General issues and precautions in the design for clinical trials of investigational new drugs

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Abstract: The general problems existing in the clinical trials of investigational new drugs involve some key aspects such as the guiding principles, research designs, quality controls and statistical analyses. This paper explores the eight general issues in the clinical trials of investigational new drugs and presents precautionary measures with high operability. Research on the clinical trials of investigational new drugs is a complex project, which should be carried out strictly according to the policies, laws, criteria and operating rules set by related agencies. The neglect of research designs and data analyses will lead clinical trials to failure.

Keywords: statistics, medical; drugs, investigational; clinical trial; research design

Clinical trials of investigational new drug are a very complex issue, as they must be carried out strictly according to policies, laws, criteria, operating rules and principles made by numerous related agencies. Unfortunately, most policies, operating rules and principles are quite general. When it comes to the detailed criteria for phase I, II, III and IV trials of investigational new drug, researchers have to make specific research plans and clinical report forms (CRFs). The key part of the plans and CRFs that influences the research quality both directly and indirectly is the clinical trial design. This paper introduces and elaborates upon eight general issues in the design for clinical trials of investigational new drug and puts forward precautions. It also gives three real examples of designs for clinical trials of investigational new drug together with discriminations, analyses and explanations.

1 Introduction of the eight general issues in the design for clinical trials of investigational new drug

The eight general issues facing designers of clinical trials are: (1) Most designs lack a systematic, rigorous, scientific and reasonable consideration on the design plans and the CRFs; (2) Researchers lack a careful consideration on the three key elements (research subjects, experimental factors and experimental effect) of trial designs; (3) Researchers do not follow the four basic principles (control, random, replication and balance) strictly; (4) Some researchers...
emphasize too much on simplification; (5) Some researchers neglect quality control when making and performing design plans; (6) Some researchers neglect common sense and specialty when setting design plans; (7) Researchers do not carry out thorough consideration on possible unusual situations during the research process and lack appropriate solutions; (8) Researchers do not think carefully about the arrangement and analysis of the experimental data, which results in a conclusion unable to stand the test of time and practice.21

2 Critical analyses of clinical trials of investigational new drug that encounter problems in research designs

2.1 Example 1 Evaluate the safety and efficacy of drug A against microwave radiation. The measuring tool used in the research was called “measuring meter of cognition and anxiety”. It listed dozens of indexes that reflected the condition of nerve function. The research subjects were designed to be observed for two weeks. Researchers chose 120 healthy males aged between 20 and 40 as the research subjects whose job was operating the radar, and divided them equally into the treatment group and the control group. The conclusion was that the difference of most indexes before and after treatment reflected by the measuring meter had no statistical significance. Analysis and explanation of example 1 are as follows.

2.1.1 Issues concerning research subjects First, the research did not set an explicit standard of the cognition and anxiety conditions of the subjects before the research started. The different length of time that the subjects worked in the microwave radiation field would lead to different levels of cognition and anxiety. Second, the subjects were aged between 20 and 40, however, there was no such an age regulation in the drug operating instructions.

2.1.2 Issues concerning experimental and non-experimental factors The experimental factor of the research was “drug type”, which includes the experimental drug and the control drug. Besides, there were many non-experimental factors that the researchers neglected, such as the type of occupation involving microwave radiation (radar, navel vessel, car or aircraft cockpit); the length of time spent working in the microwave radiation field (less than 1 year, 1 year to 2 years, 2 to 3 years, over 3 years); the occupational environment (plateau or plain, land or sea, indoor or outdoor).

2.1.3 Issues concerning observed indexes There were dozens of indexes in the research, most of which were subjective. However, the research did not name any as the major index(es). Besides this, since most of the indexes were subjective, the sensitivity and specificity were not high enough; the research lasted for two weeks, in which the efficacy of the drug might not have started to appear; there were no traditional Chinese medicine (TCM) indexes which have high reference value; there was no explicit statement about whether the chosen indexes met the specificity criteria. One thing worth mentioning here is that the evaluation criteria in the design were not the same as the criteria in the analysis. In the research design, the efficacy was divided into four categories, namely, “almost recovered”, “remarkably effective”, “effective” and “ineffective”, which indicated that the data were considered as “ordered data”. However, in the statistical analysis, the researchers analyzed the data by computing the arithmetic mean, indicating that the data were considered as “quantitative data”.

