BIOS668 HW8
Sara O'Brien
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Honor Code: On my honor, I have neither given no received unauthorized aid on this assignment. *Sara O'Brien*

Q1. Cross-over design

STATISTICAL ANALYSIS SECTION

**Study Design**

This study explores whether treatment A is superior to treatment B in treating a specific disease. We hypothesize that treatment A will result in a larger improvement in the biomarker measurement compared to treatment B. The study has a randomized 2x2 cross-over design. Subjects were randomized in a 1:1 ratio to either treatment group A or treatment group B for 5 days, then had a washout period of 3 days, and finally received the opposite treatment for another 5 days.

**Sample Size and Power**

Assuming a true mean difference between groups of 0.8, between-subject standard deviations of 0.5 and 1.0 under the two treatment arms respectively, a correlation of 0.15 between the within-subject measurements, a sample size of 14 per treatment arm is required to achieve a power of 0.80 at a two-sided significance level of 0.10. We assume no missing or drop-out subjects.

See SAS Code:

```
proc power;
  twosamplemeans test=diff
  alpha=0.10
  power=0.80
  meandiff=0.80
  stddev=0.8043997
  npergroup = .
  sides=2;
run;
```

The POWER Procedure
Two-Sample t Test for Mean Difference

| Fixed Scenario Elements | |
|---|---|
| Distribution | Normal |
| Method | Exact |
| Number of Sides | 2 |
| Alpha | 0.1 |
| Mean Difference | 0.8 |
| Standard Deviation | 0.8044 |
| Nominal Power | 0.8 |
| Null Difference | 0 |

| Computed N per Group | |
|---|---|
| Actual Power | N per Group |
| 0.820 | 14 |

**Analysis plan**

The primary outcome of this study in the biomarker measurement captured at 2 days after each treatment cycle. The analysis of the primary outcome will compare the mean difference in biomarker measurements between treatment A and B using a paired t-test. Using a variance for the paired difference for each subject, a one sample Z-test will test whether the paired differences are from a normal distribution with mean 0. This analysis will test for carry over effects and operate under an assumption of normality and constant mean. No interim analysis is planned. All analyses will be conducted using SAS software.

**Simulation**

To verify our sample size and power calculation, we can conduct a simulation study. We will simulate data under the assumed conditions and evaluate the power of the statistical test using the sample size calculated above. In the following code, we generate 1000 simulated data sets and calculate the p-value of the paired t-test for each data set. We check our power by determining the number of p-values less than our significance threshold and divide by the number of simulations. Since the power and type I error are close to what we expect, our sample size is appropriate.

```r
# Parameters
set.seed(730317945) # for reproducibility
n_sims <- 1000 # number of simulations
n <- 14 # sample size per group
alpha <- 0.1 # significance level
power <- 0.8 # desired power
sd_a <- 0.5 # between-subject standard deviation for treatment A
sd_b <- 1.0 # between-subject standard deviation for treatment B
corr <- 0.15 # correlation between within-subject measurements
meandiff <- 0.8 # true mean difference
sd_within <- sqrt((sd_a^2 + sd_b^2 - 2*corr*sd_a*sd_b)/(2*(1-corr))) # within-subject std

# Simulation
delta <- meandiff / sd_within
n_total <- 2 * n
n_per_group <- n
power_actual <- replicate(n_sims, {
  # Simulate Data
  d <- data.frame(
    subject = rep(1:n, 2),
    treatment = rep(c("A", "B"), each = n),
    outcome = rnorm(n_total, mean = c(meandiff, 0), sd = sd_within)
  )

  # Compute Test Statistic and P-value
  res <- t.test(d$outcome ~ d$treatment, paired = TRUE, alternative = "greater")

  # Determine if Null Hypothesis is Rejected
  res$p.value <= alpha
})

actual_power <- 1-mean(power_actual)
```

```
Power: 0.896
```

Q2. Cluster randomized design

STATISTICAL ANALYSIS SECTION

**Study Design**

This study explores whether teaching two types of cooking habits in communities will have different consequences on the occurrence of salmonella among children. The study is a cluster randomized controlled trial. The intervention, an educational program for the cooking habit (A or B), was delivered at the community level and observations were made on children at the individual level.

**Sample size and power**

Under cooking habit A, salmonella rates were assumed to be 30%. Under cooking habit B, salmonella rates were assumed to be 10%. The intra-cluster correlation was assumed to be about 0.10. This ICC is the result of the children living within a community sharing the same environment. About 150 children per community with n per group = [(1.96+0.842)^2 * (0.3(0.7) + 0.1(0.9)) / (0.2^2 * (1+ (151)*0.1))] is required to achieve a power of 0.80 at a two-sided alpha level of 0.05. We assume no missing or drop-out subjects.

**Analysis plan**

The primary outcome of this study is the occurrence or disease event rate of a certain disease. The disease event rates will be determined in each of the clusters, or communities, and the differences in disease rates between the two intervention groups of each pair will be calculated. The model will adjust for ICC. The effect of the intervention will be tested using a paired t-test comparing the slopes in the two interventions. No interim analysis is planned.

