Protocol Number: XG2114

Study Protocol

A Clinical Study to Evaluate the Safety and Efficacy of Biologic Hollow Bone Screws

Name of Experimental Medical Device: Biologic Hollow Bone Screws

Clinical Trial Institution: The First Affiliated Hospital of PLA Air Force Medical University

The Sponsor: Jiangxi Sike Biotechnology, China

Collaborative Research Organization: Nanjing Sigma Medical Technology Co., LTD

NCT Number:

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Experimental Design

1. Object

To evaluate the safety and efficacy of biologic hollow bone screws for the fixation of fractures in knee joint and ankle joint.

2. Experimental Method

According to the Guiding Principles for Clinical Trial Design of Medical Devices, a prospective, multicenter, randomized, single-blind, parallel-controlled clinical trial was designed, and the comparison type was non-inferior design.

Randomization Method: Subjects will be enrolled in this clinical trial after signing informed consent and meeting the inclusion criteria but not the exclusion criteria. The sample size and block length were set using the system generation or a seed number specified by the randomizer. The random number table required for the test was generated by the PROC PLAN process, and the random number table was introduced into the random system. According to the random system grouping, the subjects were randomly assigned to the experimental group or the control group, and the ratio of the experimental group and the control group was 1:1.

Masking (Single): The researchers can visually distinguish the experiment products and the control products, so the researchers cannot be blinded and the participants were blinded.

Non-Inferior Design: The control product is a marketed device whose efficacy/safety has been recognized, so the non-inferior design is used. If the difference in efficacy/safety between the test device and the control device is less than the pre-set non-inferiority threshold, the difference is within the clinically acceptable range.

Selection of Reference Products: At present, there is no biological bone hollow screw with the same principle and material in China. According to the Guiding Principles for Clinical Trial Design of Medical Devices, priority should be given to commercially available similar products whose efficacy and safety have been clinically recognized when selecting positive controls. And if reasonable reasons cannot be used for similar products already on the market, a product as similar as possible can be used as a positive control. Therefore, the absorbable screw (Inion Freedom Screw) developed by Inion Oy, Finland, was selected as the control product in this clinical trial.

3. Measures to Reduce and Avoid Bias

Investigator Training: Before the start of the clinical trial, the supervisor and the principal investigator of each trial center should train the investigators on the trial protocol and product use, so that the investigators can understand and master the trial products, trial protocol and process.

Clinical Trial Monitoring: The sponsor will appoint an auditor to

conduct regular on-site monitoring visits to the trial hospital to ensure that all aspects of the study protocol are strictly adhered to, and the CRF will be checked to ensure that the content is consistent with the original data.

4. The Diagnosis and Treatment Methods of Experimental and Control Medical Devices

4.1 Instructions for the Installation and Use of Experimental Devices

According to the specific conditions of each patient, the selection of the appropriate model and size of the implant is an important factor affecting the success rate of surgery. After implantation, the implant will be in a repetitive stress environment for a long time, so attention must be paid to patient selection, proper placement of the implant, postoperative care and functional rehabilitation to minimize the stress on the implant, otherwise such stress may lead to material fatigue and subsequent fracture, bending or loosening of the implant before bone healing is achieved. This can cause damage or require early removal of the implant.

4.2 Before Surgery

(1) Only those patients who meet the indication criteria should be selected.

(2) The condition described in the contraindications section above should be avoided.

(3) In the process of transportation and storage, avoid collision, scratches

or other forms of damage to the implant. Special care should be taken to make the storage environment of the implant.

(4) The surgeon should be familiar with the use of this product and its supporting instruments before use, and confirm that they are ready before the operation.

(5) The type of implant that should be used in each surgical patient and the approximate size range should be determined before the operation begins. A sufficient number of implants of various sizes should be prepared for surgery, including those larger and smaller than expected.

(6) Unless packaged in sterile form, all instruments should be cleaned and sterilized prior to use.

