The principle of randomization in scientific research

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Abstract: Scientific research design includes specialty design and statistics design which can be subdivided into experimental design, clinical trial design and survey design. Usually, statistics textbooks introduce the core aspects of experimental design as the three key elements, the four principles and the design types, which run through the whole scientific research design and determine the overall success of the research. This article discusses the principle of randomization, which is one of the four principles, and focuses on the following two issues — the definition and function of randomization and the real life examples which go against the randomization principle, thereby demonstrating that strict adherence to the randomization principle leads to meaningful and valuable scientific research.

Keywords: statistics; medical; research design; randomization

In conducting scientific research, researchers should not only take into consideration the three key elements, namely, the research subjects, the research factors and the experimental effects, they should also follow certain important principles, so that statistical research design will be scientific and rigorous. The four principles of statistics research design are: randomization, control, repetition and balance, which are key to the success of scientific research and should be strictly followed. This article will focus on the principle of randomization.

1 The definition and function of the randomization principle

What is the randomization principle? In a strict sense the principle of randomization refers to the requirement that in selecting a sample, each individual has an equal chance of being selected into the sample; furthermore, in dividing a sample, each individual of the sample has the same likelihood of being assigned to any group.

The function of randomization is to eliminate bias in sampling or grouping which is caused by human or psychological factors. Effective randomization gives rise to good representativeness in the samples and balance among the research subjects in each group for important non-experimental factors. Thus, the comparability of research data will be improved.

The randomization principle can be evaluated from the following perspectives: (1) the random-
ization of sampling: each research subject that meets the inclusion criteria should have the same chance of being selected into the research, that is, each individual in the population should have an equal chance to be selected into the sample; (2) the randomization of grouping: each research subject in the sample should have an equal chance of being assigned to different groups (generally, there are several experimental groups and a control group). The first aspect guarantees the representativeness of the sample so that the research conclusion will be generally applicable. The second aspect guarantees balance among research subjects in each group in order to enhance the comparability of each group.

For example, a researcher randomly catches mice with his eyes closed from a cage full of mice. He assigns the 10 mice first caught to the placebo group, the following 10 mice to the drug A group, and the last 10 to the drug B group. Although the researcher randomly catches the mice with his eyes closed, it is quite possible that the mice first caught by him are not as energetic and active as the ones caught later. Therefore, the research subjects themselves in the three groups may differ considerably. Even if the research results show some difference in the three groups, it cannot be fully attributed to the different drugs that the research subjects have taken. Therefore, the randomization principle must be adopted in grouping in order to eliminate the interference of important non-experimental factors on research results.

It is important to address whether complete randomization is always the most effective way to balance the groups. The answer is no. If the sample size is large enough, the effect of complete randomization will be satisfying; however, if the sample size is relatively small, the research subjects which are grouped by complete randomization will not be balanced with respect to many important non-experimental factors. In these cases, stratified randomization would be more appropriate. Stratified randomization divides research subjects according to important non-experimental factors which will have significant influence on observed indexes, and then subdivides the subjects into subgroups by complete randomization, which guarantees that the research subjects in each group are balanced for the important non-experimental factors. For example, there are 24 mice, of which 16 are female. If the 24 mice are divided into two groups by complete randomization, it is possible that the 12 mice in one group are all female, and the other group will have 4 females and 8 males. If “gender” is an important non-experimental factor, grouping by complete randomization will severely influence the observed results and the conclusion will probably be inaccurate. In this case, stratified randomization is recommended, that is, equally divide the 16 female mice into two groups by complete randomization, and then divide the 8 male mice into the two groups also by complete randomization. In this way, both the experimental group and the control group will have 12 mice with 8 females and 4 males. Thus, the influence of the important non-experimental factor “gender” on the experimental group and the control group will be balanced.

2 Examples that violate the randomization principle

2.1 The method of random grouping is obscure

2.1.1 Example 1 In order to observe the effects of Feixian Formula, a compound traditional Chinese herbal medicine on bleomycin-induced pulmonary fibrosis in rats, and its influence on serum transforming growth factor-$\beta_1$ and platelet-derived growth factor, 72 male Wistar rats were infused with bleomycin (1 mg/kg) through tracheal intubation to induce pulmonary fibrosis, and were randomly divided into untreated group ($n = 24$), prednisone-treated group ($n = 24$) and Feixian Formula-treated group ($n = 24$).

2.1.2 Discrimination and analysis of example 1

The author did not explain in detail how the random grouping was carried out. In random grouping, the balance of important non-experimental factors among groups should be carefully considered. Thus, when the sample size is not large enough, stratified randomization is recommended.

