of operation. The AE is more reasonably attributed to the operation than other reasons. The AE mode is consistent with the previously known mode

	generated in the operation. The AE is improved upon operation completion but appears in case of re-operation.

16.3.5 Device Deficiency

The device deficiency is defined as unreasonable risk occurred under normal use of medical device during the clinical trial, which may do harm to the human health and life safety, such as label error, quality problem and fault.

The investigators should timely report the device deficiency to the Sponsor and evaluate results of device deficiencies. The device deficiencies that may cause severe adverse events need to be reported as required by the GCP.

Device deficiencies must be observed intra-operatively and post-operatively, e.g. screw breakage.

17 Protocol Amendment and Protocol Deviation

17.1 Protocol Amendment

If neither the investigator nor the Sponsor has reached an agreement, either party is prohibited from modifying the protocol. Only after consulting and agreeing to amend, the protocol can be revised. Protocol amendment may affect the scientificity, or infringe the rights, safety or health of subjects, which should be submitted to the regulatory authorities and EC for approval before the implementation of the protocol amendment.

17.2 Protocol Violation by Individual Subjects in Emergency

An individual subject is allowed to violate the protocol only if measures are required to be taken to protect the life or physical health of the subject in an emergency, and such violation is limited to this subject. The investigator or other attending physician handling the situation should inform the EC and call the clinical study manager of Smith & Nephew (within 48 hours) (see study contact on page 13). If the study manager cannot be contacted, the investigator should contact the second contact of the Sponsor; see page 13 for details.

The investigator and Smith & Nephew should decide whether the subject who violates the study protocol can continue to participate in the study. Any protocol violations will be recorded in the written report of the investigator. The investigator should send the report and the reasons for the

violation (including the relationship with the therapeutic use of the device) to EC and Smith & Nephew. The EC can also determine that the subject should not continue to participate in this study.

17.3 Protocol deviation

Protocol deviation is defined as any case of non-compliance with the study protocol. Once the study site finds a protocol deviation, it should be reported to Smith & Nephew. According to the requirements, the investigator must also report the protocol deviation to the EC.

For protocol deviations, it is minimally required to report major protocol deviations, including GCP deviations, events affecting safety of subjects (inclusion/exclusion criteria), impact of examination or operation on study results, and the process of obtaining informed consent. A protocol deviation is judged as a major or minor one based on the information whether to affect the safety of subjects, whether to affect the study results and whether to affect obtainment of informed consent.

18 Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with the Good Clinical Practice for Medical Device Clinical Trials and regulatory and institutional requirements. In order to protect the safety and rights and interests of the subjects, to ensure the authenticity, accuracy and integrity of the study progress and data, each study site should allow and cooperate with the Sponsor's monitors, quality assurance personnel, regulatory authorities and authorized representatives to perform quality review and audit. In order to complete the above activities, the above personnel should have the right to access, review or verify source data or source files.

Source data is all information, original records of clinical findings, observations, or other activities in a specific clinical trial necessary for the reconstruction and evaluation of the trial. These original documents and data records include, but are not limited to, inpatient or outpatient medical records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, transportation, delivery, use and recovery records of the device, recorded audio tapes of counseling sessions, recorded data from automated instruments, copies certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and ancillary departments involved in the clinical trial. The CRF for recording scales is saved as a source

document. The Adverse Event and Serious Adverse Event Report Form contains more information than medical records and should be considered as the source document. In the inpatient and outpatient medical record system of the hospital, the severity of adverse events and the causality judgments are usually not recorded, and there is a lack of records of correlation between the concomitant medication and adverse events. Therefore, the Sponsor will provide corresponding forms as source documents to save and record relevant information.

19 Finance and Insurance

19.1 Surgical instruments

After the Ethics Committee of the hospital approves the start of the clinical study, the Sponsor sends the investigational device to each study site. Only qualified personnel participating in this study is allowed to receive the investigational product. When the investigational device is delivered to each site, the complete inventory list should be provided. When there are any discrepancies between the contents recorded in the device transport form and the objects provided, they should be indicated on the transport form and immediately informed to the Smith & Nephew company. The device transport forms need to be kept in the folders of the study site. For any devices received, their quantity and size should be recorded in the device inventory log.

