Clinical study protocol

Project Name: Prospective, single arm, Phase II clinical study of selmetinib hydrogen sulfate capsules in patients with neurofibromatosis type I

Sponsor: Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Version number: V2.0

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Scheme signature confirmation:

Compliance Statement

In accordance with the provisions of the Good Clinical Practice for Drug Clinical Trials and the Administrative Measures for Clinical Studies initiated by Medical Institutions (Trial) and the Declaration of Helsinki, we promise to carry out this study according to this protocol. The participants must be trained to conduct the study after the written approval of the Ethics Committee and the written informed consent of the subjects, and the protocol revision shall be re-approved again.

1. Protocol abstract (title, brief description of study, study object, outcome measures, study intervention*, Sample size, etc., in 300-500 words)

This study focused on patients with neurofibromatosis type I, currently lacking effective drug therapy and a high recurrence rate after surgical resection. Hydrosulfate sametinib capsule as a MEK inhibitor, through selective binding mitogen activated protein kinase (MEK) 1 / 2 protein, can block the regulation of key cells mitogen activated protein kinase / extracellular signal regulation kinase signaling pathway, can induce tumor shrinkage, for disease control, surgical radical resection, reduce postoperative recurrence, reduce complications. This study aims to provide hydrosulphate seletinib to patients with neurofibromatosis type I, observe the efficacy of drug treatment, change patients without surgical indications into indications for surgery, increase the proportion of surgical resection and reduce the recurrence rate. In this study, the objective response rate (ORR) as the main outcome measure, the range, duration of response (DOR), and progression-free survival (PFS) as secondary outcome measures to explore the use of surgical resection rate, reduction of surgical resection range and postoperative complications, tumor shrinkage effect, and the stability of efficacy.

2. Introduction (Rereferences should be noted in the introduction)

2.1 Research theoretical basis / background (explain why clinical studies are conducted from the limitations of disease, standard of treatment and known treatment, and explain the findings and importance of preclinical, pharmacological and related studies)

Neurofibromatosis (NF) has been included in the list of rare diseases in many countries including China, 96% of which are NF 1 subtypes, and the clinical manifestations of NF 1 are diverse[1], Involmultiple systems

and can cause serious complications such as airway obstruction, spinal cord compression and motor dysfunction[2-4]. Pleexiform neurofibromas (PN) occur in 30 to 50% of NF 1 patients[5、6], PN progress fast, accompanied by serious appearance defects, high disability, and the risk of deterioration[7-10]. According to the 2023 edition of the multidisciplinary diagnosis and treatment of type I neurofibromatosis, patients with NF 1 are more likely to have a variety of benign and malignant tumors than the normal population, including pNF, CNF, MPNST and OPG. Attention should be paid to the early identification and monitoring of the above tumors. Neurofibromas with MPNST should have accelerated growth, pain and hard texture. At the same time, systemic evaluation should be carried out, and patients with no signs of distant metastasis should undergo early surgical treatment as far as possible, and patients with distant metastasis can choose radiotherapy, chemotherapy and targeted therapy.

Neurofibromatosis type I (neurofibromatosis type 1, NF 1) is an autosomal dominant disorder with 50% of patients with familial and 50% sporadic mutations. NF 1 gene encodes neurofibromin, downregulates the activity of Ras-Raf pathway and suppresses cell proliferation; deficiency in neurofibrosis causes excessive activation of RAS pathway and causes uncontrolled cell proliferation in NF 1 patients[5]. At present stage, the operation is the most commonly used, the main treatment, and neurofibroma has the characteristics along the nerve root growth, it is difficult to solve all lesions through surgery, lesions composed of extensive nerve and vascular tissue and normal tissue, surgical resection difficult and bleeding, incomplete resection after recurrence as high as 50%.

As a MEK inhibitor, it blocks the mitogen-activated protein kinase / extracellular signal-regulated kinase signaling pathway by selectively binding to the mitogen-activated protein kinase (MEK) 1 / 2 proteins that regulate key cellular responses[11-13], And then induce tumor shrinkage,

creating conditions for disease control, surgical resection, reducing postoperative recurrence and reducing complications. Based on the targeted therapy of selmeetinib capsule, this study monitored the efficacy of the enrolled patients, so as to verify the effectiveness of selmeetinib capsule for NF 1 therapy.

2.2 Risk / benefit evaluation

2.2.1 Known potential risks

The potential risks of this study are mainly the adverse reactions after the use of selmetinib hydrosulphate capsules, the hyperprogression of tumor treatment caused by the study protocol itself, and the risk of sudden accidents in the study.