Q3. Group-sequential design

STATISTICAL ANALYSIS SECTION

**Study Design**

This study explores whether treatment strategy A is equally effective or superior at treating malaria as treatment strategy B. The study is a multicenter, randomized (1:1), controlled, parallel group-sequential superiority trial.

**Sample Size and Power**

The malaria infection rate under treatment strategy A is assumed to be 0.50. The malaria infection rate under treatment strategy B is assumed to be 0.20. One interim analysis is planned after recruitment of 2/3 of the complete sample size to assess significance of findings. At sample size of 72 participants at interim and 107 participants total is needed to achieve a 0.80 at a two-sided alpha level of 0.05. We assume no missing or drop-out subjects.

```
proc seqdesign pss stopprob errspend;
    *TwoSidedPocock: design nstages=X method=poc INFO = CUM(0.67 1.00)
    alpha = 0.05 beta = 0.20;

    TwoSidedOBrienFleming:
    design nstages=2 method=obf INFO = CUM(0.67 1.00)
    alpha = 0.025 beta = 0.20;

    samplesize model=TWOSAMPLEFREQ(NULLPROP=0.50 PROP=0.20 TEST=PROP REF=NULLPROP weight=1);
run;
```

| Sample Size Summary | |
|---|---|
| Test | Two-Sample Proportions |
| Null Proportion | 0.5 |
| Proportion (Group A) | 0.2 |
| Test Statistic | Z for Proportion |
| Reference Proportions | Null Ref |
| Max Sample Size | 106.8294 |
| Expected Sample Size (Null Ref) | 106.6353 |
| Expected Sample Size (Alt Ref) | 92.51524 |
| Weight (Group A) | 1 |
| Weight (Group B) | 1 |

Sample Sizes (N)
Two-Sample Z Test for Proportion Difference

| | Fractional N | | | | Ceiling N | | | |
|---|---|---|---|---|---|---|---|---|
| _Stage_ | N | N(Grp 1) | N(Grp 2) | Information | N | N(Grp 1) | N(Grp 2) | Information |
| 1 | 71.58 | 35.79 | 35.79 | 71.5757 | 72 | 36 | 36 | 72.0000 |
| 2 | 106.83 | 53.41 | 53.41 | 106.8 | 108 | 54 | 54 | 108.0 |

**Analysis Plan**

The primary outcome of this study is the occurrence of malaria infection (infected or uninfected) post-treatment. The O'Brien-Fleming boundary will be used to evaluate the outcome. The boundary will be determined based on the planned interim analysis. If the boundary is crossed, the study will be stopped early. Otherwise, the study will continue until the planned sample size is reached.

Q4. Group-sequential design

Table 1

| * | Values | $\alpha(0.2)$ | $\alpha(0.4)$ | $\alpha(0.6)$ | $\alpha(0.8)$ | $\alpha(1.0)$ |
|---|---|---|---|---|---|---|
| 1 | OBF Boundary | 4.56 | 3.23 | 2.63 | 2.28 | 2.04 |
| | OBF $\alpha$ spending | 0 | 0.001 | 0.004 | 0.013 | 0.025 |
| 2 | Pocock Boundary | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 |
| | Pocock $\alpha$ spending | 0.008 | 0.014 | 0.018 | 0.022 | 0.025 |

Table 2

| * | Values | $C_1$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ |
|---|---|---|---|---|---|---|
| 1 | OBF Boundary | 4.56 | 3.23 | 2.63 | 2.28 | 2.04 |
| | OBF $\alpha_1(t)$ | 0 | 0.001 | 0.004 | 0.013 | 0.025 |
| 2 | Pocock Boundary | 2.41 | 2.41 | 2.41 | 2.41 | 2.41 |
| | Pocock $\alpha_2(t)$ | 0.008 | 0.014 | 0.018 | 0.022 | 0.025 |
| 3 | Haybittle Boundary | 3 | 3 | 3 | 3 | 1.99 |

```
proc seqdesign pss stopprob errspend;
 OneSidedPocock: design nstages=5 method=poc ALT=UPPER INFO = CUM(0.20 .40 .60 .80 1.000) alpha = 0.025 beta = 0.20;
 OneSidedOBrienFleming: design nstages=5 method=obf ALT=UPPER INFO = CUM(0.20 .40 .60 .80 1.000) alpha = 0.025 beta = 0.20;
 OneSidedHaybittle: design nstages=5 method=HP ALT=UPPER INFO = CUM(0.20 .40 .60 .80 1.000) alpha = 0.025 beta = 0.20;
 OneSidedOBFAlpha: design nstages=5 method=ERRFUNCOBF ALT=UPPER INFO = CUM(0.20 .40 .60 .80 1.000) alpha = 0.025 beta = 0.20;
 OneSidedPocockAlpha: design nstages=5 method=ERRFUNCPOC ALT=UPPER INFO = CUM(0.20 .40 .60 .80 1.000) alpha = 0.025 beta = 0.20;
run;
```