During the study process, the investigator must fully record the receipt, use, loss and disposal of the investigational product in the device study log to ensure that the storage and distribution of the investigational device is always under supervision. All device supplies must be stored in accordance with the conditions specified by the manufacturer, while complying with applicable regulatory requirements. The investigational device must be stored separately from the usual facilities/conventional items in the hospital. Until distribution prior to operation, all investigational devices must be stored in a safe locked area according to the conditions required in the instructions for use and only authorized personnel is allowed to enter.

It is the responsibility of the investigator to ensure that the investigational device inventory is sufficient and is only used for the subjects enrolled in this study. When the inventory is insufficient, the Sponsor should be contacted in advance. In addition, the Sponsor will coordinate as necessary to ensure supervision.

According to the instructions of the Sponsor, the investigator should return all remaining devices after completing the recruitment of subjects in this study.

19.2 Others

Clinical study sites and principal investigators should properly manage the surgical tools, investigational devices and test equipment in accordance with regulations of applicable guidelines and trial protocol. The clinical study sites and the principal investigators cannot use and permit the use of the investigational devices and test equipment for any purpose other than the implementation of this trial, and will follow applicable guidelines, trial protocol and any instructions given by the Sponsor regarding any operation, maintenance or storage of the investigational devices and test equipment. Upon termination or expiration of this Agreement, according to the Sponsor's choice, all unused investigational devices and test equipment should be returned to the Sponsor or be disposed according to the written instructions of the Sponsor.

The Sponsor purchases insurance for this study.

20 Contents of the clinical trial report

A clinical study summary is issued after each sub-site completes the clinical study. The clinical trial report is also issued. All sub-sites confirm the contents of the summary report and submit it after signing and stamping. The clinical trial report should be consistent with the clinical trial protocol, mainly including:

- General information;
- Synopsis;
- Introduction;
- Clinical trial objective;
- Clinical trial method;
- Contents of clinical trial;
- General clinical information;
- Investigational medical device;
- Statistical analysis methods and evaluation methods adopted;
- Clinical evaluation criteria;

- Organizational structure of clinical trial;
- Ethical compliance statement;
- Clinical trial results;
- Adverse events found in the clinical trial and their handling;
- Analysis and discussion of clinical trial results, especially the indications, scope of application, contraindications and precautions;
- Conclusion of clinical trial;
- Existing problems and improvement suggestion;
- List of investigators;
- Other conditions that need to be described.

21 Confidentiality Principle

21.1 Disclosure

Clinical data obtained in this study will not be disclosed by the Sponsor other than for the purposes outlined in the protocol. Anonymized personal information may be used by the Sponsor within China or elsewhere in the world.

Personal data will be collected and processed to:

- Check subject suitability to take part in the study
- Monitor treatment with the investigational device
- Compare and incorporate treatment results with those of other subjects in clinical studies
- Support the development of the investigational device
- Support the licensing application for regulatory approval of the investigational device in the world
- Support the marketing, distribution, sale and use of the investigational device anywhere in the world.

21.2 Data Security and Confidentiality

Clinical study sites and principal investigators should truthfully, accurately, completely and timely

collect, record and submit data specified in the trial protocol to Smith & Nephew (or the related party of Smith & Nephew according to the instructions of Smith & Nephew) in accordance with the regulations of applicable guidelines and the trial protocol, including CRF (whether in paper or electronic form) and any other documents or materials which are developed for this trial and should be submitted to Smith & Nephew (hereinafter collectively referred to as "trial data"). Clinical study sites, principal investigators and Smith & Nephew should properly handle and save trial data in accordance with the regulations of applicable guidelines and trial protocol. It is agreed by each party that the trial data is exclusively owned by Smith & Nephew, but Smith & Nephew does not claim ownership of such medical records of subjects that may contain some trial data.

