Hangzhou CIRS Co., Limited (CIRS China)
11F,1# Building Dongguan High Tech Zone, 288# Qiuyi Road,
Binjiang District, Hangzhou, Zhejiang, China
Tel: 0086 571 87206541 Fax: 0086 571 87206533
Email: Edwin.wen@cirs-group.com

The Technical Guidelines for In Vitro Diagnostic Reagents Clinical Trial

Article 1

In vitro diagnostic reagents clinical trial (include comparison experiment with marketed products) refers to the systematically study of in vitro diagnostic reagents performance in the corresponding clinical environment.

Applicant shall choose the clinical trial institution which confirm with the regulation. Applicant shall formulate the clinical trial protocol which can demonstrate the clinical performance according with intended use of the product, prevalence rate of related disease and statistics requirements, under the premise of meeting the requirement of minimum clinical sample size, and farthest control test errors, improve the test quality and analyze the result scientific and reasonable at the same time. Clinical trial report refers to the summary of clinical trial process and result. It is the important basis to evaluate the effectiveness and safety of the product which apply for listing. Also it is one of the important files for registration.

The technical guidelines provide general requirement of in vitro diagnostic reagents only. Due to in vitro diagnostic reagents have the features of developing rapidly, the wide distance between fields of specialization, different intended use, so the clinical trial measure and content are different for the products with different intended use. Applicant formulates the rational clinical trial protocol according to the feature and intended use of product. State Food and Drug Administration shall properly revise the technical guidelines according to the needs of the developing condition of medical device.

Article 2

Basic principle of clinical trial

1 Basic requirements

1.1 Clinical trial shall comply with the ethical guidelines of Declaration of Helsinki, and obtain permission from the ethics committee of clinical institution. Researcher shall consider the risk which caused by the obtained way of samples such as blood, amniotic fluid, pleural fluid, ascites, interstitial fluid, pleural effusion, tissue section, and bone marrow and so on, or the test result, and shall submit the review opinions of ethics committee and informed

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

consent. With the exception, such as impossible to obtain informed consent objectively or there is no risk of the clinical trial for subjects, the researchers can exempt from submitting informed consent after verified and approved by ethics committee.

1.2 Interests, safety, health of subjects shall over scientific and societal interests.

1.3 Protect subject's confidentiality and respect personal privacy to prevent subject from discrimination or harm for the testing results.

1.4 The result of the research before the clinical trial support for clinical trials.

2 Requirements of clinical trial institution and personnel

2.1 The clinical trial institutions are no less than 3 (including 3) for in vitro diagnostic reagents of Class III, and no less than 2 (including 2) for in vitro diagnostic reagents of Class II. The clinical trial shall be conducted according with relevant regulations.

2.2 The clinical trial institutions shall be certified by State Food and Drug Administration.

2.3 Applicant choice clinical trial institution according to product feature and intended use and combine with the factors such as race, epidemiology, pathogenic microorganism and so on. Clinical trial institutions must have professionals and equipments to guarantee the conduction of the clinical trial.

2.4 Applicant shall develop the file to clear assignment of responsibility. Applicant negotiates a conformed clinical trial protocol with all clinical trial institution, develops standard operating procedures according to clinical trial protocol, and trains the all researchers to carry out clinical trial protocol and use in vitro diagnostic reagents, to ensure the operations are consistent and facilitate communication between all researches.

2.5 Before the start of clinical trial, applicant shall makes a preliminary tests with clinical researchers, to makes clinical researchers more familiar with and master the proper equipments, operations, technical performance and so on, and maximize control of experiment errors.

2.6 In clinical trials, applicant shall consider to absorb other relevant professional personnel such as epidemiology, statistics, clinical medicine, laboratory medicine and so on, to ensure the clinical trial is conduct in science and rational.