2.2.2 Known potential benefits

The potential benefit of the subjects is the subjects to achieve partial tumor remission, delay progression, reduce recurrence, and improve function; Entering the clinical study can get more attention from researchers and manage the disease changes in time, which is beneficial to the treatment of the disease.

2.2.3 Potential risk and benefit evaluation

Smetinib Insulphate capsule is indicated for pediatric patients with neurofibromatosis type I (NF 1) aged 3 years and older with symptomatic, inoperable plexiform neurofibromas (PN). It was approved to list in China on April 28,2023, and was included in the medical insurance directory on December 13,2023. Several guidelines, consensus and diagnosis and treatment norms in China recommend selmetinib hydrohydrogen sulfate for the treatment of NF 1-PN. The most common toxicity of selmetinib sulphate capsules are grade 1 and 2 gastrointestinal symptoms (nausea, vomiting, or diarrhea), asymptomatic elevated creatine phosphokinase levels, acnes rash, and paronychia with good safety and tolerability. Therefore, this

clinical study protocol has a low risk of disease progression and serious adverse events on the treatment of NF 1[14、15]. At the same time, in the future studies, the investigators will pay more attention to the subjects' systemic condition and tumor treatment condition, and the subjects will also gain some clinical benefit in this study.

3. Study objective and endpoint (list presentation objective (specific issues to be addressed), corresponding to the outcome measures)

3.1 Purpose

3.1.1 Main Purpose

The primary objective of this study is to explore the objective response rate (ORR) of tumors in patients with neurofibromatosis type I (NF 1).

3.1.2 Secondary Purpose

The secondary objective of this study is to explore the improvement in surgical resectable range, duration of remission (DOR), progression-free survival (PFS) in patients with neurofibromatosis type I (NF 1) treated with selmeetinib capsules.

3.1.3 Exploratory Purpose

The exploratory purpose of this study is to explore the long-term efficacy and stability of efficacy in patients with neurofibromatosis type I (NF 1) treated with selmeetinib capsules.

3.2., study indicators

3.2.1 Main Indicators and Definitions

Objective response rate (ORR): percentage of patients in partial response after 6 cycles of drug therapy. Partial response was defined as a 20% reduction in the target neurofibroma volume from baseline. Confirmconfirmed partial response was defined as a 3-examinations at 33

months examinations assessed as partial remission.

3.2.2 Secondary indicators and Definitions

Scope of surgical resection: on the premise of not damaging the important organs and neurological functions invaded by the tumor, the proportion of resection can be divided into total resection / near total resection (90% resection range), subtotal resection (90% resection range 50%), and partial resection (resection range <50%).

Duration of response (DOR): the time between the start of CR or PR and the first assessment of PD or death from any cause.

Progression-free survival (PFS): the time from the start of treatment in the trial to tumor progression or death from any cause (whichever occurs first).

3.2.3, safety indicators

The subject's vital signs, blood routine, liver function, blood biochemistry, urine routine, stool routine, coagulation function, left ventricular ejection fraction (LVEF), creatine phosphokinase, vitamin E, and bleeding risk.

4. study population

4.1 Inclusion criteria

(1) Age≥18 years old

(2) According to the updated NF 1 diagnostic criteria of the National Institutes of Health (NIH) in 2021,

① 6 or more CALMs:d> 5 mm before puberty or d> 15 mm after puberty;

② 2 or more neurofibromas of any type or 1 plexiform neurofibroma;

③ Plaques in the axillary or inguinal area;

④ Optic glioma (OPG);

⑤ Slit lamp examination of 2 or more Lisch nodules, or optical coherence tomography (OCT) / imaging of two or more near infrared (NIR) abnormalities;

⑥ Characteristic bone lesions, such as sphenoid dysplasia and anterolateral curvature of the tibia;

⑦ Pathogenic heterozygous NF 1 variants with allelic variant scores of 50% in normal tissues (such as leukocytes);

Patients with no parental history and fulfilling 2 or more clinical characteristics could be diagnosed with NF 1

Parents with a history of 1 or more clinical features can be diagnosed with NF 1

(3) Before enrollment, a head and neck surgeon performed a pathological biopsy of the solid tumor to clarify the pathological diagnosis and exclude the malignant peripheral schwannoma (MPNST)

(4) At least one measurable tumor lesion according to the efficacy evaluation criteria of solid tumors RECIST 1.1

(5) The tumor infringes on the brain, spine and other important organs, with no indication for surgical resection

(6) The performance status of the Eastern Cooperative Oncology Group (Eastern Cooperative Oncology Group, ECOG) was 0-1

(7) Blood routine: white blood cell count (WBC) $3.0 10^9$/ L; Absolute neutrophil count (ANC) $1.5 10^9$/ L; Platelet (PLT) $100 10^9$/ L; hemoglobin level (HGB) 9.0 g/dL (no corresponding supportive care, such as transfusion and increased leukocytes within 7 days).