All parties should follow the principles of medical confidentiality related to the subjects involved in this trial. The principal investigator and clinical study sited may disclose the personal data specified in the relevant data protection laws applicable to the clinical study site (the "relevant data protection regulations") to Smith & Nephew (or the related party of Smith & Nephew according to instructions of Smith & Nephew) only if disclosure is necessary to meet the requirements of the trial protocol or for the purposes of monitoring, adverse event reporting or investigation, or claims or proceedings brought by subjects in respect of this trial. Except in accordance with the relevant data protection regulations, neither party can disclose the identity information of subjects to any third party other than Smith & Nephew and its related party without the prior written consent of subjects, unless such disclosure is related to the claims or proceedings brought by subjects in respect of this trial.

Each party should ensure that any confidential information disclosed to the other party is only disclosed to the managers and employees (in terms of Smith & Nephew, related party of Smith & Nephew and their respective managers and employees are also included) directly involved in the implementation of this agreement. In addition, all parties should keep strictly confidential and cannot disclose any such confidential information of the other party to any third party, except as required by the regulatory authorities or the law. The party requiring disclosure should notify the other party in advance on the disclosure requirements and the information to be disclosed within a reasonable time before the disclosure is required. Each party undertakes not to use any such confidential information of the other party for the purposes other than this agreement without the prior written consent of the other party.

22 Agreement on the Publication of Study results

The main objective of this study is to support the registration of investigational device in China

researched and developed by Smith & Nephew. However, after the study is completed, the study results may be submitted and announced. The publication policy is detailed in the Clinical Trial Agreement (CTA). If the investigator wishes to publish the clinical study results or the results of the activities in the clinical study, the manuscript should be submitted to Smith & Nephew for review before the manuscript for publication is submitted. Before publication of the total study or at 2 years after the end of the study (based on the earliest time), any sites may not publish this study.

After completion of this trial, the principal investigator should collate the data generated from this trial for publication. The principal investigator should submit the data and materials to be publicly disseminated to Smith & Nephew at least sixty (60) days in advance, and can submit them for publication, public dissemination or review by the publication committee after obtaining the written consent of Smith & Nephew; and the principal investigator should write the reasonable revision comments proposed by Smith & Nephew into the contents to be published. If Smith & Nephew considers that any contents to be published contain any information related to applicable patent matters, disclosure of the contents to be published by the clinical study site and/or principal investigator to any third party may be delayed by up to six (6) months in order to allow Smith & Nephew to submit the relevant patent application.

The principal investigator has the right to introduce the methods and results of this trial at seminars and academic conferences, or to publish them in journals or academic dissertations, or though other ways. Such rights may be exercised before or after the methods and results of the trial are disclosed in any other manner, but the specific contents should have been previously reviewed and approved by Smith & Nephew.

23 Responsibilities of each party

23.1 Responsibilities of Sponsor

The Sponsor is responsible for the initiation, application, organization and monitoring of a clinical trial and is responsible for the truthfulness and reliability of the clinical trial.

The Sponsor is responsible for the organization to establish and modify the investigator's brochure, clinical trial protocol, informed consent form, CRF, relevant standard operating procedures and other relevant documents, and carry out the training required for the clinical trial.

The Sponsor should, according to the characteristics of the investigational medical device, select the study sites and the investigators with qualifications. Before signing the clinical trial protocol with

the study site, the Sponsor should provide the latest investigator's brochure and other relevant documents for the study site and investigators, for their decision whether they can undertake this clinical trial.

During the clinical trial, in case of important information affecting the study process, the Sponsor should accordingly revise the investigator's brochure and related documents in a timely manner, submit through the study site's administrative department for clinical trial of medical device to the Ethics Committee for review and approval.

The Sponsor is responsible for the safety of investigational medical device in clinical trial. When the trial is found to affect the safety of the subjects or the trial implementation may change the approval of the Ethics Committee to continue the trial, the Sponsor should immediately notify all study sites and investigators and deal with them accordingly.

Where suspension or termination of the study is decided, the Sponsor should notify all the administrative departments for clinical trial of medical device of all the study sites within 5 days, and give reasons in writing. The administrative department for clinical trial of medical device of all the study sites should notify promptly corresponding investigators and Ethics Committees. The suspended clinical trial should not be resumed without the consent of the Ethics Committee. Upon end of clinical trial, the Sponsor should report in writing form to the local food and drug administration at the provincial, autonomous regional and municipal level.