2.2 Casual grouping results in violation of the randomization principle

2.2.1 Example 2 A total of 200 cyasma patients from a gynecology clinic of traditional Chinese medicine (TCM) were divided into a treatment group and a control group based on their own will. The 100 patients in the treatment group were aged between 20 and 48 with an average age of 34.5 years. The duration of disease ranged between 6 months and 24 years with an average of 11 years and 1 month. They were treated with TCM. The 100 patients in the control group were aged between 21 and 50 with an average age of 34.0 years. The duration of disease ranged between 5 months and 24 years with an average of 11 years and 1 month. The patients in the control group had good economic conditions, and were treated with Western medicine and facial massage because they were not willing to be treated by TCM. The duration of disease, age, disease severity and cyasma area of the two groups were statistically insignificant.

2.2.2 Discrimination and analysis of example 2

In example 2, the research subjects were divided into a treatment group and a control group according to their own will instead of the randomization principle. The control group was composed of 100 patients with good economic conditions. However,
the economic condition may be an important non-experimental factor. The researcher divided the subjects into two groups based on their own will, which directly caused imbalance between the two groups and an unreliable conclusion.

2.3 Retrospective studies usually have difficulty following the randomization principle in selecting research subjects

2.3.1 Example 3 In order to investigate the pathogenic factors, prognosis, preventive and therapeutic interventions of severe acute pancreatitis (SAP) complicated by hepatic insufficiency, 152 patients with SAP (from January 2003 to June 2004) were divided into two groups, SAP with hepatic insufficiency group (67 cases) and SAP without hepatic insufficiency group (85 cases). The related factors, such as serum biochemical criteria, complications, mortality and course of disease were observed.

2.3.2 Discrimination and analysis of example 3 In this example, the researcher chose SAP patients from January 2003 to June 2004 as the research subjects, which is a typical retrospective study. However, the retrospective study can not meet the randomization principle requirements for selecting research subjects because it has a time limit, sometimes even a specific place. The chosen patients vary considerably in age, disease course, disease severity and so on, which can not be resolved by retrospective study. Therefore, the conclusion based on the retrospective research is unreliable. The more appropriate way is to randomly select a certain amount of patients in the appropriate population.

Some clinicians think that clinical trials are simple because the only thing they need to do is to summarize their experience, which causes the low quality and reliability of the clinical research. Prospective studies are strongly recommended for clinical trials, because random controlled trials are the most persuasive. Under the premise of not violating moral issues, more large-scale prospective clinical trials should be carried out. Researchers should strictly follow the four principles, select observed indexes with high sensitivity and specificity, improve quality control during research and adopt appropriate statistical methods for data analysis in order to gain convincing and reliable conclusions.

2.4 Stratified randomization is replaced by complete randomization

2.4.1 Example 4 In order to observe the therapeutic effects of Yiqi Sanju Formula (YQSIF), a compound traditional Chinese herbal medicine, in the treatment of non-alcoholic fatty liver disease (NAFLD), the researchers randomly divided 67 NAFLD patients into two groups according to the random number table. YQSIF-treated group (39 cases) and placebo group (28 cases). The YQSIF-treated group was composed of 25 males and 14 females, with a mean age of 52.6 ± 12 years. The placebo group was composed of 19 males and 9 females with the mean age of 54.8 ± 11.0 years. The baseline data in the two groups were tested to be statistically insignificant.

2.4.2 Discrimination and analysis of example 4 In example 4, the researchers divided the research subjects according to the random number table, that is, they divided the subjects by complete randomization. Although the baseline data were tested to be statistically insignificant, when the sample size is not large enough, the result of complete randomization is more often than not unsatisfactory. A more appropriate method is to divide the subjects by stratified randomization, that is, divide the patients who meet the inclusion criteria into subgroups based on several important non-experimental factors so that the subjects in each group will be balanced in age, gender, the severity of NAFLD and so on. Then subdivide the patients in each group into the YQSIF-treated group and the placebo group by complete randomization. In this way, the influence of important non-experimental factors will be balanced and the result and conclusion will be more reliable.

3 Competing interests

The authors declare that they have no competing interests.

REFERENCES

科研设计应遵循随机原则

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摘要：科研设计包括专业设计和统计学设计，而统计学设计又可分为实验设计、临床试验设计和调查设计。统计学教科书中认为，科研设计的核心内容为三要素、四原则和设计类型，而这个核心内容贯穿于整个科研设计之中，成为任何一个科研课题成败的关键。本文讨论四原则中的随机原则，重点分析以下两个问题：随机原则的概念与作用及违背随机原则的实例。通过若干实例揭示随机设计的重要性及科学价值。

关键词：统计学，医学，研究设计，随机

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