4.3 During Surgery

(1) For Easy and Safe Screw Insertion:

A. The fracture site should be anatomic reduction or functional reduction. The 1.2mm Kirchner needle should be drilled to the required depth, and the nail path should be established along the Kirchner needle using a hollow drill.

B. Insert the appropriate size tap along the Kirschner needle to form the thread path. The size is consistent with the intended screw length. Screw in to the same depth as the corresponding screw length. Screw into the appropriate depth, counterclockwise out of the tap.

C. Select the appropriate size of the bio-type bone hollow screw and

press the screw head into the tail of the screw to ensure that the whole screw can be picked up. Screw along the Kirschner needle until complete implantation into the bone. The screw and screw are kept parallel to the direction of the bone.

(2) Ensure aseptic operation during the surgery.

(3) Peripheral nerves and blood vessels should be protected during operation.

(4) Breakage, slip or misuse of an instrument or implant during implantation may result in injury to the patient or the surgery.

(5) For more detailed surgical instructions, please refer to the appropriate surgical technical literature.

4.4 After Surgery

(1) The physician should provide the patient with a detailed description of the limitations of the product. Patients should be warned that complications such as bending, loosening or breaking of the implant may be caused by excessive weight bearing, excessive muscle activity or sudden impact on the surgical site. Patients should be told how to limit and control physical activity and advised to avoid strenuous exercise and excessive weight bearing.

(2) During the healing stage of the fracture, the physician should advise the patient not to smoke or drink too much alcohol.

(3) It is very important to confirm whether bone healing occurs after the

operation by X-ray. Bone non-union or delayed healing during the treatment stage will cause the implant to be subjected to repeated stress for a long time, which may fatigue the product and eventually bend, loosen or fracture. Therefore, if non-healing occurs or if the implant is loose, bent or broken, the implant should be adjusted or removed when serious damage is imminent.

(4) Any removed implants should be properly disposed of to ensure that the product will not be used in other surgeries.

4.5 Control Instrument Operation Methods

The operation was carried out by professional doctors participating in this clinical trial according to the instructions.

4.6 Product Information

Items	Experimental Device	Control Device
Name	Biologic Hollow Bone Screws	Inion Freedom Screws
Type	SL30, SL32, SL34, SL36, SL38, SL40, SL42, SL44, SL46, SL48, SL50	Diameter :3.5mm/4.5mm Type: Hollow screw
Main Components	The product is made of silk fibroin protein, and the degradation products are amino acids and peptides, which are harmless to human body. The structure includes head thread, tail thread, rod part and hollow hole. The screw is a double-headed compression screw to achieve compression fixation at both ends of the fracture. It is hollow structure, which is not only easy to guide needle through, but also conducive to bone trabecular growth. Co60 irradiation sterilization package.	The product consists of an absorbable screw (L-lactic-D mixed with L-lactic acid copolymer) and a metal adapter (auxiliary screw screwing without contact with the human body). Made of 316 stainless steel according to ASTM F899 standard. Sterilized packaging.

Application	Used for fixation of fractures of the knee joint and ankle joint	Used in conjunction with suitable auxiliary fixation, such as a strong fixation implant, cast, or brace, intended for reduction of a fracture during fracture healing Maintain.
Source	Jiangxi Sike Biotechnology Co., LTD	Inion Oy Company, Finland.
Registration Number	NA	National Medical Device Registration: 20153130029

5. Subject Selection

5.1 Inclusion Criteria

(1) Aged 18-75 years old (inclusive), both sexes;

(2) Patients with knee and ankle fractures requiring internal fixation confirmed by imaging examination;

(3) Voluntary participation in the clinical trial and signing of the informed consent.

5.2 Exclusion Criteria

(1) The following conditions exist at the fracture site: infection, osteofascial compartment syndrome, osteitis, pathological fracture, open fracture, severe tissue or vascular and nerve injury, or insufficient bone mass of the affected limb affecting screw implantation, etc.