Ensure that all investigators who implement clinical trials strictly follow the clinical trial protocol and correct any incompliance of the study sites and investigators with the relevant laws and regulations, the GCP of medical devices and the clinical trial protocols; in case of serious violation or absence of rectification, the trial should be terminated and the report should be reported to the food and drug administrations of province, autonomous region and municipalities directly under the Central Government where the study site is located and to the China Food and Drug Administration.

The Sponsor should bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of subjects, with the exception of damages due to the fault of medical institution and medical staff in the diagnosis and treatment.

The Sponsor should be responsible for monitoring the clinical trial and selecting qualified CRA to perform monitoring duties.

For the multi-center clinical trial, the Sponsor should ensure that the protocol document has been established before the clinical trial, giving clear assignment of responsibility of the coordinating investigator and other investigators.

23.2 Responsibilities of Study Sites and Investigators

The study sites should evaluate the relevant resources according to the features of investigational medical device prior to the clinical trial, so as to decide whether to perform this clinical trial.

It is the responsibility of the investigators to ensure that the study is carried out in accordance with the clinical study agreement, this protocol and applicable local laws and regulations. About the definition of responsibilities of the investigator, please refer to the Good Clinical Practice for Medical Devices.

The administrative department for clinical trial of medical device of study site should cooperate with the Sponsor to apply to the Ethics Committee and submit the relevant documents prior to the clinical trial according to requirements.

The investigators should ensure that the relevant staff involved in the trial are familiar with the principles, scope of application, product performance, method of operation, installation requirements and technical specifications of the investigational medical device, understand the pre-clinical study data and safety data of the investigational medical device, and grasp the prevention and emergency treatment methods of possible risk in clinical trial.

The investigators should ensure that all clinical trial participants are fully aware of the clinical trial protocol, the relevant regulations, the characteristics of the investigational medical device, and the responsibilities associated with clinical trials, and ensure that a sufficient number of subjects who meet the criteria for inclusion in clinical trials are admitted to clinical trials, and ensure that there is sufficient time to securely implement and complete the clinical trial within the agreed study period of the agreement according to the relevant provisions.

The investigators should ensure to use the investigational medical device only for the subjects of this clinical trial, and may not charge any fee.

The investigators should strictly follow the clinical trial protocol, and should not deviate from the protocol or substantially change protocol without the consent of the Sponsor and the Ethics Committee or without approval from the China Food and Drug Administration as required. Where there is emergency in which the subject faces the direct risk and which needs to be immediately tackled, report can be submitted in writing afterwards.

The investigators are responsible for recruiting the subjects, communicating with the subjects or their legal guardians. The investigators have a responsibility to explain to the subject the related

details of the investigational medical device and the clinical trial, inform the subject of possible benefit and known, foreseeable risk, and obtain the signature and informed consent dated of the subject or his/her guardian.

The investigators or other personnel participating in the trial should not compel or induce the subject to participate in the trial in any other improper manner.

In clinical trials, when investigators found unexpected adverse events of the investigational medical device, they should modify the relevant contents of the informed consent form together with the Sponsor. After reporting to the Ethics Committee for review and approval in accordance with the relevant work procedures, the affected subjects or their guardians resign and confirm the amended informed consent form.

The investigators are responsible for making medical decisions related to clinical trials. In the event of adverse events associated with clinical trials, the study site and the investigator should ensure that the subject is provided with adequate and timely treatment and management. The investigators should inform the subjects in time when the subjects suffer from concurrent diseases requiring therapy and treatment.

In case of any SAE during the clinical trial, the investigators should immediately take appropriate therapeutic measures for subjects, report the event in written to the administrative department for medical device clinical trial of the study sites, and then the study site reports the event to the Sponsor in writing. The administrative department of medical device clinical trials shall send written reports to corresponding EC, the food and drug administration of the concerned province or autonomous region or municipality directly under the central government, and the competent authority of health and family planning within 24h. Regarding adverse events of death, study sites and investigators should provide all required data to the corresponding Ethics Committees and Sponsor.

The investigators should record all adverse events occurred and device defects found during the clinical trial, work with the Sponsor to analyze the causes of the events, prepare the written analysis report, make decision on whether to continue, suspend or terminate the trial. The decision will be reported to the Ethics Committee for review by the administrative department for clinical trial of medical device in the study site.

