Detection Evaluation of a Novel Blood-based DNA Methylation Assay in Early-stage Hepatocellular Carcinoma Patients

Study Document

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Content

1. Background

Primary liver malignancy (primary liver cancer) occurs at the epithelial or mesenchymal tissue of the liver, mainly including hepatocellular carcinoma, intrahepatic cholangiocarcinoma and combined hepatocellular cholangiocarcinoma, in which hepatocellular carcinoma accounts for more than 85%~90%, being the most common malignant tumor in China.

Currently, the incidence of liver cancer is steadily increasing at a rate of 3% per year around the world. The Asia and China have the highest burden of liver cancer, 70% of patients with newly-developed liver cancer is from Asia and 50% from China. Correspondingly, the number of patients died from liver cancer in China also accounts for half of that in the world. Chinese Cancer Center published the latest data about the cancer on Chinese Journal of Oncology in January 2018: In total number of patients with newly-developed malignant tumors in China, the frequency of liver cancer ranks fourth (365,000 cases/year); In total number of patients died from malignant tumors, the frequency of liver cancer ranks second (319,000 cases/year). The risk of liver cancer is especially higher in men older than 40 years old.

The pathogenesis and exact molecular mechanism of primary liver cancer are not yet fully understood. At present, the pathogenesis of primary liver cancer is believed to be a complex process with multiple factors and steps, which is affected by both environment and diet. The data of epidemiology and relevant studies show that infections of hepatitis B virus (HBV) and hepatitis C virus (HCV), aflatoxin, water pollution, alcohol, liver cirrhosis, sex hormones, nitrosamines, trace elements are associated with liver cancer. Secondary liver cancer (metastatic liver cancer) can induce the disease through different pathways, such as blood, lymphatic metastasis, or direct invasion of the liver.

At present, the routine surveillance and screening indicators for the early diagnosis of liver cancer mainly include alpha-fetoprotein (AFP) and liver ultrasound examination (US). Based on domestic and foreign reports and clinical verification, the sensitivity of

AFP in diagnosing liver cancer is about 60%, the false negative rate is 40%, the specificity is about 80%, and the false positive rate is 20%. For these reasons, AFP is no longer a screening indicator in AASLD guideline. For nodules larger than 2 cm, the sensitivity of US is still 84%; but for nodules of 0.5~2 cm in the liver, the sensitivity is only 33%. Therefore, there is an urgent need to find out a new biomarker for auxiliary diagnosis of liver cancer with higher sensitivity and specificity compared with current screening methods.

ctDNA, also known as Cell-free tumor DNA or circulating tumor DNA, circulates freely in the blood of patients with cancer. The analysis and comparison between ctDNA mutation and the site of normal genome by means of invasive approach can provide the useful information for tumor diagnosis, prognosis, and monitoring.

ctDNA generates from necrotic or apoptotic tumor cells, circulating tumor cells, and exosomes secreted by tumor cells. In the body of cancer patients, the number of ctDNA is small, the half life is short, and the size of ctDNA is about 160~180 bp. These fragments can reflect the number of tumor cells and its change. ctDNA is the "identity fingerprint" released by tumor cells into the blood, which is a tumor marker with high sensitivity and specificity . ctDNA is a non-invasive alternative for patients who are not suitable for tumor biopsy, which not only relieves the suffering, but also serves as an alternative to repeated invasive biopsy.

DNA methylation refers to the covalent bonding of a methyl group at the 5’ carbon position of cytosine of genomic CpG dinucleotides under the action of DNA methyltransferases. DNA methylation is an important epigenetic mark information and one of the earliest discovered DNA modification pathways. It plays an important role in maintaining normal cell function, genetic imprinting, embryonic development and human tumorigenesis, and is also one of the popular topics of study. Alterations in DNA methylation level and pattern are an important factor in tumorigenesis. In normal cells, the CpG island located in the promoter region of tumor suppressor genes is in a low level or unmethylated state. At this time, tumor suppressor genes are in a normal open state, and the expression of tumor suppressor genes inhibits tumorigenesis. In tumor cells, the CpG

island in this region is highly methylated, the chromatin conformation is altered, and tumor suppressor gene expression is turned off, resulting in cell entry into the cell cycle, loss of apoptosis, defective DNA repair, dysfunction of vessel growth and cellular adhesion, eventually leading to tumorigenesis. DNA methylation is an ideal biomarker and evaluation indicator for prognosis and early diagnosis of tumors, and it is of great significance for tumor screening, risk assessment, early diagnosis, staging, prognosis judgment, treatment and monitoring.