(2) Abnormal liver and kidney function with clinical significance (ALT, AST 2 times the upper limit of normal value and Cr 2 times the upper limit of normal value);

(3) Abnormal coagulation function with clinical significance (APTT > 2

times the upper limit of normal value);

(4) Patients with difficult-to-control diabetes (any blood glucose > 11.1mmol/L or glycosylated hemoglobin > 9%);

(5) Past allergies to silk protein materials;

(6) Mental illness;

(7) Patients who cannot guarantee to quit smoking during the fracture healing period;

(8) Pregnant or lactating women or women of childbearing age who plan to get pregnant within 6 months;

(9) Those who have participated in other pre-clinical trials within 1 month before the trial;

(10) Those who are considered inappropriate to participate in the clinical trial.

5.3 Remove Criteria

(1) No devices were used after enrollment.

(2) Violation of inclusion or exclusion criteria.

5.4 Drop-out Criteria

All subjects who signed informed consent and were screened for inclusion in the trial, regardless of when and for any reason, were drop-out cases, including:

(1) The subject requested to withdraw from the clinical trial.

(2) Adverse events or serious adverse events (SAE) occurred, which

prevented the subject from continuing to participate in the trial.

(3) The subjects had poor compliance or lost follow-up, and failed to follow up according to the trial protocol.

(4) The investigator considers it medically necessary to suspend the subject test.

5.5 Criteria and Procedures for Trial Termination

(1) Major errors or deviations in the clinical trial protocol are found in the trial, making it difficult to evaluate the safety and effectiveness of the test products.

(2) The sponsor (e.g., for financial reasons, administrative reasons, etc.) requested termination of the trial.

(3) The administrative authority revokes the trial.

In case of the above situation, the sponsor shall promptly notify the researchers, the medical device clinical trial institutions and the ethics Committee. For subjects who have been treated with experimental devices, the sponsor shall fulfill its responsibilities to the subjects during the trial in accordance with the contents of the signed informed consent.

5.6 Group Entry Time

After signing the informed consent form, meeting the inclusion criteria and not meeting the exclusion criteria, the time when the subject underwent randomization was the enrollment time.

5.7 Expected Duration of Participation for Each Subject

According to the Guiding Principles for the Technical Review of Product Registration of Metal Intramedullary Nail System and the Guiding Principles for the Technical Review of Registration of calcium phosphorus/Silicon bone filling Materials, the clinical healing time of periarticular fractures of limbs is about 24 weeks, and the tissue reaction of degradable implants should be followed up until the tissue reaction of the products reaches a stable state after implantation. According to the literature search of controlled products, absorbable screws can reach a stable state about 12 months after implantation. In order to fully observe the clinical safety of the product, the participation time of each subject will be 18 months after surgery, so the expected participation time of each subject is about 18 months.

5.8 The Expected Overall Duration of Clinical Trials and the Reasons for Determination

The overall duration of the clinical trial includes the ethical approval of all clinical trial institutions and the modification of opinions after the ethical review, the signing time of the clinical trial agreement, the filing time of the clinical trial, the start of the clinical trial, the enrollment time and the examination time of the subjects, the collection time of clinical trial data, the statistics time and the writing time of the summary report. Combined with the number of cases to be completed in this study, the number of cases in each research center and other factors, the final

estimated time to complete this clinical trial is about 18-22 months.

5.9 Number of Subjects Required for Clinical Trials

A total of 160 subjects were planned to be included, and 80 subjects in the experimental group and the control group respectively. The trials were conducted in 6 medical institutions qualified to carry out clinical trials of medical devices, and were distributed according to the capacity of the medical institutions to bear the number of subjects and the principles of statistics.