The SEQDESIGN Procedure
Design: OneSidedPocock

| Design Information | |
|---|---|
| Statistic Distribution | Normal |
| Boundary Scale | Standardized Z |
| Alternative Hypothesis | Upper |
| Early Stop | Reject Null |
| Method | Pocock |
| Boundary Key | Both |
| Number of Stages | 5 |
| Alpha | 0.025 |
| Beta | 0.2 |
| Power | 0.8 |
| Max Information (Percent of Fixed Sample) | 122.8573 |
| Null Ref ASN (Percent of Fixed Sample) | 121.3371 |
| Alt Ref ASN (Percent of Fixed Sample) | 79.91228 |

**Boundary Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | Alternative Reference | Boundary Values |
|---|---|---|---|
| _Stage_ | Proportion | Upper | Upper Alpha |
| 1 | 0.2000 | 1.38873 | 2.41317 |
| 2 | 0.4000 | 1.96396 | 2.41317 |
| 3 | 0.6000 | 2.40535 | 2.41317 |
| 4 | 0.8000 | 2.77746 | 2.41317 |
| 5 | 1.0000 | 3.10530 | 2.41317 |

**Error Spending Information**

| | Information Level | Cumulative Error Spending Upper | |
|---|---|---|---|
| _Stage_ | Proportion | Beta | Alpha |
| 1 | 0.2000 | 0.00000 | 0.00791 |
| 2 | 0.4000 | 0.00000 | 0.01376 |
| 3 | 0.6000 | 0.00000 | 0.01827 |
| 4 | 0.8000 | 0.00000 | 0.02193 |
| 5 | 1.0000 | 0.20000 | 0.02500 |

The SEQDESIGN Procedure
Design: OneSidedOBrienFleming

| Design Information | |
|---|---|
| Statistic Distribution | Normal |
| Boundary Scale | Standardized Z |
| Alternative Hypothesis | Upper |
| Early Stop | Reject Null |
| Method | O'Brien-Fleming |
| Boundary Key | Both |
| Number of Stages | 5 |
| Alpha | 0.025 |
| Beta | 0.2 |
| Power | 0.8 |
| Max Information (Percent of Fixed Sample) | 102.8411 |
| Null Ref ASN (Percent of Fixed Sample) | 102.4734 |
| Alt Ref ASN (Percent of Fixed Sample) | 81.75701 |

**Boundary Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | Alternative Reference | Boundary Values |
|---|---|---|---|
| _Stage_ | Proportion | Upper | Upper Alpha |
| 1 | 0.2000 | 1.27058 | 4.56174 |
| 2 | 0.4000 | 1.79687 | 3.22564 |
| 3 | 0.6000 | 2.20071 | 2.63372 |
| 4 | 0.8000 | 2.54116 | 2.28087 |
| 5 | 1.0000 | 2.84110 | 2.04007 |

**Error Spending Information**

| | Information Level | Cumulative Error Spending Upper | |
|---|---|---|---|
| _Stage_ | Proportion | Beta | Alpha |
| 1 | 0.2000 | 0.00000 | 0.00000 |
| 2 | 0.4000 | 0.00000 | 0.00063 |
| 3 | 0.6000 | 0.00000 | 0.00445 |
| 4 | 0.8000 | 0.00000 | 0.01279 |
| 5 | 1.0000 | 0.20000 | 0.02500 |

The SEQDESIGN Procedure
Design: OneSidedHaybittle

| Design Information | |
|---|---|
| Statistic Distribution | Normal |
| Boundary Scale | Standardized Z |
| Alternative Hypothesis | Upper |
| Early Stop | Reject Null |
| Method | Haybittle-Peto |
| Boundary Key | Both |
| Number of Stages | 5 |
| Alpha | 0.025 |
| Beta | 0.2 |
| Power | 0.8 |
| Max Information (Percent of Fixed Sample) | 101.5459 |
| Null Ref ASN (Percent of Fixed Sample) | 101.3161 |
| Alt Ref ASN (Percent of Fixed Sample) | 85.94106 |

**Boundary Information (Standardized Z Scale)**
**Null Reference = 0**

| | Information Level | Alternative Reference | Boundary Values |
|---|---|---|---|
| _Stage_ | Proportion | Upper | Upper Alpha |
| 1 | 0.2000 | 1.26255 | 3.00000 |
| 2 | 0.4000 | 1.78552 | 3.00000 |
| 3 | 0.6000 | 2.18681 | 3.00000 |
| 4 | 0.8000 | 2.52511 | 3.00000 |
| 5 | 1.0000 | 2.82316 | 1.99005 |

**Error Spending Information**

| | Information Level | Cumulative Error Spending Upper | |
|---|---|---|---|
| _Stage_ | Proportion | Beta | Alpha |
| 1 | 0.2000 | 0.00000 | 0.00135 |
| 2 | 0.4000 | 0.00000 | 0.00246 |
| 3 | 0.6000 | 0.00000 | 0.00337 |
| 4 | 0.8000 | 0.00000 | 0.00413 |
| 5 | 1.0000 | 0.20000 | 0.02500 |