DNA methylation changes are an early event in the tumorigenesis of hepatic cancer, including increased methylation of tumor suppressor genes or decreased methylation of proto-oncogenes, and this change precedes mutation of driver genes. Therefore, changes in methylation patterns are considered to be the first detectable indicator closely related to tumorigenesis, providing a screening window for early diagnosis of liver cancer. By analyzing the ctDNA methylation model in a large number of patients with liver cancer and normal individuals, we finally screened out 6 liver cancer ctDNA-specific gene methylation sites, and established a comprehensive methylation diagnostic model with high-sensitivity and specificity. On this basis, the human 6 gene methylation test kit (PCR-fluorescent probe method), which is a novel blood-based DNA methylation assay, was developed.

2. Objective of Clinical Trial

1) Test performance evaluation
2) Diagnostic performance evaluation

3. Overall Design of Clinical Trial

3.1 Selection of clinical trial centers

The representative centers are selected to conduct this clinical trial, based on the consideration of the characteristics of the product, the intended use, the demographics, the epidemiologic background, the features of pathogenic microorganism, the study population, the clinical conditions (expected use environment and users).

3.2 Test performance evaluation

3.2.1 Test performance evaluation method

Following the principle of concurrent blinding, the blood samples are collected from the non-HCC patients and patients with liver cancer who had been diagnosed according to the clinical diagnostic criteria for primary liver cancer. The clinical diagnosis of primary liver cancer is determined in accordance with the clinical diagnostic criteria in Guidelines for diagnosis and treatment of primary liver cancer (2019 Edition) set by the National Health Commission. The enrolled subjected are coded. The selected samples are tested with test reagent and the control method high-throughput human methylation sequencing (NGS sequencing method), the test results are compared.

3.2.2 Determination of the sample size for test performance evaluation

According to the pre-clinical independent cohort verification results of 6 liver cancer-specific methylation sites that were screened out, the number of positive samples should be not less than 78; the number of negative samples should be not less than 238; the samples available in this study should be not less than 316 cases.

Considering that the mutation rate of some genes is extremely low (AK055957, DAB2IP, TBX15, GRASP, PPFIA1, PSD4), the subjects should be enrolled sequentially, and at least one positive case should be screened out in each type of gene mutation. If the requirements are not met, more subjects should be enrolled for testing. It should be ensured that all samples are traceable.

3.2.3 Inclusion Criteria

1) Confirmed primary hepatocellular carcinoma or confirmed non-HCC;

2) I or my legal representative can read, understand and sign the informed consent;

3) Agree to provide blood samples and have good clinical compliance;

4) The basic clinical information is complete, including: the patient's unique traceability number (ID number/outpatient clinic number/medical insurance card number), age, gender, imaging and/or pathological diagnosis results (for patients with primary liver

cancer), imaging examination confirmed non-identical Liver cancer (non-HCC patients).

3.2.4 Exclusion Criteria

1) pregnant women;

2) Have received an organ transplant;

3) Non-HCC patients diagnosed with other tumors;

4) Patients with primary hepatocellular carcinoma combined with other tumors;

5) The investigator judges that they are not eligible for inclusion.

3.3 Diagnostic performance evaluation

3.3.1 Diagnostic performance evaluation method

According to the clinical diagnosis results of typical primary liver cancer imaging, the enrolled subjects at a high risk of primary liver cancer should undergo alpha-fetoprotein (AFP) test, liver ultrasound examination (US), test with test reagent and dynamic contrast-enhanced MRI examination, and the sensitivity and specificity of the test reagent should be calculated. AFP will be tested by the conventional method of each center and the method specified by the sponsor.