6 Effectiveness Evaluation

6.1 Validity Parameter

6.1.1 Primary Outcome: Clinical fracture healing rate at 24 weeks after surgery

6.1.2 Secondary Index:

(1) Clinical fracture healing rate at 12, 48 and 72 weeks after surgery

(2) Pain score

(3) Joint function score

(4) Device performance index

6.2 Description of Validity Parameters

6.2.1 Main Efficacy Evaluation Index: Clinical fracture healing rate at 24 weeks after surgery

Evaluation Criteria:

(1) No local tenderness and longitudinal tapping pain, no local

abnormal activity.

(2) The X-ray shows a continuous callus or trabecular bone across the fracture line, which has been blurred.

Note: If both of the above two points are satisfied, it is considered healed; otherwise, it is not healed.

Healing rate = (Healing cases/Total cases) × 100%

Evaluation Time: 24 weeks ± 4 week

6.2.2 Secondary Efficacy Evaluation Index

(1) Evaluation criteria for clinical fracture healing rate at 12, 48 and 72 weeks after surgery:

A. No local tenderness and longitudinal tapping pain, no local abnormal activity.

B. The X-ray shows a continuous callus or trabecular bone across the fracture line, which has been blurred.

Note: If both of the above two points are satisfied, it is considered healed; otherwise, it is not healed.

Healing rate =(Healing cases/Total cases) × 100%

Evaluation time: 12 weeks ± 1 week, 48 weeks ± 4 weeks, 72 weeks ± 4 weeks.

(2) Pain score

Evaluation Method: Visual Analog Scale (VAS)

Evaluation Criteria:

A. A score of 0 represents no pain;

B. A score of 1-3 means mild pain, tolerable;

C. A score of 4-6 indicates moderate pain that affects sleep and is tolerable;

D. A score of 7-10 indicates severe pain, unbearable pain, affecting appetite and sleep.

Evaluation Time: Screening period, within 1 week after surgery (≦7 days), 6 weeks after surgery ± 1 week, 12 weeks after surgery ± 1 week, 24 weeks after surgery ± 4 weeks, 48 weeks after surgery ± 4 weeks after surgery, 72 weeks after surgery ± 4 weeks.

(3) Joint function score

Evaluation Method: AKS knee function rating scale and Mazur ankle function rating scale were used to evaluate the knee function.

Evaluation Time: 6 weeks after surgery ± 1 week, 12 weeks after surgery ± 1 week, 24 weeks after surgery ± 4 weeks, 48 weeks after surgery ± 4 weeks after surgery, 72 weeks after surgery ± 4 weeks.

(4) Device performance index

Evaluation project	Result
Whether the aseptic packaging is complete	☐Y ☐N
Whether the device label instructions are clear, complete, and	☐Y ☐N

easy to identify	
Whether the supporting equipment is suitable	☐Y ☐N
Whether the device is easy to implant	☐Y ☐N

Evaluation Time: Before surgery

7. Safety Evaluation Methods

7.1 Security Parameters

Vital signs, laboratory tests, adverse events occurring during clinical trials,

7.2 Description of Security Parameters

7.2.1 Vital Signs: Body temperature, respiration, heart rate, blood pressure;

Recording Time: Screening period, before surgery, during surgery, within 1 week after surgery (≦7 days), 6 weeks after surgery ± 1 week, 12 weeks after surgery ± 1 week, 24 weeks after surgery ± 4 weeks, 48 weeks after surgery ± 4 weeks after surgery, 72 weeks after surgery ± 4 weeks.

7.2.2 Laboratory Examination: Coagulation function, blood routine, urine routine, blood biochemistry;

Recording Time: Screening period, within 1 week after surgery (≦7

days), 24 weeks after surgery ± 4 weeks, 48 weeks after surgery ± 4 weeks after surgery, 72 weeks after surgery ± 4 weeks.

7.2.3 Adverse Events Occurred During Clinical Trials

Recording Time: Before surgery, 1 week after operation (≦7 days), 6 weeks after surgery ± 1 week, 12 weeks after surgery ± 1 week, 24 weeks after surgery ± 4 weeks, 48 weeks after surgery ± 4 weeks after surgery, 72 weeks after surgery ± 4 weeks.

