

WHITE PAPER

Common Mistake in Adjusting Sample Size for Anticipated Dropouts in Clinical Trials

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Day by day the clinical trial field is expanding like anything. New molecules are needed to be experimented in human beings and the existing drugs are needed to be monitored for long term safety. Thus Phase I to IV clinical trial activities are increasing exponentially all over the world. However, it is difficult to work with large populations and hence researchers work with representative samples of the patient population. Estimation of sample size is critical in planning clinical trial because this is usually the most important factor determining the time and cost of the study. In most of the studies, the sample size calculations are based on the primary research question/objective that the investigator wants to do research. The sample size calculation must be taken into account of all available data, cost of the study, support facilities, and ethics of subjecting patients to research. Basic elements considered for estimating sample size include level of significance, power of the study, clinically meaningful difference, and the variability or standard deviation and of course the availability of patients.

The initial sample size estimated in the study need to be increased in accordance with the expected response rate, loss to follow up, lack of compliance, and any other predicted reasons for loss of subjects. Previous studies in the same population will give an estimate of the expected number of subjects dropped out at the end of the study. Adverse events due to study treatment, follow up length, lack of efficacy etc. will influence the dropout rate. The final number arrived should be increased to include a margin for required sample size to accommodate the dropout rate, so that the number needed for evaluation remains same after expected loss of study subjects. While reviewing some protocols, authors found that researchers are using different methods for adjusting the sample size for dropout rate. The objective of this paper is to demonstrate the correct procedure for adjusting the sample size for dropout rate in clinical trial.

Common Mistake in Adjusting for Dropout

Researchers are often doing mistake while adjusting the dropout rate in sample size calculation. They simply add a percentage of the number to the estimated number of sample size as an adjusted sample size for dropout. For example, N is the final adjusted sample size and n is the calculated sample size and $z\%$ is the expected dropout rate, then the adjusted sample size, $N = n + (n * z/100)$, which is **not the correct** adjustment procedure. The **correct procedure** is to divide the number (n) by 1 minus the dropout rate to get the adjusted sample size (N). i.e., $N = n / (1 - (z/100))$.

Illustration

Suppose the researcher wants to compare the effectiveness of two drugs A and B. He is expecting that both drugs are almost equally efficacious. He is also expecting 95% success rate in both drug groups. So this study becomes an equivalence trial. Further he is expecting an equivalence margin of 10%. His past experience shows that about 20% dropouts are expected in this proposed trial. By assuming 5% level of significance and 80% power of the test, we can estimate the sample size by using the following formula

$$n = \frac{(Z_{\alpha} + Z_{\beta/2})^2 (p_1(1-p_1) + p_2(1-p_2))}{(\delta - |\varepsilon|)^2}$$

Where,

P_1 =Expected success rate in Drug A (95%)

P_2 = Expected success rate in Drug B (95%)

ε =Expected difference in success rate between two study groups (P_1-P_2)

δ =Equivalence limit (10%)

α =Level of significance (5%)

Z_{α} =1.64

$1-\beta$ =Power of the study (80%)

$Z_{\beta/2}$ =1.28

$$n = \frac{(1.64 + 1.28)^2 (0.95(1 - 0.95) + 0.95(1 - 0.95))}{(0.10 - |0|)^2}$$

$$= 82$$

Thus 82 subjects are required for the present study without considering the dropout rate in each treatment group. Next step is to adjust the dropout rate of 20%.

$82 \div 0.2 = 410$. Thus a total of 410 subjects are required to conduct a clinical trial (205 in treatment group and 205 in control group).

If we follow the incorrect method as mentioned above, the adjusted sample size in one group =

$82 \div 0.2 = 410$. Thus we require about 410 subjects for the proposed study. However, this method of adjustment is inappropriate. Thus there is a difference of 8 patients between two procedures. Thus, this type of adjustment in sample size estimation gives always underestimated sample size.

Conclusion and Recommendation

As with other basic elements of sample size calculations, the proportion of eligible subjects who will refuse to participate or provide inadequate information or who will be dropout from the study due to lack of efficacy and AEs will be unknown at the beginning of the study. However, a good estimate or a brilliant guess would often be possible using information from similar studies in comparable populations or from an appropriate pilot study. It is particularly important to account for dropouts when planning a clinical trial. Also researchers must aware about the correct method of adjusting the dropout rate while estimating the sample size. Thus, a well planned and well designed clinical trial would give better results.