2.1.4 Issues concerning randomization and balance

The research divided all the subjects into two groups, the experimental group and the control group by complete randomization. However, the research did not mention whether all the important non-experimental factors of the subjects were the same. In fact, when the sample size is not large enough, complete randomization is not very effective most of the time. Therefore, instead of complete randomization, stratified randomization of the subjects according to several important non-experimental factors based on common sense and specialty is recommended.

2.1.5 Issues concerning sample size estimation

The research had a sample size of 120, but did not mention the foundation of the sample size estimation. Therefore, whether or not the test power was sufficient could not be ascertained.

2.2 Example 2 Evaluate the safety and efficacy of drug B in the treatment of chronic renal insufficiency. The clinical research plan stated clearly that drug B is a supplementary drug which can be used with other drugs. The researchers divided a total of 240 patients who were suffering from chronic renal insufficiency into the experimental group (with drug B) and the control group (with placebo) by complete randomization. The research listed many TCM and Western medicine indexes without mentioning the major indexes. The regional effect of the multi-clinical centers was clear. However, the research did not give an explanation or data processing method. Analysis and explanation of example 2 are as follows.

2.2.1 Issues concerning randomization and balance

Generally, there are four stages of renal insufficiency: first, the compensatory stage, second, the decompensatory stage, third, renal failure and finally, uremia. From stage 1 to stage 4, the degree of nephrosis becomes more and more severe. However, the research did not perform the stratified randomization according to the stages of the disease, which failed to guarantee the balance between the experimental group and the control group when the sample size was not large enough. If the number of patients in each stage in the
2.2.2 Ensuring consistency between the two groups concerning the initial condition of subjects prior to complications As drug B is a supplementary drug, the patients were allowed to use other drugs because the researchers were focusing only on the mitigation of complications of nephrosis. Since the patients could choose any drug except the experimental or the control drug, it cannot be guaranteed that the initial conditions of the subjects before the complications started in the experimental group and in the control group were the same. Thus, even if the difference of incidences of the complications between the experimental group and the control group had statistical significance, it could not be attributed to the difference between drug B and the placebo. Whether “the main drug” in the experimental group and the control group were comparable will directly influence the reliability of the conclusion.

2.2.3 Issues concerning the selection of the major indexes The research did not specify which indexes were the major areas of study. Instead, it listed numerous TCM and Western medicine indexes, thereby putting the reliability of the conclusion into question. Below are some major indexes for reference: the number of patients in a stable condition at each stage; the number of patients in a serious condition at each stage; time of postponing the exacerbation of disease.

2.2.4 Issues concerning quality control in clinical trials There were significant potential regional effects in this multi-regional clinical trial. The main reason is that researchers did not carry out adequate quality control, which was shown in the following aspects: the inconsistency of inclusion criteria, experimental operators, equipment characteristics, reagent quality and methods of measurement and evaluation. To be strict, if there are serious regional effects in a clinical trial, the research fails.

2.3 Example 3 Evaluate the safety and efficacy of drug C in the treatment of chronic cholecystitis. Researchers divided the subjects into groups by stratified randomization based on the clinical trial centers. The research took the non-inferiority design and divided a total of 240 patients equally into the experimental group and the control group in every clinical trial center. The plan did not mention how to tell from biliary infection and cholecystitis, and did not give the non-inferiority dividing value. The researchers used index of imaging as the major index to evaluate the efficacy but did not state the quality control criteria of the index. Analysis and explanation of example 3 are as follows.

2.3.1 Issues concerning research subjects The research did not exclude patients suffering from acute cholecystitis, and it also failed to group the patients based on the following two factors: the cholecystitis with or without gallstones and the gallstone type.

2.3.2 Issues concerning experimental factors and non-experimental factors Factors that directly influence the effect of treatment for cholecystitis include: the drug type, cholecystitis with or without gallstones (simple cholecystitis, cholecystitis with gallstones), the gallstone type (cholesterol stone, cholecromone stone, mixed stone), the gallstone volume (small, middle, large) and the frequency of relapse. The above four factors are important non-experimental factors in this research and may cause an inaccurate conclusion if neglected.

