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**Cytel**  
STATISTICAL SOFTWARE & SERVICES

# Right SiZ™ Your Trials

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$$f_{Z_1}(z_1) = \Pr(Z_1 \leq b_1 | Z_1 = z_1, \delta = 0)$$

# Introducing SiZ™

$$f_{Z_2}(z_2) = \Pr(Z_2 > b_2 | Z_2 = z_2, \delta = 0)$$



# SiZ™

# Outline

- What is SiZ™?
- Examples
  - Continuous outcomes
  - Discrete outcomes
  - Time to event outcomes
- Summary



# What is SiZ™?

- SiZ™ is a user-friendly validated software package for the design, simulation and analysis of fixed sample clinical trials
- SiZ™ will quickly and easily generate multiple study plans, then compare and contrast with tables and graphs the various design options
- SiZ™ will simulate designs under deviations from model assumptions in a type of sensitivity analysis



# Available procedures in SiZ™

- Test procedures for continuous, discrete, binomial and time-to-event outcomes
- Superiority, non-inferiority and equivalence tests
- Single-arm, parallel groups and 2 x 2 crossover study designs
- ANOVA and regression procedures
- Studies of inter-rater agreement



# Example 1: Single Mean Test

- Trial to study the effect of a diet plan on weight gain in malnourished children
- Twenty children are to be studied
- Let  $\mu$  be the mean weight gain in pounds
- The null hypothesis  $H_0 : \mu = 3$  lbs is to be tested against the alternative hypothesis  $H_1 : \mu = 4$  lbs
- Two-sided z-test with  $\alpha = 0.05$
- Standard deviation of weight gain is assumed known and to be  $\sigma = 1.8$



# Example 2: Difference of Means

- Trial of Orlistat – an inhibitor of fat absorption – to study its effectiveness in promoting weight loss
- 90% power desired to detect an extra 3 kg in weight loss from 6 kg in the control arm to 9 kg in the test arm
- The null hypothesis  $H_0 : \mu_t - \mu_c = 0$  lbs is to be tested against the alternative hypothesis  $H_1 : \mu_t - \mu_c = 3$  lbs
- Subjects are to be randomized 3:1 in favor of Orlistat
- One-sided t-test with  $\alpha = 0.05$
- Assume that the common standard deviation of observations (weight change) is  $\sigma = 8$  kg



# Example 3: Bioequivalence

- Dose equivalence study comparing pellet formulation of theophylline at same daily dose, but administered at different dosage strengths - 200 mg + 300 mg (Reference) vs. 500 mg (Test)- in a randomized 2 x 2 crossover trial with 1 week washout
- From historical data mean AUC of reference is 5.5 on lognormal scale, while mean AUC in 500 mg arm is believed to be between 5.1 and 5.5
- Two one-sided t-tests with  $\alpha = 0.05$
- 80% power for a test of the ratio of mean AUC using conventional equivalence limits of (0.8, 1.25)
- Within-subject variability from crossover ANOVA model on the natural logarithm scale is  $\sqrt{\text{MSE}} = 0.2$



# Example 4: One way ANOVA

- Study comparing Glucocorticoid Receptor (GR) sites per Leukocyte Cell in normal subjects (group 1) to patients with hairy-cell leukemia (group 2) chronic lymphatic leukemia (group 3) chronic myelocytic leukemia (group 4) or acute leukemia (group 5)
- Interested in testing whether there is a difference in mean GR response between patients in groups 2 or 3 versus patients in groups 4 or 5
- Two-sided test with  $\alpha = 0.05$
- Total sample size is 37
- Calculate power to detect an effect size of 1



# Example 5: Single Proportion

- Single-arm oncology trial to determine whether tumor response rate of a new cytotoxic agent is at least 15%
- The null hypothesis  $H_0 : \pi = 0.15$  is to be tested against the alternative hypothesis  $H_1 : \pi = 0.25$
- One-sided test with  $\alpha = 0.05$
- 80% power is desired



# Example 6: Non-inferiority

- The Coronary Artery Revascularization in Diabetes (CARDia) trial was designed to compare coronary bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) as strategies for revascularization, with the goal of showing PCI to be non-inferior to CABG
- Event rate for CABG is  $\pi_c = 0.125$
- Claim of non-inferiority can be sustained if one can demonstrate statistically that  $\rho = \pi_t / \pi_c$  is at most 1.3
- Test the null hypothesis  $H_0 : \rho = 1.3$  against the one-sided alternative hypothesis  $H_1 : \rho < 1.3$
- Want to determine the sample size to have 80% power when  $\rho = 1$  and significance level  $\alpha = 0.05$



# Example 7: Agreement

- Study to develop and validate a set of clinical criteria to identify patients with minor head injury who do not need to undergo a CT scan
- CT scans were first reviewed by staff neuroradiologist
- An independent staff radiologist then reviewed 50 randomly selected CT scans and the two sets of responses checked for agreement
- Let  $\kappa$  be the level of agreement
- The null hypothesis  $H_0 : \kappa = 0.9$  is to be tested against the one-sided alternative hypothesis  $H_1 : \kappa < 0.9$
- Wish to compute power of the test at the alternative  $\kappa_1 = 0.6$
- Expect both raters to identify 8% of CT scans as positive



# Example 8: Survival outcomes

- Multi-center randomized placebo-controlled study of regular administration of the beta-blocker propranolol for subjects with myocardial infarctions (BHAT trial)
- Three-year survival rate in the control group assumed to be 82.54%
- Wish to power the study for a 90% probability of detecting an improved 3-year survival rate of 86.25% in the propranolol arm
- Two-sided logrank test with  $\alpha = 0.05$
- Trial will accrue in 2 years with a minimum of 1 year follow-up on all subjects



# Summary

- Broad set of validated methods for designing clinical trials
- Quickly and easily generate and compare multiple designs in tabular and graphic formats
- Clear and concise summary statements are provided for insertion into trial documentation
- Simulate designs with deviations from original assumptions
- Analyze and visualize data
- Help and references to all procedures are provided