Article 3

Design principles of clinical trial

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

1 Clinical trial protocol

In order to conduct the clinical trial, applicant shall formulate a scientific and rational clinical trial protocol according with the features of in vitro diagnostic reagents such as category, risk, and intended use and so on. Including the following in generally:

1.1 General information(including product information, clinical trial information about data, personnel and so on, relevant information of applicant)
1.2 Background Information of clinical trial
1.3 Clinical trial objective
1.4 Clinical trial design
1.5 Clinical trial evaluation
1.6 Statistical methods
1.7 Provisions for clinical trial correction
1.8 Ethical problems and explanation of clinical trial, informed consent (if so)
1.9 Data Processing and records retention
1.10 Other content necessary to explain

2 Clinical trial methods

2.1 Clinical trial for newly developed in vitro diagnostic reagents

2.1.1 For newly developed in vitro diagnostic reagents, researcher shall choice proper subjects, and use blinded simultaneous comparison to compare the tested in vitro diagnostic reagents with gold standard of the disease diagnosis.

For in vitro diagnostic reagents which are used to early diagnosis, monitoring of efficacy, prognosis and so on, while compare with the gold standard, need to conduct follow-up study. Researcher shall clear inclusion criteria, follow-up criteria and follow-up time.

2.1.2 Determination of gold standard

Gold standard refers to the recognized, reliable, authoritative diagnosis methods under the present conditions. The common gold standards in clinic are histopathological examination, imageological examination, and identification for isolated and cultured pathogens, conclusion of long-term follow-up, and other common methods of identification in clinic and so on.

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

2.1.3 Subjects selection

Subjects shall be divided into two groups: one group is diagnosed with disease as case group by gold standard. Another group is diagnosed without disease or normal people as control group by gold standard. The case group shall include different case of this disease, such as typical and untypical, the early, middle, late stage of illness course, light, middle, serious of illness condition, different sexual, different age cohorts and so on, to reflecting all characteristics of this disease. Control group shall include patients without this disease, and patients with a disease which confuse with this disease.

2.1.4 Blinded simultaneous test

The samples of case group and control group which are determined by gold standard are redetected by tested in vitro diagnostic reagents. Comparing the results gained from both methods and calculating coincidence rate or difference level of the statistical index of the two methods. The effectiveness of the tested in vitro diagnostic reagent shall be evaluated according to the statistical index. During the process of test operation and test result analysis, it is the key to take blinded methods (take double-blinded as possible) to ensure the results of the clinical trial is authentic.

2.2 Clinical trial of product what the same variety has be marketed

Selecting marketed product and taking comparison experiment between tested in vitro diagnostic reagents and the marketed same variety to ensure that the in vitro diagnostic reagents is equivalent to the marketed same variety.

2.2.1 Contrast reagent selection

Based on the premise of taking the marketed same variety as the contrast reagent, the better product that has been considered better in clinical shall be selected. Understanding the technical information of the selected product fully, that about methodology, intended use, main performance index, calibrator, positive standard or reference intervals and so on, in order to analyze the result scientifically.

2.2.2 Subjects selection follow “2.1.3”

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

2.2.3 If the result of sample is not consistent in the comparison experiment, it shall take golden standard or other methods to reexamine the sample, as to analyze the clinical trial result. If it does not need to reexamine, it shall be detailed explanation of the reasons.

2.3 About clinical trial on application regarding changes

According to the impact of change on product performance, taking a comparison test between post-alteration product and pre-alteration product or the marketed same variety, to ensure the post-alteration produce is equivalent to the contrast product.

2.4 About clinical trial of imported product

For the imported product, the change of target population species and region may make effect on the technical index and effectiveness of product. Applicant or researchers shall consider the factor of different national or the different area such as epidemiology background, characteristics of different diseases, and positive standard or reference intervals of different species and so on, to take a targeted clinical trial in China.

3 Sample sizes of clinical trial

Applicant or researcher shall determine the sample sizes and sample distribution according to intended use of the product and clinical occurrence rate of the relevant disease. The sample sizes and sample distribution shall conform to the relevant requirement of minimum sample size of guide principle and the statistical requirement. The sample sizes and sample distribution of clinical trial institution shall be relative balanced.