2.3.3 Issues concerning observed indexes The researchers chose the index of imaging (type-B ultrasonic result) as the major index, which, unfortunately, was semi-objective. Different physicians with different experiences and backgrounds may give different results based on what they saw from the equipment. Therefore, the data from multi-regional clinical trials should not be analyzed together if there were no strict quality control methods and uniform skill training because the data were not homogeneous. Besides, the research did not follow the steps of the non-inferiority research since it did not give the non-inferiority critical value.

2.3.4 Issues concerning random grouping and balance Although the researchers adopted stratified randomization, they only treated the clinical trial centers as a stratified factor, but did not group the subjects in stratified randomization based on important non-experimental factors, such as “cholecystitis with or without gallstones” and “gallstone type”. Therefore, it could not be ensured that the experimental group and the control group were balanced in the above two important non-experimental factors. Thus, the two groups were not comparable.

3 Explanation of the eight general issues in the design for clinical trials of investigational new drug

(1) Many clinical research plans and CRFs have contradictory statements about the same issues, including the research objective, the quality and quantity of the subjects, the definition of the data sets, the major and minor curative effects and the safety indexes. (2) The inclusion and exclusion criteria for research subjects are not set appropriately. Sometimes, even some important information is missing. In terms of determining factors, some important experimental factors like the drug dose and time are neglected, let alone some important non-experimental factors which may have a huge influence on the result. In terms of indexes, researchers often list many subjective indexes, but do not indicate which constitute the major index (es). (3) Researchers frequently think that
complete randomization is the best way for grouping. Therefore, clinical trials of investigational new drug frequently group the subjects by complete randomization. However, when the sample size is not large enough, the results of complete randomization may be unusable as the groups are not balanced in many important non-experimental factors, which results in non-comparable groups. Researchers often mistakenly think that a clinical trial of investigational new drug only needs to set an experimental group and a control group to draw a convincing conclusion. However, the control groups are often set unreasonably. Sometimes researchers even make the mistake of incomplete control or false control. In terms of the principle of replication, most clinical trials of investigational new drug only determine the sample sizes based on researchers’ experience, but not on convincing foundations. Since the principles of randomization and control are not performed well, most clinical trials of investigational new drug are not balanced in groups. To sum up, there are few clinical trials of investigational new drug that strictly follow the four basic principles of experimental design. (4) Researchers frequently adopt the design of one factor with two levels when doing new designs, data expressions and descriptions and statistical analyses. In fact, there are always several important non-experimental factors in every research. Therefore, not only should we use stratified randomization in grouping, but we should also take proper methods for data expressions and descriptions and statistical analyses. (5) In clinical trials of investigational new drug, the research subjects, researchers and reviewers are all people. Factors concerning conditions, environment, mentality and benefits will influence the observed results and evaluation directly or indirectly. To ensure that the whole research process is under strict supervision and management, it is necessary to make rigorous plans of quality management and control, and make sure that they have a high operability. (6) When setting clinical research plans, researchers usually lack a thorough thinking about the details of the research, because they do not pay enough attention to “common sense and speciality”, which is shown by the fact that they frequently forget to consider the important non-experimental factors in grouping and in doing statistical analysis. (7) The particularity and complexity of clinical trials of investigational new drug determine the uncertainty of the research as a whole. Lack of a thorough thinking before the research starts may cause serious consequences. For example, researchers may be caught unprepared when unusual problems occur during the research, and the emergency measures they take to solve the problems may not be appropriate or effective, which may lead to the failure of the research. (8) After research data have been collected, statistical analysis should not be performed immediately. Instead, researchers should check the numbers and the quality of the CRFs. Data management of new trails should be arranged scientifically beforehand, which includes how to create databases, how to record and check data, how to lock and save databases, how to carry out unblinding, etc. Data analysis and statistical reporting include how to perform statistical expressions and descriptions of the data, how to carry out a systematic analysis of the data, and how to deliver a scientific and systematic report of the results, which should be stated clearly in the new drug clinical research plans. Besides, researchers should also set detailed implementation plans, for instance, data management plans and statistical analysis plans.