The study site and investigator should accept the monitoring and audit of the sponsor, and the supervision of the Ethics Committee, and provide all required records related to the trial. When the food and drug regulatory authorities and competent departments of health and family planning send

the inspection personnel to carry out the inspection, the study site and investigator shall cooperate with them.

When the study site and investigator conclude that the risk outweighs the possible benefit or that the safety and efficacy of the investigational medical device have been validated, and suspension or termination of the trial may be necessary, the subjects should be informed and it should be ensured that the subjects can receive the proper care and follow-up. The study site and investigator should also report in accordance with the provisions, and provide the detailed written explanation. Relevant report should be submitted to the local food and drug administration at the provincial, autonomous regional and municipal level if necessary.

When investigator is notified by the Sponsor or the Ethics Committee to suspend or terminate the clinical trial, the subjects should be informed, and it should be ensured that the subjects can receive the proper care and follow-up.

When the sponsor alters the trial data and conclusions in violation of the relevant provisions or requirements, study sites and investigators should report to the food and drug administration of the province or autonomous region or municipality directly under the Central Government where the sponsor is located or CFDA.

The investigators should ensure to complete all records and reports at the end of clinical trial. At the same time, the investigators should also ensure that the investigational medical device received is consistent with the amount used, discarded and returned, ensuring that the remaining investigational medical device is properly processed and documented.

Investigators may, based on the need of clinical trial, authorize the relevant staff to undertake the subject recruitment, communication with subjects, recording of clinical trial data and management of investigational medical device. The investigator shall provide training for the authorized persons and form the corresponding document.

The investigator should make sure that the clinical trial data are accurately, completely, clearly and timely recorded into the CRF. CRF is signed by the investigator, and any data changes should be signed and dated by the investigator; meanwhile, the original record should be retained and should be legible. The study sites and investigators should make sure that the data, documents and records generated in the clinical trial are true, accurate, clear and safe, including but not limited to the following data:

- Communications with the Sponsor, clinical monitors, other investigators, EC or NMPA/regulatory authorities.

- Signed investigator agreement as well as resumes of the principal investigator and any important investigators.
- The records of subjects in the study include: informed consent form with signature and date, all original documents, CRFs of subjects, data query and the use record of devices by each subject;
- All relevant observations, including records and reports of adverse reactions (whether expected or unexpected);
- The date and detailed reasons for all versions of the study protocol and any protocol deviations (which may affect the scientific quality of the study or rights, safety or health of subjects);
- Approved blank informed consent form and blank case report form of subjects;
- All necessary study documents

The study sites should properly keep the records and documents of clinical trial according to the agreement with the Sponsor until 10 years after the end of the clinical trial. Prior to the transfer or destruction of the study documents, the investigators must obtain the written consent of the Sponsor. If the investigators are unable to save these records in their file, the investigators must obtain permission from the Sponsor to make other arrangements. If the investigator leaves the study site, another responsible person must be appointed to keep these records. The specific arrangements need to be recorded in a written form, and then submitted to the Sponsor and the EC.

The responsibilities of each party are detailed in the Clinical Trial Agreement.

24 Bibliography

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using V-Y tendinous flap and transfer of flexor hallucis longus tendon [J]. Chinese Journal of Orthopaedic Trauma, 2008(3):238-241.

Investigator's Statement

I agree:

1. To conduct this clinical trial in strict compliance with Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol.
2. To accurately record all data required into the Case Report Form (CRF) and complete the report of the clinical trial on time.
3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained throughout the clinical trial.
4. To allow CRA and auditor authorized by the Sponsor as well as regulatory authorities to conduct monitoring, verification and inspection on the clinical trial.
5. To strictly perform the articles of clinical trial contract/agreement signed among parties.

I have already read the clinical trial protocol entirely, including the above statement and I fully agree all the above contents.

Comments of investigator

Signature:

MM/DD/YYYY

Comments of sponsor

Signature (stamp)

MM/DD/YYYY

Comments of medical device study site GCP office

Signature (stamp)

MM/DD/YYYY