The Use of Power Analysis in Small Sample Pre-clinical Imaging Studies
Edward J. Soares, Ph.D.1, Jacob Y. Hesterman, Ph.D.2, Jack W. Hoppin, Ph.D.2

Objective
The importance of determining the correct sample size for clinical and pre-clinical studies is well established [1-3]. Power analysis (PA) is a method by which a direct relationship between effect size and sample size may be derived. The goal is to determine the sample size required to identify a certain effect size as statistically significant. Typical effect sizes include:

- Difference between group means (independent samples)
- Difference between baseline/follow-up means (matched pairs)
- % change in these differences relative to one group or time point

A z-statistic related to the standard normal distribution is often used as the basis for sample size calculations [1,4]. However, for small sample sizes typically seen in pre-clinical studies, this approach can underestimate the number of subjects required to identify an effect size as significant [5-6]. Scheibe [7] described an equivalent approach to PA using the independent samples t-statistic. The non-centrality parameter of the t-distribution allows one to establish a direct relationship between effect size and sample size.

Results: Effect of Unequal Variability (Independent Samples) and Correlation (Matched Pairs)

Here, we review and compare small- and large-sample methods for performing PA. Included are the methods for matched pairs (MP) comparisons and independent samples (IS) comparisons based on the t-distribution, as well as their large-sample approximations. Also, we demonstrate the influence of the proportionality between group variations on sample size (IS), as well as the influence of correlation between baseline and follow-up observations on sample size (MP). Finally, we quantify the % decrease in effect size when adding additional subjects (based on n=3) for both IS and MP analyses.

Methodology
Power analysis requires the identification of the following:

- Null (H₀) and alternate (Hₐ) hypotheses
- Test statistic and corresponding probability distribution
- A form of the non-centrality parameter (δ) for the distribution
- Significance level (α) and power (1-β)
- Either pilot data or assumptions about the other parameters of the distribution (value or relationship between standard deviations, correlation coefficient, etc.)

Computational Procedure (IS or MP power analysis):

- Choose a value for n
- Set significance level α = 0.05 and power = 0.8 (β = 0.2)
- Determine degrees of freedom for the t-distribution
- Use cumulative distribution function (CDF) of the non-central t-distribution to find the value of the non-centrality parameter δ
- Compute effect size δμ
- Plot effect size δμ versus sample size n

Examples of non-centrality parameters:

- IS (equal vars): \( \delta = \frac{\Delta \mu}{\sigma \sqrt{2/n}} \)
- MP (unequal vars): \( \delta = \sqrt{\frac{\sigma_1^2 + \sigma_2^2}{n}} \)
- MP (unequal vars): \( \delta = \frac{\Delta \mu}{\sigma_\text{eff} \sqrt{n}} \)

Summary
- As variability in the second sample increases relative to the first (IS test), the number of subjects required to identify a fixed effect size as significant increases.
- As correlation between the two measurements decreases (MP test), the number of subjects required to identify a fixed effect size as significant increases.
- For small sample sizes, use of the z-statistic will underestimate the n required to find the effect size statistically significant.
- Adding two additional subjects decreases effect size by 35%, while adding two additional subjects decreases effect size by 49%; b) Plots of effect size versus sample size for the two-sided MP t-statistic. As correlation between the two measurements decreases, the number of subjects required to identify a fixed effect size as significant increases.

Results: Comparison of Large vs. Small Sample Methods

Results: Percent Decrease in Effect Size Achieved By Adding Additional Subjects

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Figure 1. a) Plots of effect size versus sample size for the two-sided IS t-statistic. As variability in the second sample increases relative to the first, the number of subjects required to identify a fixed effect size as significant increases; b) Plots of effect size versus sample size for the two-sided MP t-statistic. As correlation between the two measurements decreases, the number of subjects required to identify a fixed effect size as significant increases.

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Figure 3. a) Plots of % decrease in effect size when adding additional subjects (from n=3) versus sample size for the two-sided IS t-statistic. An additional subject per group decreases effect size by 23%, while adding two additional subjects decreases effect size by 35%; b) Plots of % decrease in effect size when adding additional subjects (from n=3) versus sample size for the two-sided MP t-statistic. An additional subject per group decreases effect size by 35%, while adding two additional subjects decreases effect size by 49%.

References