4 How to prevent serious mistakes that may occur in the design for clinical trials of investigational new drug

Since the subjects of the clinical trials of investigational new drug are human beings, most researchers attach great importance to ethics (the research should be approved by a qualified ethics committee, and researchers should sign the informed consent form with the subjects) and compliance of the subjects (usually, the double-blind or triple-blind method is adopted) which are decisive. Most researchers mention the issues concerning ethics and the compliance of the subjects in their clinical research plans. However, only a few of them will pay special attention to them. The serious mistakes in the clinical research plans involve “the three key elements, the four basic principles and the design types”, which are the essence of the research design. Serious problems concerning ethics and compliance will be fatal to all research.

How to ensure that there are no serious problems involving the selection of subjects: the key is to make logical “inclusion and exclusion criteria” for subjects with high operability and promotional value.

How to ensure that there are no serious problems concerning the selection of factors: the key is to ascertain what the experimental factors of the research are (the investigational new drug and the standard drug, the investigational new drug and the placebo, or the different doses of the investigational new drug) and what the important non-experimental factors are, which may influence the effectiveness and the safety of the research.

How to ensure that there are no serious problems involving the selection of indexes: identify the objective, sensitive and specific indexes that can reflect the efficacy and safety of the investigational new drug. Then, indicate one or two indexes with the best representation to be the main index(es) in terms of efficacy and safety.
How to ensure that no serious problems arise concerning the four basic principles: carry out the stratified randomization based on the important non-experimental factors. The control drug should be selected among many drugs after serious comparison and consideration. The sample size should be calculated following certain formulas based on the results of the pilot test or the information provided by generally acknowledged literature, the design type, the comparison type, the characteristics of the main indexes and the precision requirement of the results.

How to ensure that the design type of the research is appropriate: The design type of a research should be determined by the combination of experimental factors and important non-experimental factors and their influence on results. For instance, in multi-regional clinical trials of investigational new drug, “clinical trial center” is one of the important non-experimental factors if there is no strong evidence showing that it is not. In fact, in clinical trials of investigational new drug, factors like “the disease type”, “the disease state”, “time of being ill”, and “physical conditions of the patients (for instance, perimenopause or postmenopause)” could all be important non-experimental factors. Experimental factors and non-experimental factors should be considered together whether in conducting statistical description or statistical analysis. They should also be treated as certain multi-factor designs, for example, multi-factor design or multi-factor design with a block, multi-factor design with one repeated measurement factor or two repeated measurement factors, multi-factor nested design, etc. Besides, the important non-experimental quantitative factors should not be neglected in clinical trial designs and statistical analyses. If there are important non-experimental quantitative factors, they should be considered as covariates and should be collected from each research subject during clinical trial. When it comes to statistical analysis of quantitative covariates, ANCOVA (analysis of covariance) of quantitative data of the corresponding designs should be adopted.

5 Conclusion

Setting clinical research plans for investigational new drug are very challenging, because a high-quality plan requires the researchers to give full play to common sense, specialty and statistics. Therefore, joint efforts of many experienced and responsible researchers who are involved in basic scientific research, clinical research, statistics and software application research are required. To sum up, a scientific, convincing, logical, reliable and economic clinical research plan for investigational new drug is achieved by understanding the crystallization of the collective wisdom of numerous successful researchers[2].

REFERENCES


新药临床试验设计中普遍存在的问题及防范措施

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摘要：新药临床试验设计中存在的问题涉及指导思想、科研设计、质量控制、统计分析等临床试验研究过程中的关键环节。本文揭示了新药临床试验设计中存在的 8 大问题，并提出具有可操作性的防范措施。新药临床试验研究是一个非常复杂的系统工程，在新药 I、II、III、IV 期临床试验研究过程中，特别是在新药临床试验研究方案和临床病例报告表的研制和实施过程中，必须严格参照国家相关部门制定的政策、法规、标准和操作规程。忽视临床试验设计与数据分析的科学性与严谨性，必将导致临床试验研究的失败。

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