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Proper Design of Human Intervention Studies, Power Calculations

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1. Introduction

Several elements are mandatory for a trial, particularly a trial on humans, to adhere to modern scientific demands. The basic elements are an a priori defined primary hypothesis and definition of primary and secondary endpoint and in some cases also tertiary endpoints. Once this is defined the design of the trial, the statistical analysis and the control group can be defined.

2. Designs

Only two major design types will be dealt with here, cross-over and parallel groups designs, also called paired and un-paired designs.

2.1 Historical controls

A large number of studies use comparison of people before and after, say e.g. antioxidant intervention. Such a design is considered based on historical controls and should not be performed.

2.2 Cross over designs

Rather, the persons should be randomised to two different treatments, placebo and active treatment one after the other, with a wash-out period between, the randomisation gives the random order of the treatments. By such a design effects e.g. due to season is randomly allocated to the groups. The advantage of the paired design is that each person serves as his own control, and the number of subjects in the trial is reduced compared with the un-paired trial. Among the disadvantages are that every time a person drops out the first measurement he/she cannot be included in the analysis. Furthermore, if the variation within individuals is comparable with that between individuals, extra power is not obtained.

2.3 Parallel groups

The parallel group is a more simple design. A group of people is randomised to two treatments, e.g. active treatment and placebo or two different active treatments, and the primary variable is then compared between the groups.

More complicated designs can be used but is not mentioned here. Most important is to stress the proper use of randomisation and controls.

2.4 Power analysis

In the planning of a trial it is necessary to calculate the number of persons needed to be able to detect a predefined difference. In many countries, e.g. in Denmark, ethical approval is not given if a proper statistical power analysis is not given.

The power analysis is a calculation of the number of people to enter the trial, provided there is knowledge about the defined type I error risk (significance level), the type II error risk (power), the defined difference the trial is supposed to detect (delta Δ) and the variation of the measurement in the trial. A simple mathematical relationship between these factors exists. For details readers should look in statistical textbooks. Also electronic books are available on the net, e.g. http://www.graphpad.com/articles/interpret/principles/stat_principles.htm.

The calculation of number of persons needed in a trial can be done by several statistical programs, such as nQuerry® and Statistica®. Also there are websites where calculations can be made. For simple designs it is very easy to make this calculation by hand or a simple electronic calculator. For the most common design two parallel groups, e.g. one active treatment and one placebo group, and assuming that both group are of equal size the number in each group is calculated as:

$$N1 = N2 = 2(t_{2\alpha,df} + t_{\beta,df})^2 \times (SD^2 / MIREDIF^2)$$

where the t-values can be obtained from a statistical t-table, SD is the standard variation of the measurement measuring on e.g. a control population, and MIREDIF is the MInimum REIevant DIFference.

If the N1 = N2 is large i.e. about 200 the t-values are about 2 and 1.7. This simplifies the equation to

$$N1 = N2 = 2(2+1.7)^2 \times (SD^2 / MIREDIF^2) = 27.4 \times (SD^2 / MIREDIF^2) \cong$$

$$30 \times (SD^2 / MIREDIF^2)$$

As an example you want to find a change of 8% in the excretion of 8-oxodG in a group given antioxidants compared with a placebo group and you know that the SD of the urinary 8-oxodG is 32%. The number needed in each group is therefore about $30 \times (32/8)^2 = 30 \times 4^2 = 30 \times 16 = 480$ (note that SD and MIREDIF are given in percent). It is quite straight forward that the most important factor in the power calculation is the SD of the measurement, and that the best way to reduce the number needed for the trial is to reduce SD.

2.5 Conclusion

Power calculation is thus a simple task to perform and should be included in the planning of all biological experiments.

References

Readers are referred to standard textbook in Statistics or similar items available on the net:

[1] http://www.ebook.stat.ucla.edu/calculators/powercalc/

[2] http://www.davidmlane.com/hyperstat/power.html/