(8) Liver function: 2.5 times aspartate aminotransferase (AST) and alanine aminotransferase (ALT); albumin (ALB) 30 g / L.

(9) Renal function: serum creatinine 1.5 times ULN or creatinine clearance (CrCl) 50 mL/min (using the Cockroft / Galt formula); urinary protein (UPRO) <(+ +), or 24-hour urinary protein <1.0 g.

(10) Cardiac function: blood creatine phosphokinase 200U / L, left ventricular ejection fraction (LVEF) 50%;

(11) Did not participate in other clinical trials within the previous 30 days;

(12) Patients who voluntarily participate in the project and sign the informed consent form.

4.2 Exclusion criteria

(1) The patient had abnormal blood index, abnormal liver and kidney heart function, and cannot tolerate the clinical study process after multidisciplinary consultation and evaluation

(2) The patient has become a malignant peripheral nerve schwannoma (MPNST) or has other serious complications such as malignant tumors and heart disease, or has previously undergone anti-tumor therapy such as surgery, chemotherapy and radiotherapy

(3) The whole clinical study cannot be completed due to personal, social and economic reasons

(4) There are previously serious systemic system diseases and the disease cannot be cured or drug control

(5) Patients who are present in pregnancy

4.3 Lifestyle considerations (lifestyle related restrictions: smoking, drinking, exercise, diet, etc., and what measures will be taken if the subject needs drugs, treatments or surgery prohibited in the protocol)

After entering the clinical study, the subject needs a light diet, food, tobacco, alcohol, and no strenuous exercise. If the subject needs the medication, treatment or surgery unrelated to the clinical study, the investigator needs to evaluate the cause of the need for the drug, treatment and surgical treatment is the cause of the study, additional treatment due to accident or other reasons, consider the influence of the treatment on the study, and suggest the subject to receive conventional

treatment after withdrawal and seal the subject data.

4.4 Screening failures (definition of screening failures and how to process screening failed subjects)

Screening failure refers to the recruitment of subjects who failed to meet the inclusion criteria or the exclusion criteria after multidisciplinary evaluation. The study will inform the multidisciplinary consultation and give the current best treatment advice.

4.5 Recruitment and retention strategy (how to recruit subjects (location, method, expected number of people.....); How to retain subjects (multiple contact information, incentive); such as involving vulnerable groups: reason + safeguard measures; if having compensation or incentive measures: object, quantity, form, time, etc.)

This study will take offline, combining online recruiting subjects, offline main location for sun Yat-sen memorial hospital oral and maxillofacial surgery, including but not limited to posters, leaflets, lectures and other forms to attract more subjects, each interested patients on-site registration, leave contact information and continue to one-on-one explanation. If the subject is in financial difficulties, the investigator team will assist the subject in providing assistance with the charity fund application to reduce the financial burden of the subject.

5. research design

5.1 Overall design (including assumptions, type, etc.)

This study hypothesized selmetinib hydrosulphate capsules for neurofibromatosis type I, including improving the resectable range of surgery, shrinkage, delaying progression, reducing recurrence, and improving function. A prospective, single-arm, phase study design is

estimated to improve the resectable range of NF 1 surgery, with objective response rate (ORR) in 40%, duration (DOR) in more than 30% of patients, and progression-free survival (PFS) in more than 12 months in 90% of patients.

5.2 Study design process

5.2.1 Study the specific implementation process

This study started from the recruitment of subjects, with clinical diagnosis, definite diagnosis by pathological biopsy, primary screening according to inclusion criteria, and exclusion criteria, and enrollment after signed informed consent. Patients evaluated as no indication for surgical resection and treated with selmetinib hydrosulphate capsules. Based on individualized patient body surface area (BSA), oral selmetinib hydrosulphate capsules daily (20-50mg bid) were evaluated for shrinkage efficacy, ORR and surgical resection after 6 cycles.