Trial Procedure

2.1 Screening Period (V0 period: -7-0 days)

Informed consent must be signed prior to any trial-related procedure, after which subjects are assigned a unique screening number that remains unchanged throughout the trial. If the subject is undergoing elective surgery, it is at the discretion of the investigator whether to re-examine the subject if the preoperative examination exceeds the acceptable time range.

(1) Sign informed consent;

(2) Demographic data: gender, age, height, weight;

(3) Complete medical history: previous disease history within 3 months before signing the informed consent, drug use history, smoking history, drinking history, surgical history and allergy history within 1 month;

(4) Vital signs: body temperature, respiration, heart rate, blood pressure;

(5) Blood pregnancy test: only applicable to women of childbearing age;

(6) Bone mineral density examination (test site);

(7) Blood glucose test: including blood glucose and glycated hemoglobin, only for diabetic patients;

(8) Coagulation function test: prothrombin time (PT), activated partial thromboplastin (APTT), fibrinogen (FIB), thrombin time (TT);

(9) Blood routine: hemoglobin (HB), red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hematocrit (Hct);

(10) Urine routine: urinary white blood cells (WBC), urinary protein (PRO), urinary red blood cells (RBC), urinary glucose (GLU);

(11) Blood biochemistry: creatinine (Cr), Urea nitrogen (BUN) / Urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST);

(12) C-reactive protein;

(13) Infectious disease examination: HBSAg, HBsAb, HBeAg, HBeAb, HBcAb, HCV-rna/ HCV-antibody, syphilis TPPA, HIV antibody;

(14) X-ray examination;

(15) Determine the inclusion and exclusion criteria;

(16) VAS score;

(17) Recording device defects;

(18) Record drug combination.

2.2 Day of Surgery (Stage V1: Day 0)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) Random grouping;

(3) Record surgical information;

(4) Instrument performance index;

(5) Recording device defects;

(6) Record adverse events;

(7) Records of combined drug use (except glucose, normal saline and

narcotic drugs);

2.3 Follow-up Period (Phase V2: Within 1 week after surgery)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) Blood routine: hemoglobin (HB), red blood cell count (RBC), autologous cell count (WBC), platelet count (PLT), hematocrit (Hct);

(3) Urine routine: urinary white blood cells (WBC), urinary protein (PRO), urinary red blood cells (RBC), urinary glucose (GLU);

(4) Blood biochemistry: creatinine (Cr), Urea nitrogen (BUN) / Urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST);

(5) X-ray examination;

(6) CT (3D reconstruction);

(7) MRI examination;

(8) VAS score;

(9) Recording device defects;

(10) Record adverse events;

(11) Record drug combinations (except glucose, normal saline and narcotic drugs);

2.4 Follow-up period (Stage V3: 6 weeks after surgery±1 week)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure

(2) X-ray examination;

(3) Physical examination;

(4) Joint function score;

(5) VAS evaluation;

(6) Recording device defects;

(7) Record adverse events

(8) Record drug combinations (except glucose, normal saline and narcotic drugs)

2.5 Follow-up Period (V4 period: 12 weeks after surgery±1 week)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) X-ray examination;

(3) Physical examination;

(4) Joint function score;

(5) VAS evaluation;

(6) Recording device defects;

(7) Record adverse events,

(8) Records of drug combinations (except glucose, normal saline and narcotic drugs)

2.6 Follow-up Period (V5: 24 weeks after surgery±4 weeks)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) Blood routine: hemoglobin (HB), red blood cell count (RBC), autologous cell count (WBC), platelet count (PLT), hematocrit (Hct)

(3) Urine routine: urinary white blood cells (WBC), urinary protein (PRO), urinary red blood cells (RBC), urinary glucose (GLU)

(4) Blood biochemistry: creatinine (Cr), Urea nitrogen (BUN) / Urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST);

(5) X-ray examination;

(6) CT (3D reconstruction)