According to the clinical diagnostic criteria in Guidelines for diagnosis and treatment of primary liver cancer (2019 Edition) set by the National Health Commission: The clinical diagnosis of liver cancer can be made, when a nodule with a diameter ≤ 2 cm is found, and minimum 2 examination results in dynamic contrast-enhanced MRI, dynamic contrast-enhanced CT, ultrasound examination and hepatocyte-specific contrast agent Gd-EOB-DTPA contrast MRI show significant brightness during arterial phase, lower brightness of lesion than liver parenchyma during portal venous phase and equilibrium phase (The concentration of the contrast is significantly higher than that of the normal hepatic tumor tissue during arterial phase in a very short period, then decreases during portal venous phase. It's a typical characteristic of liver cancer); The clinical diagnosis of liver cancer can be made, when a nodule with a diameter > 2 cm is found. Therefore, for subjects with typical imaging manifestations of liver cancer but the diameter of

intrahepatic nodule ≤ 2 cm, an additional imaging examination will be performed to confirm the diagnosis.

3.3.2 Sample size for diagnostic performance evaluation

In this study, the useful samples are planned to be no less than 4500. And each clinical trial center should cherry-pick the subjects and avoid serious bias. If the relevant regulations and policies change during the clinical trial, the trial protocol should be reasonably adjusted to meet the requirements of relevant national regulations and policies, if necessary.

3.3.3 Inclusion Criteria

1) Have high risk factors for liver cancer such as HBV and/or HCV infection, alcoholic liver disease, non-alcoholic steatohepatitis, long-term consumption of food contaminated with aflatoxin, liver cirrhosis caused by various other reasons, and family history of liver cancer Wait;

2) I or my legal representative can read, understand and sign the informed consent;

3) Agree to provide blood samples, be able to receive imaging examinations and have good clinical compliance;

4) The complete clinical basic information includes: the patient's unique traceability number (ID number/outpatient clinic number/medical insurance card number), age, gender, etc.

3.3.4 Exclusion Criteria

1) pregnant women;

2) Have received an organ transplant;

3) Diagnosed with other tumors;

4) The investigators judged that they were not eligible for inclusion.

3.3.5 Judgment criteria for negative and positive result of test reagent

The test results of the test reagent are judged according to the positive value in the instructions for use:

When the HCCscan value is greater than 58, the sample is judged to be positive; when the HCCscan value is less than or equal to 58, the sample is judged to be negative.

For the examinations of "US+AFP", the negative result and positive result are determined according to the following criteria:

1） The results of "US+AFP" is positive if one of the following situations is met:

(1) Serum AFP > 400 ng/mL, regardless of whether any nodule is detected by ultrasound examination;

(2) A nodule ≥ 2 cm is detected by ultrasound examination, regardless of AFP serum concentration;

(3) A nodule ≥ 1 cm but < 2 cm is detected by ultrasound examination, and serum AFP ≥ 200 ng/mL

2） Results that do not meet the above criteria are recorded as "US+AFP" negative.

3.4 Sample requirements

3.4.1 Sample collection

1） Test performance evaluation: 20 mL of peripheral venous blood is needed for the testing with test reagent and control method (note: 10 mL/tube, in total of two tubes). Transfer the blood into a disposable vacuum blood collection tube, mix the blood and anticoagulant by gently inverting the tube 5~6 times.

2） Diagnostic performance evaluation: 10 mL of peripheral venous blood is needed (note: 10 mL/tube). Transfer the blood into a disposable vacuum blood collection tube, mix the blood and anticoagulant by gently inverting the tube 5~6 times.

3.4.2 DNA extraction and sample testing

Samples are processed in strict accordance with standard operating procedures. After nucleic acid extraction, samples should be tested with the test reagent and control method according to the instructions for use, and the raw data should be kept at the same time.

3.4.3 Storage and transportation

Blood samples in disposable blood collection tubes should be stored at 6~37℃ for no more than 7 days.

The separated plasma samples should be subject for extraction immediately. If the samples cannot be processed immediately, they should be stored in a -20±5℃ refrigerator for no more than 6 months.

The extracted cfDNA should be stored at -20±5℃ for no more than 6 months. The the extracted cfDNA should be transported upon dry ice and the transportation period should not be more than 110 hours.

3.5 Trial Implementation Process

3.5.1 Number of included samples

The included samples are numbered before testing, and the numbers are recorded in Screening Inclusion Form. Each clinical trial center will appoint a designated person responsible for numbering the sample that meet the inclusion criteria.