The sample sizes of in vitro diagnostic reagents which are used for rare disease and public health emergencies could be reduced suitably. But it shall make an explanation, and the sample sizes shall meet the need of evaluation.

3.1 General requirements

3.1.1 The product of Class III: the sample sizes of clinical trial shall be 1000 at least.

3.1.2 The product of Class II: the sample sizes of clinical trial shall be 200 at least.

3.2 Special requirements

3.2.1 In vitro diagnostic reagents which are used for pathogen detection by nucleic acid amplification method: the sample sizes of clinical trial shall be 1000 at least.

3.2.2 In vitro diagnostic reagents which relate to the detection of narcotic drugs, psychotropic drugs, and medicinal toxic drugs: the sample sizes of clinical trial shall be 500 at least.

3.2.3 In vitro diagnostic reagents which support the use of Flow Cytometry: the sample sizes of clinical trial shall be 500 at least.

3.2.4 Immunohistochemistry antibody reagent and detection kit: the sample sizes of clinical trial shall be 1000 at least if the marker of the product related to clinical treatment and drug use, or the marker has new clinical significance. The sample sizes of clinical trial shall be 500 at least if the marker of the product is one of markers of comprehensive diagnosis which need multiple indexes or the marker related to auxiliary diagnosis, differential diagnosis, monitoring of disease.

3.2.5 In vitro diagnostic reagents which are used for blood group test: the sample sizes of clinical trial shall be 3000 at least.

3.2.6 The sample sizes of newly developed in vitro diagnostic reagents of clinical trial shall be same with Class III.

3.2.7 Clinical trial related to change: if the changes involve product testing optimization, increase other sample type which is comparable with original sample type and so on, the sample sizes of clinical trial for Class III shall be 200 at least, and the sample sizes of clinical trial for Class II shall be 100 at least, and applicant should select at least 2((inclusive 2) clinical trial institutions for the clinical trial.

If changes involve suppliers of main raw materials such as antigen, antibody and so on, positive standard or reference intervals, clinical applicability increase, and so on, the sample sizes of clinical trial shall be appropriate increased according to the concrete situation.

3.2.8 If the guiding principle of in vitro diagnostic reagents which is issued by State Food and Drug Administration has the provisions on the sample sizes, the sample shall be determined according to relevant guiding principle.

4 Signature requirement of clinical trial protocol

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

The clinical protocol need to be signed by main researcher, clinical trial institutions, principals of statistics and unit, applicants.

Article 4

Clinical trial report writing

The report must details the design and key points, and clearly describes the implementation of the experiment, raw data and statistical methods.

Applicant or clinical trial auspices shall gather the summaries which are submitted by clinical trial institution and draw a conclusion. The format and content of clinical trial report as following:

1 Preface

Preface is the first part of clinical trial report, and all the report shall include this part.

1.1 Cover title

Cover title shall include the common name of in vitro diagnostic reagents, start date completion date of clinical trial, main researchers (signature), clinical trial institution (signature), principals of statistics (signature) and units (signature), applicant (signature), contacts and contact information of applicant, report date, preservation location of raw data.

1.2 Directory

List the contents of directory and corresponding page number of the clinical trial report.

1.3 Abstract

Introduce the clinical trial simply

1.4 Research staffs

List the name, unit, responsibility and resume (listed in the attachment) of main research staffs. The main research staffs include main researcher, and main attendees of institutions, principals of statistics, writer of clinical trial report.

1.5 Abbreviation

1.6 The full name of abbreviation used in the clinical report.

2 Body content and report form

2.1 Basic contents

2.1.1 Introduction

Introduce the background of clinical trial: include ①source, biological characteristics, physicochemical property of the tested product; ② intended use, target population, and the clinical or laboratory diagnostic method which is aimed at target indication and so on; ③ method, principle, technical requirement and so on. ④ application status of marketed product at home and abroad, and so on. Introduce the partnership between the applicant and the clinical trial institutions.