(7) MRI examination;

(8) Physical examination;

(9) Joint function score:

(10) VAS score;

(11) Recording device defects:

(12) Record adverse events;

(13) Record drug combinations (except glucose, normal saline and narcotic drugs)

2.7 Follow-up Period (Phase V6: 48 weeks after surgery±4 weeks)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) Blood routine: hemoglobin (HB), red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hematocrit (Hct);

(3) Urine routine: urinary white blood cells (WBC), urinary protein (PRO), urinary red blood cells (RBC), urinary glucose (GLU);

(4) Blood biochemistry: creatinine (Cr), Urea nitrogen (BUN) / Urea,

alanine aminotransferase (ALT), aspartate aminotransferase (AST);

(5) X-ray examination;

(6) MRI examination;

(7) Physical examination;

(8) Joint function score;

(9) VAS score;

(10) Recording device defects;

(11) Record adverse events;

(12) Record drug combinations (except glucose, normal saline and narcotic drugs);

2.8 Follow-up Period (Stage V7: 72 weeks after surgery± 4 weeks)

(1) Vital signs: body temperature, respiration, heart rate, blood pressure;

(2) Blood routine: hemoglobin (HB), red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hematocrit (Hct);

(3) Urine routine: urine white blood cell (WBC), urine egg (PRO), urine red blood cell (RBC), urine glucose (GLU);

(4) Blood biochemistry: creatinine (Cr), Urea nitrogen (BUN) / Urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST);

(5) X-ray examination;

(6) MRI examination;

(7) Physical examination;

(8) Joint function score;

(9) VAS score;

(10) Recording device defects;

(11) Record adverse events;

(12) Record drug combinations (except glucose, normal saline and narcotic drugs);

Specifications for Use of Devices

(1) All investigators performing the device operation in this clinical trial must be GCP certified, trained and skilled physicians.

(2) For unified handover of medical devices for testing, there should be a special person to check and process records. After the handover of the product, the medical device clinical trial management department.

(3) Each research unit shall establish a strict test instrument management system. For the special purpose of the device administrator form registration.

(4) The sponsor shall refer to the provisions of the State Drug Administration on the management of medical device instructions and labels, the experimental medical devices for appropriate identification, and marked "experimental" .

(5) The records of experimental medical devices including production date, product batch number and other production-related records and product quality and stability related inspection records, Records of transportation and delivery of medical devices to clinical trial management departments for use, as well as post-trial recovery and disposal dates, etc.

(6) The use of investigational medical devices is the responsibility of the clinical trial institution and the investigator, and the investigator shall ensure that all investigational medical devices are used only for the

subjects of the clinical trial, and the investigator shall not transfer the investigational medical devices to any non-participants in the clinical trial. Before use, sterilization should be carried out according to the requirements and instructions.

Statistical Analysis

1. Statistical Design

A prospective, multicenter, randomized, single-blind, parallel-controlled clinical trial was conducted. The comparison type was non-inferiority design.

2. Analytical Methods

95% confidence interval method was used for the main efficacy indicators, and bilateral tests were used for all statistical tests, and $P \leq 0.05$ was considered to be statistically significant.

The description of quantitative indicators will calculate the mean, standard deviation, median, minimum, maximum. The classification index is described by the number of cases and percentage of each type. Statistical analysis was performed using SAS 9.4 software.

Data Management

(1) Data Recording and Transfer

Electronic Case report Form (eCRF): The data manager designed and constructed according to the experimental scheme, and set logical verification according to the data verification plan (DVP). After passing the test and obtaining the sponsor's approval, the ECRF will be released for use.

Data entry: The eCRF data comes from the original records, and the data entry personnel fill in the instructions according to the eCRF, and enter the subject's visit data into the EDC in time.

(2) Data Processing and Record Preservation

Source data on-site verification (SDV): The inspector can query the consistency of eCRF data and source data.