Interview	Screening period	Drug 6 cycles						Surgery / continued medication / follow-up	
	V1	V2	V3	V4	V5	V 6	V 7	V 8	V9
Follow-up time	*1 Day before enrollment*	*And 1 cycle after V 1*	*And 1 cycle after V 2*	*And 1 cycle after V 3*	*Cycle 1 after V4*	*And 1 cycle after V 5*	*And 1 cycle after V 6*	*For 3 cycles after V 7*	*For 3 cycles after V 8*
Signed the informed consent form	√								
Inclusion / exclusion criteria	√								
Demographic data	√								
medical history	√				√			√	√
ECOG grade	√	√	√	√	√	√	√	√	√
check-up	√	√	√	√	√	√	√	√	√

vital sign	√	√	√	√	√	√	√	√	√
electrocardiogram	√				√			√	√
routine blood test	√		√	√	√	√	√	√	√
Blood biochemical	√		√	√	√	√	√	√	√
Liver, kidney, and heart function	√		√	√	√	√	√	√	√
coagulation function	√		√	√	√	√	√	√	√
Heart ultrasound	√				√			√	√
Pathological biopsy	√								
Infectious disease examination (hepatitis B, hepatitis C, HIV, syphilis)	√								
Imaging examination	√				√			√	√
complication And adverse event assessment			√	√	√	√	√	√	√

5.3 Methods to reduce bias (e. g., randomization, blindness, matching method, etc.)

The end of this study was defined as the last subject who completed the last follow-up or was lost to follow-up or died

5.4 Definition of end of study (e. g. last subject completes last follow-up)

5.5 Statistical analysis

5.5.1 Sample size and calculation basis

The estimated sample size was based on the objective response rate. The study hypothesis is that selmetinib sulphate capsule has shrinkage effect on NF 1. The study parameters are set: α =0.025 (one side),

Power=90%. Based on the results of relevant study or pre-test, the objective response rate (ORR) is expected to reach 40%, 29 cases were calculated using PASS 15.0 software, and considering 10% shedding rate, 33 subjects should be included.

5.5。2 Data analysis set (e. g. full analysis set, compliance protocol set, safety analysis set)

Statistical analysis will be performed using the SAS statistical software (V.9.4, SAS Institute) Statistical analysis software for calculation, if no special instructions, the main indicators use one-sided test, control the first class error α is 0.025, the remaining indicators use two-sided test, one class error is α =0.05. To calculate confidence intervals, calculate two-sided 95% confidence intervals if not otherwise specified.

(1) Full analysis set (full analysis set, FAS): consisting of all subjects who received at least one drug / treatment and obtained efficacy assessment. This dataset was derived from all subjects after removing subjects in the least and reasonable way.

(2) Safety analysis set (safety analysis set, SS): a population treated at least once / once and having at least one safety evaluation data. In the safety analysis, all patients will be analyzed by the actual drug drug group.

(3) Compliance with the protocol set (per-protocal set, PPS): all concomitant medications that met the trial protocol and did not use the impact effectiveness evaluation, good medication compliance (between 80% and 120%), excluded subjects who had major protocol violations and were judged to have a significant impact on the results. All protocol deviations excluding subjects from the compliant protocol set will be described in detail in the Statistical Analysis Plan (SAP) and completed prior to data lock.

5.3 5 Statistical analysis plan

Data description of statistical analysis, analysis method of primary / secondary indicators / safety indicators, statistical school positive method, control of bias, stratification / subgroup / sensitivity analysis, etc

Demographic, and other baseline characteristics

Based on the analysis of FAS set, the demographic data, medical history, vital signs and other baseline data were statistically described, where the measurement data (age, BMI, XX, etc.) gave mean, SD, minimum, maximum, median, and gave frequency and corresponding percentage for count data (gender, XXX, etc.).

Analysis of efficacy indicators

(1) Main efficacy indicators

Point estimates for the main evaluation index (ORR) and estimated two-sided 95% confidence intervals using the Clopper-Pearson exact probability method. If the lower limit of the 97.5% confidence interval was less than the ORR rate of the historical control, the efficacy was considered better than the historical control.

(2) Secondary efficacy indicators: analysis using FAS and PPS analysis sets. For survival metrics, the digit survival time and its two-sided 95% confidence intervals were calculated. For the rate of each index, point estimates were performed and two-sided 95% confidence intervals were estimated using the Clopper-Pearson exact probability method. For the continuity index, the mean and two-sided 95% confidence intervals were calculated based on the normal distribution method, otherwise the median and two-sided 95% confidence intervals were calculated based on the percentile method.

