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***Biostatistician's Eyes** / Biyoistatistikçi Gözünden*

Genes predisposing tunneled catheter thrombosis in hemodialysis patients: Determination of sample size in clinical trials

Hemodiyaliz hastalarında tünelli kateter trombozuna yatkınlaştıran genler: Klinik çalışmalarda örneklem büyüklüğünün belirlenmesi

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One of the most important steps in planning clinical trials is determining the sample size. In most studies, it is not possible to examine the entire population in terms of cost, time and personnel effort. Therefore, a group of participants called "sample", which is less in number than the population but assumed to represent the population well, is selected and an estimate is made about the population with the help of this selected sample. While determining the size of the sample representing the population, a scientific, ethical and economic evaluation should be made.[1] From a scientific point of view, working with fewer units than required may result in not detecting a clinical effect that should actually be scientifically. Working with more sample units than necessary may reveal a statistically significant, but actually a clinically insignificant effect. What is important here is that researchers can correctly distinguish between statistical and clinical significance. When the sample size is evaluated from an ethical point of view, it is possible that including more subjects in the research will harm the subjects, especially in animal and human studies. On the contrary, working with a small number of units is unethical and does not make a scientific contribution. The inclusion of unnecessary units in the research would increase the cost and the increase in the sample size would make the use of sampling economically useless. Considering the evaluations made from all these aspects, it is recommended to calculate the power of the study before calculating the sample size in all scientific studies. If the power of the study is too low, more time may be needed in the study. Therefore, indeed, sample size calculation starts with power analysis.

The sample size is one of the first practical steps and statistical principal in designing a clinical trial to answer the research question[2] The sample size to be determined at the design stage should be large enough to provide reliable answers to the questions about the population parameter. The following factors should be taken into account while determining the sample size: type of outcome variable of interest in the study, type of study design, p value (alpha), study power, effect size, and variability. When the studies on sample size are examined, it can be seen that the sample size formulas depend on the type of study design and the type of outcome variable. There may be two types of outcome variables most commonly encountered in clinical trials. They are categorical variables expressed in a percentage of the incidence of side effects or improvement related to a disease, or quantitative variables obtained with the help of a measurement tool to indicate body functions. Since the statistical analyses to be applied would differ according to the type of outcome variable, the method of determining the sample size is also different. On the other hand, which type of study

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design would be used in the study is also effective in determining the minimum sample size required. Clinical research studies can be classified into two general categories: observational and experimental studies.[3] Observational studies, which are divided into two as descriptive and analytical, are studies that produce hypotheses. The difference between descriptive and analytical studies is that descriptive studies provide a description of exposure and/or outcome, and analytical observational studies provide a measure of the relationship between exposure and outcome. Experimental studies are about hypothesis testing and include an intervention that tests the relationship between exposure and outcome. The important thing in research is to choose the design that would give the most correct answer to the question in mind.[4] Another factor to be considered in determining the sample size is the "*p*" value. The "*p*" value determined within an acceptable limit in each clinical trial, also known as type 1 error, is the probability of finding a false difference as a result of the research, when there is no real difference in efficacy in a controlled study in which the efficacy of any drug/method is investigated. In clinical studies, it is recommended to choose a "*p*" value of at most 0.05. The *p* value is less than or equal to the significance level, the results refer to statistical significance. However, not every statistically significant result may be clinically significant. So, what is clinical significance? The term "clinically significant" may be used for studies in which clinically relevant results or outcomes are used to evaluate the efficacy or effectiveness of a treatment modality. When the term "clinically significant" is used, it is the findings that improve the patient's quality of life, make him feel good and fulfill his function. Thus, clinicians and researchers should give importance to both statistical and clinical significance. Another factor to be considered in determining the sample size is the power of the study. The power of a study represents the probability of finding an existing difference in a population. It depends on the significance level chosen, the difference we are looking for (effect size), the variability of the measured variables, and the sample size. Performing power analysis in determining sample size increases the value of clinical research. The main purpose of the power analysis, which should be done without data collection, is to help the researcher determine the smallest sample size suitable for determining the effect of a particular test at the desired significance level. The researcher is willing to work with a smaller sample and, accordingly, to reduce the cost. It helps determine whether a result from a survey is due to chance or whether it is real and significant. In a controlled study where the efficacy of any drug/method is investigated, it is the probability of finding that there is no difference in the result of the study when there is actually a difference in efficacy, and "1-β" indicates the power of the study. In clinical studies, it is recommended to consider the lowest power value as 0.80 and accordingly "β" (type II error) as a maximum of 0.20. Another factor that has a place in determining the sample size is the effect size (d), and it is a criterion that shows whether a statistically significant difference is clinically significant. It can be defined as the minimum difference to be considered clinically significant between the mean or ratio of the two groups. The difference between groups (d) represents the absolute difference between groups to be compared in clinical studies. If the primary variable of interest (primary outcome) in a clinical trial is a ratio, then the difference in the observation rate of the event of interest between the treatment group and the control group represents "d". When the number of groups is more than two, then it is expressed as the difference between the highest rate and the lowest rate. When the event of interest is a quantitative value, the difference between the treatment group mean and the control group mean represents "d". Dividing the obtained difference by the standard deviation of the control group gives the effect size. The denominator standardizes the difference by transforming the absolute difference into standard deviation units. Cohen's term "d" is an example of this type of effect size index. The Cohen classified effect sizes as small (d=0.2), medium (d=0.5), and large (d≥0.8).[5] The standard deviation is used to estimate the population variance of the predicted outcome variable in calculating the sample size. As population variance is often unknown, researchers use estimates derived from previous studies. If the population has a homogeneous structure, the small sample size would be sufficient for the study, as the standard deviation would be low, while the required sample size would increase as it moves away from homogeneity.

In clinical trials, estimates of sample size are often made based on ratio or mean. The disadvantage of mean-based sample size estimation is that a "good" estimate of population variance is required. Studies often do not find a good estimate. Also, sample size can vary greatly from one attribute to the next, as each is likely to have a different variance. Due to

these problems, sample size estimation is usually preferred for ratio rather than mean. Considering all these factors in the study, the sample size obtained should be reported and justified. Most studies include general statements such as "The sample size required for each treatment group was calculated as 0.05 alpha and 0.80 power of 100". This type of summary explanation constitutes a limitation in terms of the adequacy of the study. For the reliability of the research, a more detailed explanation of how the sample size was obtained is required. Sample size planning is inevitable in clinical research. If not, it indicates the poor quality of this study and the results would be viewed with suspicion.

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