Data questions and answers: Questions come from EDC logical verification system questions, inspectors, data administrators and other manual questions, researchers need to answer questions in time. The data manager and the monitor give the question approval and issue the question again if necessary until the data is "cleared".

Researcher signature: After data entry is completed and passed through the SDV, the researcher will conduct an electronic signature review and confirmation.

If the data is modified after the signature, you need to re-sign it.

Adverse events were coded using the MedDRA (21.0 or above) dictionary, and drug combinations were classified by WHO ATC.

(3) Database Locking

Database locking: After the principal investigator, sponsor, statistical analyst, and data manager jointly sign the database locking record, the data manager performs the database locking.

Database submission: Data manager submits database to statisticians, eCRF archive: eCRF generated PDF electronic document for each subject is saved, data management report: written by data manager,

EDC shutdown: After statistical analysis is complete, the data administrator closes the database.

Feasibility Analysis

(1) Analysis of the Possibility of Success

A. The test products have passed strict inspection, and the test results are qualified.

B. After training, the researchers are proficient in the use of the test equipment and operate in strict accordance with the plan.

C. Participants were selected according to strict inclusion/exclusion criteria.

(2) Possibility Analysis of Failure

This test routine does not fail, which may result in failure if :

A. Enrolled subjects who do not meet the inclusion criteria.

B. Failed to test relevant laboratory indicators according to the scheme.

C. The operator is not skilled in operation and makes mistakes in use.

Quality Control of Clinical Trials

(1) Training of Researchers

Before the start of clinical trial, the experimental institution or sponsor should conduct product training, program training and clinical trial process training according to the investigator's manual, specification and clinical protocol.

(2) Measures to Improve Subjects' Compliance

Researchers should carefully implement informed consent so that subjects fully understand the requirements of the experiment and cooperate with the experiment.

(3) Supervision of Clinical trials

An auditor appointed by the sponsor conducts regular site visits to the trial hospital to ensure that all aspects of the study protocol are strictly adhered to and the CRF is checked to ensure consistency with the original data.

Ethical Protection and Informed Consent in Clinical Trials

(I) Ethical Considerations

Clinical trials must be conducted in accordance with the Declaration of Helsinki and relevant clinical trial research norms and regulations in China. Before the start of the trial, the clinical trial can be carried out only after the trial protocol is approved by the ethics committee of the clinical trial unit.

Before each subject is enrolled in this study, it is the investigator's responsibility to provide him or his legal representative with a complete and comprehensive written description of the purpose, procedures, and possible risks of this study. Subjects should be made aware of their right to withdraw from the study at any time. A written informed consent must be given to each subject before enrollment, and the investigator is responsible for ensuring that each subject obtains informed consent before entering the study. Informed consent should be kept as clinical trial documentation for future reference.

(2) Informed Consent Process and Informed Consent

Before the participants participate in the clinical trial, the investigator shall fully explain the details of the clinical trial to the participants or their family members, guardians and legal representatives, including known and foreseeable risks and possible adverse events. After

full and detailed explanation, the subject or his legal representative shall sign the name and date on the Informed consent, and the researcher performing the informed consent shall also sign the name and date on the informed consent, and the informed consent shall be signed before the subject accepts any test procedure, and any amendment shall be accompanied by a written explanation of the reason behind the Informed Consent.

The Informed consent should indicate the date of preparation or the date of the revised version. This information will help confirm that the correct version is being used. If the Informed Consent Form is revised during the experiment, the revised Informed Consent form shall be reviewed and approved by the Ethics Committee again before execution. After the revised Informed Consent is approved and sent to the clinical trial institution for record, all subjects who have not completed the trial process must sign the newly revised Informed Consent.

Requirements for Reporting Adverse Events and Device Defects

(1) Definition and Reporting of Adverse Events

A. Definition of adverse events

Adverse events refer to adverse medical events that occur during clinical trials of medical devices, whether or not they are related to the experimental medical devices. Adverse events were recorded from device use.