Safety index analysis

The SS set was used to provide a statistical description of the incidence of adverse events / serious adverse events and adverse reactions, and to list the details of the occurrence of each adverse event in each subject, including the type and severity of adverse events. Evaluation of laboratory indicators, vital signs, electrocardiogram and other safety related indicators, compare and evaluate the changes before and after treatment, and give a statistical description of the clinical evaluation (normal, abnormal without clinical significance, abnormal with clinical significance, not checked) before and after treatment.

Principles of handling missing / deletion / follow-up data

LOCF (last observation carried forward), that is, the main index data is not observed at the last time; the secondary indicators and safety indicators are not filled.

6. Research intervention*

6.1 Study intervention content (description of intervention content, implementation steps, dose and route of intervention drug, frequency of intervention, product of test group and control group, etc.)

All patients received oral selmetinib hydrosulphate capsules (20-50mg bid) daily for 30 days for 6 cycles on patient body surface area (BSA).

6.2 Preparation / handling / storage / responsibilities (allocation plan for the drug and control article when the intervention is drug)

Use of a medication must be recorded in the patient's medical record and in the appropriate location of the CRF. After the enrollment of the subjects and at the 1st and 2nd months of follow-up, the executive nurse shall receive the corresponding number of drugs at the drug administrator, and the remaining drugs and packaging boxes shall be returned to the drug

administrator. If the drug is found or damaged during the preparation process, this box of drugs should not be used, the damaged drugs shall be treated as empty bottles, and other undamaged drugs shall be returned to the drug administrator together with the packaging box. The study center shall be responsible for the management of test drugs, including receiving, distribution, counting and recovery. The investigator shall ensure that the test drug is stored in a safe, independent and locked place at the study site and that the storage conditions shall meet the storage requirements of the test drug. No one can be contacted without the consent of the investigator. Empty boxes shall be stored and managed as the test drug.

6.3 Study Intervention Compliance (How to maintain, evaluate, and verify study compliance)

After each medication, the subject should be required to return to the study center for review, and the compliance of the study can be verified according to the subject's review. During the late follow-up, the study team members must conduct a telephone follow-up communication with the subject and reasonably arrange the review visit.

6.4 Concomitant therapy (permitted adjuvant medication, complementary / replacement therapy)

If the subject has hypertension, diabetes, coronary heart disease and other diseases that need long-term drug control, the investigator and the relevant specialist should evaluate the impact of the disease and the relevant study protocol and determine the dose and duration of adjuvant medication.

6.4.1 Rescue (drug, treatment methods, relevant records.....)

The life hazards during the implementation of the clinical study protocol should be implemented in accordance with the clinical rescue plan, such as cardiopulmonary resuscitation, emergency airway management,

emergency surgical treatment, relevant records during hospitalization should be recorded in the medical record system, after discharge should be recorded in the adverse event record form, and the investigator should analyze whether the rescue causes are related to the study and discuss and discuss synchronously in the rescue records.

7. Discontinuation of the study intervention / subject discontinuation and withdrawal*

7.1 Study Intervention discontinuation (reasons / criteria: such as how many adverse events occurred, length of study discontinuation, how data were collected during discontinuation and how to reactivate the study intervention, whether follow-up was continued during discontinuation)

If the Grade 5 adverse event of CTCAE 5.0 standard reaches 10% of the number of subjects, the study should be discontinued, and the drug safety of the study protocol should be discussed to determine whether to adjust the dose of drugs in the study protocol, continue the follow-up during the study suspension, and maintain the follow-up record of the original subject.

7.2 Subjects discontinuation / withdrawal from the study (possible reason for subject discontinuation; involving implantable device, discuss how to remove / replace, obtain alternative materials, later contact with the subject, etc.)

When the subject stops or withdraws from the study due to dissatisfaction with the treatment effect of the study plan or his own economic reasons, he should actively communicate with the subject, encourage the subject to actively treat and help them apply for public welfare funds to complete the treatment. If the subject clearly withdraws, the investigator can continue to complete the follow-up without the study intervention.

7.3 Loss to follow-up (measures to reduce and reduce missing data due to loss to follow-up)

The investigator should keep the contact information of multiple subjects and the contact information of the family members after the subjects are enrolled. The investigator should actively contact the subjects by phone after leaving the hospital, timely understand the condition and arrange the subject to the hospital in advance for the next stage of treatment.