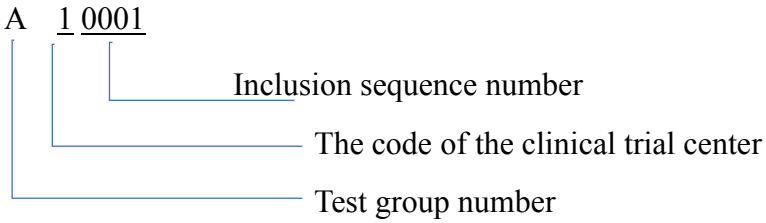
Principle of sample numbering:

Each sample has a 1 letter (A/B, group number) plus a unique 5-digit number.

A represents the group for performance evaluation of test reagent, and B represents the group for percent agreement evaluation of test reagent.

The 1st digit of the number represents the code of the clinical trial center, and the 2nd to 5th digits represent the sequence of inclusion:

For example: the first included sample from the Third Affiliated Hospital of Sun Yat-sen University in the group for performance evaluation: A10001.



3.5.2 Blinding

In principle, one subject only provides one sample, and each subject should have a unique clinical trial number (secondary code). After the samples are included and before the test implementation, the blinding personnel should stick the secondary number on the tube, and save the mapping table of the secondary number and primary number (the

unique traceable number of the subject). Before sample testing, the Blindness Record should be developed by an investigator and reviewed by another investigator for both of them who do not participate in sample testing, then retained by the blinding personnel independently. During the test, only the secondary code of the sample is knowable.

3.5.3 Unblinding

After the samples are tested with the test reagent and control method, the results are unblinded.

3.6 Duration of Clinical Trial

This clinical trial went through protocol drafting, project establishment, ethics review, agreement signing, human genetic resources approval, registration and back-up, clinical initiation and pre-test, enrollment, completion of enrollment, statistical analysis, completion of report, and seal, the duration is about 18 ~ 36 months. If the sample collection is smooth and the number of samples meets the test requirements, the duration clinical trial can be shortened; if it is not smooth, the duration can be appropriately extended.

3.7 Statistical Method of Clinical Trial

3.7.1 Principles of statistical analysis

SAS9.4 software (or higher version) is used for statistical analysis, and PASS16 software (or higher version) is used for sample size calculation. All statistical tests are two-sided (unless otherwise stated).

Basic principles of statistical description: The quantitative data (such as age, gender, etc.) are expressed in forms of mean, standard deviation, median, minimum value, maximum value, lower quartile (Q1), and upper quartile (Q3) according to the distribution of the data; the qualitative data are expressed in forms of the number of cases and the corresponding proportion.

3.7.2 Analysis of general data

The basic demographics and information (such as age, gender and medical history, cancer stage, etc.) of the included cases are statistically described. The quantitative data

are expressed in forms of mean, standard deviation, median, minimum value, maximum value, lower quartile (Q1), upper quartile (Q3); categorical data are expressed in forms of the number of cases and the proportion.

3.7.3 Statistical evaluation of test performance

Evaluation indicators: positive percent agreement, negative percent agreement and overall percent agreement, and the corresponding 95% confidence interval.

A four-fold table is used to calculate the positive percent agreement, negative percent agreement, positive predictive value, negative predictive value, overall percent agreement and 95% confidence interval of the test reagent and the control method.

Table 1 Statistics of clinical results of test reagent and control method

Test product	Control method		Total
	Positive	Negative	
Positive	A	B	A+B
Negative	C	D	C+D
Total	A+C	B+D	A+B+C+D

Note: A sample with a mutation genotype is judged as positive, and a sample with no mutation genotype is judged as negative.

The calculation formula of the percent agreement is as follows:

Positive percent agreement =A/(A+C)×100%

Negative percent agreement = D/(B+D) ×100%

Overall percent agreement = (A+D)/(A+B+C+D)×100%

The calculation formula of 95% confidence interval: $p \pm 1.96 \times [p(1-p)/n]^{1/2}$ (where p is the positive percent agreement, negative percent agreement, and overall percent agreement, n is the sample size. If p>0.9, use Wilson score method for correction).