B. Severity determination of adverse events

Observe the process, extent, disposal and outcome of adverse events in detail, and fill in the adverse event report form. Adverse events were classified as mild, moderate, and severely mild according to the following criteria:

Mild: Tolerable to the subject, does not affect treatment, does not require special treatment, and has no impact on the health of the subject

Moderate: The subject is unbearable, requires special treatment, has a direct impact on the health of the subject.

Severe: Endangering the life of the subject, causing death or disability, requiring immediate emergency treatment.

C. Evaluation of adverse events

According to the test product is definitely relevant, very likely to be relevant, possibly relevant, possibly irrelevant, definitely irrelevant five

levels of evaluation.

Must be relevant: the occurrence of the reaction is consistent with a reasonable time sequence after the use of the product, consistent with the type of reaction known to the product, the disappearance of the reaction after discontinuation, and the reaction cannot be explained by clinical manifestations of the disease or other causes other than the product.

It is likely to be relevant: the occurrence of the reaction is consistent with a reasonable time sequence after the use of the product, consistent with the type of reaction known to the product, the reaction improves significantly after discontinuation, and the reaction cannot be explained by clinical manifestations of the disease or other causes other than the product.

May be relevant: The occurrence of the reaction is consistent with a reasonable time sequence after the use of the product, consistent with the type of reaction known to the product, the response improves after discontinuation, and the patient's clinical status or other treatment may cause a similar reaction.

May not be relevant: The occurrence of the reaction is not consistent with a reasonable time sequence after the use of the product, is not consistent with the type of reaction known to the product, the reaction improves after discontinuation, the patient's clinical status or other treatment may cause a similar reaction, and may be mitigated with

disease improvement or other measures.

Certainly not: The occurrence of the reaction does not conform to a reasonable time sequence after the use of the product, does not conform to the type of reaction known to the product, the reaction does not improve after discontinuation, the patient's clinical status or other treatment may cause a similar reaction, the disease status improves or the response disappears after discontinuation of other treatment.

(2) Device Defect

Device defect refers to the unreasonable risks that may endanger human health and life safety under normal use of medical devices in the course of clinical trials, such as label errors, quality problems, failures, etc. In the course of this clinical trial, if the use of devices fails due to device defects, the investigator shall conduct routine treatment according to clinical needs. The investigator should document all discovered device defects that occur during clinical trials.

(3) Definition of Serious Adverse Events

A. Definition of serious adverse events

Serious adverse events refer to those that occur during clinical trials of medical devices resulting in death or serious deterioration of health. Including fatal diseases or injuries, permanent defects in body structure or body function, the need for hospitalization or prolonged hospitalization, the need to take medical measures to avoid permanent defects in body

structure or body function: events leading to fetal distress, fetal death or congenital abnormalities, birth defects, etc., during screening or follow-up, Prospective or elective surgery performed by subjects was not recorded as a serious adverse event.

B. Serious adverse event reporting process

If a serious adverse event occurs in a clinical trial, the investigator shall immediately take appropriate treatment measures for the subject; meanwhile, the investigator shall report the serious adverse event to the sponsor, the management department of the medical device clinical trial institution, and the ethics committee within 24 hours after learning about it; Serious adverse events were followed up in accordance with the provisions of the clinical trial protocol, and serious adverse event follow-up reports were submitted.

Direct Access to Source Data and Files

Clinical trial institutions and investigators should allow trial-related monitoring, verification, ethics committee, and regulatory inspections with direct access to source data/documents.

Confidentiality Principle

This trial protocol is confidential and is intended to be provided to medical experts, researchers participating in the trial and other staff involved in the trial, as well as relevant business entrusting institutions such as medical institutions, ethics committees and contract research organizations undertaking the trial. Except to explain the situation to the subject, no content of this test protocol shall be disclosed or disclosed to any third party without the prior written consent of the sponsor. In addition, the written consent of the sponsor is required for the partial or full results of this clinical trial to be published externally to the society, journal, etc.