2.1.2 Objective

Introduce the objective of the clinical trial.

2.1.3 Management of clinical trial

Introduce the management structure of clinical trial

Management structure includes main researcher, main attendees, and quality control of laboratory, control of statistics/data, problems arising in clinical trial and its treatment measures and so on.

2.1.4 Clinical trial design

2.1.4.1 Introduce the total design and protocol of clinical trial

The total design and protocol of clinical trial shall be detailed clearly and simply, can use intuitive way like chart. The

The modifications of protocol and the source of the information which beyond the protocol shall be detailed

2.1.4.2 Clinical trial design and selection of test method

Address: 11/F., Building 1, Dongguan Hi-Tech Park, 288 Qiuyi Road, Binjiang District, Hangzhou 310052, China
Tel: +86 571 8720 6555 | Fax: +86 571 8720 6533 | Email: Edwin@cirs-reach.com

Clinical trial design shall include the following:

a. Sample sizes and basis for determination

b. Basis for selection of sample, the inclusive criteria, exclusive criteria and eliminated criteria

c. Sample collection, storage and transportation and so on.

d. Establishment of golden standard and contrast reagent

e. Record the name, specification, source, a batch, validity and preservation condition of the tested reagent, and the register condition of contrast reagent.

f. Quality control method. Make a brief exposition about quality control method.

g. Statistical methods of clinical trials data

h. Modifications of protocol

In general, the clinical trial protocol shall not be modified. Modifications of protocol shall be illustrated. Elaborate the change of time, reason, change process and whether record or not, and discuss the effect on the whole research result caused by the change.

2.1.5 Clinical trial results and analysis

2.1.6 Discussion and conclusions

2.2 Specifically states related to clinical trial

2.3 Attachment

2.3.1 Record the other clinical trial methods or basic information of other diagnostic reagent, such as test methods, the source of diagnostic reagent, institution and register condition.

2.3.2 The test data of the clinical trial shall be signature by the operator and reviewer, and stamped by clinical trial institution (cover seal and across-page seal).

2.3.3 The main reference literature

2.3.4 Leading researcher resume

2.3.5 Other Situations shall be explained by applicant and so on.

Article 5

The noun explanation

The test in vitro diagnostic reagents refers to the in vitro diagnostic reagents which shall be confirmed or verified their safety and effectiveness by clinical trial.

Clinical trial protocol refers to the file about title, objective, design, methodology, statistics, and organization and so on of clinical trial. It usually includes background and theoretical basis of the clinical trial.

Researcher refers to the person who conducts the clinical trial in the clinical trial institution. If a group of persons conduct the clinical trial, so the researcher refers to the in charge of the group, also known as a leading researcher.

Subject refers to the person who is recruited to take in the clinical trial. Subject can be the person who detected by test in vitro diagnostic reagent, also can be the control person.

Informed consent refers to the progress that subjects confirm that they volunteer for the clinical trial after they are advised the all sides condition of the clinical trial. The subjects must signature and date on the informed consent form which as the documentary evidence.

Informed consent form refers to the documentary evidence which can prove that subjects volunteer for the clinical trial. Research shall advise the subject on the clinical trial about tentative, objective, possible benefits and risks, other diagnosis methods to be selected, and the rights and obligations of subjects which conform to Declaration of Helsinki, let the subject fully understood the clinical trial to make a decision that they agree to take part in the clinical trial on their own.

Ethics committee refers to the independent institution which is made up by medical professional and non-medical professional from clinical trial institution. It is the responsibility of ethics committee to consider the scientificity and ethic of the clinical trial. To be specific, approve the clinical trial protocol, consider and puts forward relevant advice on personnel qualification, facility instrument and methods of informed consent and so on, to ensure the safety, health and benefits of subjects.

Standard operating procedure refers to the standard and detailed documented procedures about conducting and finishing everything works of one clinical effectively.