3.7.4 Statistical evaluation of diagnostic performance

Table 2 Comparison of statistical results between the test reagent and clinical diagnostic standards

Test product	Clinical diagnostic criteria		Total
	Positive	Negative	
Positive	A (true positive)	B (false positive)	A+B

Negative	C (false negative)	D (true negative)	C+D
Total	A+C	B+D	A+B+C+D

The calculation formula of the sensitivity is as follows:

Sensitivity = A/(A+C)×100%

Specificity = D/(B+D)×100%

Overall percent agreement = (A+D)/(A+B+C+D)×100%

Positive predictive value (PPV)=A/(A+B)×100%

Negative predictive value (NPV)=D/(C+D)×100%

The calculation formula of 95% confidence interval: $p \pm 1.96 \times [p(1-p)/n]^{1/2}$ (where p is sensitivity, specificity, positive predictive value, negative predictive value, total percent agreement, n is the sample size. If p>0.9, use Wilson score method for correction.)

At the same time, compare the diagnostic performance of test reagent + AFP, test reagent + AFP + US, AFP + US to the clinical diagnostic criteria.

3.7.5 Comparison of sensitivity across different test methods for screening liver cancer

Make statistical tests on the sensitivity superiority of test reagent + AFP to conventional method (AFP+US) for screening liver cancer, the sensitivity superiority of test reagent + AFP + US to conventional method for screening liver cancer, the sensitivity non-inferiority of test reagent + AFP + US to conventional method for screening liver cancer, the sensitivity non-inferiority of test reagent + AFP + US to conventional method for screening liver cancer.

3.8 Quality control of clinical trials

Quality control is applied at every stage of clinical trials to ensure that all data are credible and correct. The quality control methods are as follows:

1） Qualification of researchers participating in clinical trials: researchers participating in clinical trials must have professional expertise, qualifications and abilities in clinical trials, and pass the qualification review, and the personnel requirements should be relatively fixed.

2） Training and pre-trial: The sponsor is responsible for the training of researchers

before the start of the clinical trial, so as to help the clinical researchers fully understand and understand the clinical trial protocol, the testing of clinical trial products, the filling of original records and forms, etc. know.

3） Laboratory quality control: Clinical laboratories should strictly comply with relevant molecular biology laboratories, clinical The management of gene amplification laboratories is implemented.

4） The test data is valid only if the control quality control test of the clinical trial product meets the requirements.

5） Clinical trial monitoring: The monitor should formulate a complete monitoring plan before the start of the clinical trial, and monitor the clinical trial according to the monitoring plan to ensure that the clinical trial is carried out in accordance with the clinical protocol and ensure the original trial data. and completeness and accuracy of records.

3.9 Controls for bias

Subject samples should be blinded to avoid the introduction of bias due to the fact that the operator and the evaluator of the test results are aware of the subject's disease diagnosis or comparative reagent test results. The detection of in vitro diagnostic reagents for testing should be carried out simultaneously with the judgment of clinical reference standards or the detection of comparative reagents, so as to avoid the deviation of clinical trial conclusions from the true value due to different disease processes or large differences in sample storage time. Bias control is required in each stage of clinical trial institution selection, subject selection, trial process, and statistical analysis.

3.10 Data processing and record keeping

Investigators should fill in the clinical trial case report form and record the contents of the form truthfully, in detail, and carefully to ensure that the contents in the form are complete, authentic and reliable. All observations and findings in the clinical trial should be verified to ensure the reliability of the data and to ensure that the conclusions in the clinical trial are derived from the original data. The clinical trial personnel should truthfully fill in the relevant clinical information and the test results of the clinical trial, and have a designated person to review and sign.

The clinical trial institution shall preserve the clinical trial data for 10 years after the end of the clinical trial. The sponsor shall save the clinical trial data until the medical device is not used.

3.11 Management of samples and instruments

During the development of this trial, investigators who have been trained and qualified by the sponsor and authorized by the principal investigator shall independently manage the samples, reagents, and instruments used in the study to ensure the traceability of the preservation and use of the samples and reagents used in the study. in this test.

3.12 Auditing

The sponsor should send qualified inspectors to monitor the trial process to ensure the quality of the trial. Inspectors should have corresponding professional backgrounds, have undergone necessary training, be familiar with relevant regulations and norms, be familiar with the non-clinical and clinical aspects of the in vitro diagnostic reagents for investigational and similar products, clinical trial protocols and related documents, and be familiar with the relevant documents. Follow the relevant standard operating procedures formulated by the sponsor, and urge the clinical trial to be implemented according to the protocol.