8. Adverse events and unexpected events

Adverse events (AEs) are adverse medical events occurring after the subject receives treatment, but they are not necessarily causally related to the treatment. An adverse event can be any adverse and unexpected signs (including abnormal laboratory findings), symptoms, or illness associated to the use of treatment, regardless of relation to treatment. It includes, but is not limited to,:

(1) the exacerbation of the preexisting disease before the use of the study treatment measures;

(2) The frequency or severity of existing episodes before the use of study treatment;

(3) Abnormal changes detected or diagnosed after the use of the study treatment measures, although such abnormal changes may have existed before the treatment;

(4) deterioration of disease or symptoms that persisted before the study.

Causal relationship between adverse events and treatment measures: In the trial, the investigator should make a comprehensive analysis according to the specific situation of adverse events and the past history, concomitant diseases and concomitant medication to judge the relationship between adverse events and treatment measures. The relationship between

adverse events and treatment measures is divided as "definitely related, most likely related, likely related, possibly unrelated and unrelated".

None: Adverse events were not associated with treatment measures.

Probably unrelated: The occurrence of adverse events is more likely related to other factors such as medication or concomitant

Disease, or the timing of the event suggests that it is unlikely to be causally related to treatment measures.

Possible concern: Adverse events may be caused by therapeutic measures. Cannot exclude whether it may be caused by other

Factors, such as: medication conditions or concomitant diseases. The occurrence of adverse events and treatment measures have a reasonable time order, and the causal relationship between events and treatment measures cannot be excluded.

It is likely that: adverse events may be caused by treatment measures. There is a reasonable temporal sequence of event occurrence and treatment measures.

Positive concern: The type of adverse event has been identified as treatment and no other reason

Explanation, such as: medication status and concomitant diseases. The timing of the event strongly suggests causality.

The adverse event severity criteria can be according to the CTCAE 5.0 (US Department of Health and Human Services). Beyond the above criteria list, refer to the following criteria:

Mild: Symptoms or signs but tolerable.

Moderate; discomfort enough to interfere with normal life.

Severe: Normal activities are already impossible.

All information about adverse events, whether mentioned by the patient, found by the investigator, or found by physical examination, laboratory examination, etc., should be recorded on the study medical

record and case report form. During the trial, the time, duration, symptoms, signs, severity, measures taken, outcome and relationship assessment of adverse events should be carefully observed and recorded, and the trial should be appropriately followed up.

Possible adverse events include: medication-related complications; procedure-related complications; and related complications after withdrawal.

The investigator should use medical terms / concepts to record AEs or SAEs. Its type, degree, occurrence time, duration, treatment measures, treatment are recorded in detail. The association of the combination of complications and medication with the study treatment was evaluated. All AEs (including SAEs) should be recorded on the Adverse Event Form for the CRF. Any patient who is treated must be evaluated for toxicity. The occurrence of any adverse events (AEs) should be graded according to the NCI Common AE classification criteria (NCI-CTCAE version 5.0).

9. Data collection and management

9.1 Case report form / electronic data records

Prior to the study start, the Redcap electronic database / EDC database was established based on the content of the paper version of the case report form.

9.2 Data management (data collection form, data storage carrier: electronic / paper, data integrity inspection, database establishment method, data management system, data quality detection method, definition of data lock library, etc.)

The original data should be uniformly recorded in the study medical records. According to the content of the study medical record, the case report form can be completed in the electronic database to ensure the integrity and accuracy of the information. In order to ensure the accuracy

of the data, the researcher should conduct self-examination no less than twice a year, regularly appoint personnel to the sub-center for project quality control, and accept the examination by the hospital and school management departments. If the data registered in the case report form / electronic database are inconsistent with the original records (study medical records), the investigator shall organize timely verification of the data, modify the wrong part according to the requirements of GCP regulations, and make corresponding explanations if necessary.

10. Ethics requirements

This study complied with the provisions of Good Clinical Practice and the Administration of Investigator-Initiated Clinical Studies (Trial) and the Declaration of Helsinki. This study will be conducted only before the ethics committee of the trial. In the course of the study, the revised protocol must be resubmitted to the Ethics Committee for review, and the investigator must wait until the consent of the Ethics Committee before implementing the new protocol.

Each enrolled patient must sign an informed consent form. Copies of the informed consent form and contact information of the investigator and the ethics committee must be provided to the requested patients*. This study will collect the clinical data and personal information of the research subjects for scientific research, which will involve the privacy rights of the patients. The study participants and the data analysts signed a confidentiality agreement not to disclose the personal patient information and disease-related information to any individuals and institutions unrelated to the study. The collected patient data should be managed to prevent personal privacy leakage.

11. References

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