4. Ethical issues and informed consent

4.1 Ethical considerations

This clinical trial strictly complies with relevant laws and regulations such as the "Quality Management Practice for Clinical Trials of Medical Devices" of the State Drug Administration and the "Declaration of Helsinki". This clinical validation trial involves patient-related data. Such as: patient's unique traceable number, age, gender, clinical diagnosis and imaging results, etc. The relevant information of the patient will be kept confidential by the hospital and Beijing Genetron Genetics Co., Ltd. The clinical trial implementer and clinical verification unit promise not to disclose the content related to the subject's specimen.

This clinical trial strictly follows the ethical guidelines established by the Declaration of Helsinki of the World Medical Association and the relevant regulatory requirements such as the "Measures for Ethical Review of Biomedical Research Involving Humans". This trial should be approved by the ethics committee of the clinical trial institution prior to initiation. Any modifications to the study protocol must also be notified and approved by the ethics committee before the changes are implemented.

4.2 Informed consent process and informed consent text

The informed consent form can only be used after it has been approved by the ethics committee of the clinical trial institution, and the revision of the informed consent form can only be implemented after the approval of the ethics committee of the clinical trial institution.

1） Sign the informed consent form:

The samples used in this clinical study are all prospective samples, which are specially collected for this clinical trial, and an informed consent form must be signed with the subjects.

Before each subject is enrolled in this study, the research doctor is responsible for giving him or his designated representative a complete and comprehensive introduction to the purpose, procedures and possible risks of this study in writing. And inform the subjects to withdraw from the research at any time after notifying the investigator without discrimination or retaliation, and any medical treatment and rights will not be affected by this.

2） Informed consent text

The subjects screened and enrolled in this clinical trial are required to sign the informed consent. The sponsor provides the text of the informed consent form to the clinical trial institution, and obtains the consent and approval of the ethics committee of each clinical trial institution before the start of this clinical trial.

5. Analysis of the possibility of adverse events, and provisions for reporting adverse events and product defects

This study will involve blood sample collection and examination with dynamic contrast-enhanced MRI. The collection of blood samples will be performed by professionals in strict accordance with aseptic requirements. There may be some very small risks in the collection of blood samples, including transient pain, local bruising, mild dizziness in a few people, or extremely rare needle infection; The injection of contrast agent used in dynamic contrast-enhanced MRI examination may cause the risk of allergy to the human body; if some subjects are claustrophobic, it may lead to disease attacks, and claustrophobia should be inquired in advance and excluded when subjects are screened patient. If there is any damage related to the blood sample collection and the contrast agent used in the dynamic enhanced MRI in this clinical study, the investigator will treat the subject according to the specific situation of the subject to ensure the safety of the subject and the cost of the treatment. shall be borne by the sponsor.

5.1 Adverse event

Adverse events refer to adverse medical events that occur during clinical trials of medical devices, regardless of whether they are related to the experimental medical devices.

In the event of adverse events related to this study, the principal investigator should provide the subjects with adequate and timely treatment and treatment, and inform the subjects in a timely manner when the subjects develop concurrent diseases that require treatment and treatment.

5.2 Serious adverse event

Serious adverse events refer to medical device clinical trials that lead to death or serious deterioration of health status, including fatal diseases or injuries, permanent defects in body structure or function, requiring hospitalization or prolonged hospitalization,

and requiring medical treatment. To avoid permanent defects in body structure or function; events such as fetal distress, fetal death, or congenital anomalies and congenital defects.

The principal investigator should report to the sponsor, the management department of the medical device clinical trial institution, and the ethics committee within 24 hours after the serious adverse event is known, to ensure that the subjects receive appropriate treatment and follow-up, and submit a follow-up report and/or summary of serious adverse events Report. When necessary, report to the drug regulatory department and health management department of the province, autonomous region, or municipality directly under the Central Government where it is located.

After the first serious adverse event report, the investigator should actively follow up the patient and provide the sponsor or designee with further information about the patient's condition and follow up until the event resolves, the condition has stabilized, the event is otherwise reasonably explained or accepted The subjects were lost to follow-up.

The sponsor or designee may request or schedule additional examinations and/or evaluations by the investigator to clarify the nature and/or causality of the serious adverse event to the extent possible. It is the responsibility of the investigator to provide support. If a patient dies while participating in the study, a copy of any autopsy report should be provided to the sponsor.

5.3 Device defect

Device defects refer to the unreasonable risks of medical devices that may endanger human health and life safety under normal use conditions during clinical trials, such as label errors, quality problems, malfunctions, etc.

Some of the reagents in this clinical trial are stored at low temperature, and this part of the reagents may fail the sample test due to improper storage. During the whole experimental process, the reagents and samples involved in this experiment were stored in accordance with the corresponding instructions and the requirements of this clinical trial protocol. In the event of the above situations, the investigators should timely and truthfully record them in the relevant trial records, and analyze and summarize them in the clinical

trial report.

6. Provisions on the revision of clinical trial protocols

After the trial protocol is determined and approved by the ethics committee, its clinical research design should not be changed in general, but may be modified in the following circumstances: During the trial process, if it is found that it is difficult to select qualified samples according to the original inclusion/exclusion criteria , it is necessary to analyze the reasons and take corresponding measures to modify the original inclusion/exclusion criteria.

Any modification to the trial protocol should be stated in the revised protocol, which must be agreed by the sponsor, the clinical trial institution and the investigator, and the reasons for the modification must be recorded. The revised protocol needs to be re-approved by the ethics committee.

7. What should be covered in a clinical trial report

After the clinical trial is over, the investigators of each clinical trial institution shall summarize their respective clinical trial data, issue a clinical trial summary, and attach the clinical trial data sheet, other test methods used in the clinical trial, or other basic information on in vitro diagnostic reagents and other products. and other information.

The clinical trial report should include the names, units, responsibilities in the research, clinical trial methods, enrolled cases, sample allocation, result analysis, etc.

8. Confidentiality

The personal data of the subjects participating in this clinical study in the trial are kept confidential. The research physician and other researchers will use the subject's medical information to conduct the research. This information may include the subject's name, address, telephone number, medical history, and information obtained during your study visit. Subject files are to be kept in locked filing cabinets for researcher access only. A number is used in the study to identify the subject's research information and laboratory test specimens. Only investigators and research team members can look up the number. In

order to ensure that the research is carried out in accordance with the regulations, when necessary, the research sponsor, the members of the government management department or the ethics review committee can access the personal data of the subjects in the research unit according to regulations. When the results of this study are published, no personal information on the subjects will be disclosed.

9. Responsibilities of each party

9.1 Responsibilities of the sponsor

1) Provide free test products that have passed the inspection, and provide test-related documents, research funds, etc.

2) As the responsible party for quality assurance of clinical trials, qualified inspectors should be dispatched to monitor the quality of the trials to ensure that all trial data meet relevant requirements.

3) Select a qualified clinical trial institution to jointly study and formulate a clinical trial plan with the principal investigator.

4) Responsible for training the researchers of the clinical trial institution related to the trial.

5) The institution and the principal investigator should be informed of problems in the trial in a timely manner, so that the institution can take relevant measures to improve and protect the subjects.

6) Before deciding to suspend or suspend a clinical trial, the research institution, investigator and ethics committee must be notified in writing, and the reasons shall be stated.

7) After the trial, submit the final report and clinical trial summary (sub-center) report to the Ethics Committee and Institutional Office as required.

8) Without the subject's written consent, the subject's personal information/specimens cannot be used for commercial purposes or other research without authorization.

9.2 Responsibilities of clinical trial institutions

1) Design and formulate a clinical trial protocol together with the sponsor, and strictly

follow the protocol.

2) Ensure that the data are truthfully, accurate, complete, timely and lawful in the medical records and case report forms.

3) In case of serious adverse events caused by the assessment products, appropriate treatment measures should be taken immediately for the subjects, and at the same time, they should be reported to the institutional ethics committee and the sponsor, and reported to the relevant departments within the specified time.

4) Accept the supervision of the supervisor dispatched by the sponsor and the inspection of the drug regulatory department to ensure the quality of the clinical trial.

5) The information and clinical trial data provided by the sponsor shall not be leaked without the consent of the sponsor.

6) If the trial progress is affected or the trial is interrupted due to the quality problem of the trial product and the failure to provide the trial product and consumables in time, the clinical trial institution shall not be held responsible.

7) Responsible for writing the clinical trial summary (summary) report, signed and dated by the clinical trial personnel, and handed over to the sponsor after the clinical trial institution seals it.