Statistics 520 Homework # 4

1. A four arm trial is about to be conducted where three new treatments, say, treatments 1, 2, and 3, are to be compared to the standard treatment 0. The response is a continuous measurement which we denote by $Y$ and, absent any additional information, we will assume that the treatment-specific variances are all equal for design purposes. The null hypothesis of treatment equality

$$H_0 : \mu_0 = \mu_1 = \mu_2 = \mu_3,$$

where $\mu_0$, $\mu_1$, $\mu_2$ and $\mu_3$ denote the treatment-specific mean responses for treatments 0, 1, 2, and 3 respectively is to be tested against the alternative that some treatment difference exists. The investigators of the trial come to you for advice on sample size considerations. They are mostly interested in comparing the new treatments to the standard treatment and not particularly interested in comparing the new treatments to each other. After quizzing the investigators about important differences they tell you that the average response on the standard treatment is about 100 with a standard deviation of 40. They also tell you that if a new treatment can increase the mean response to 115 or more, then this would be an important treatment difference to detect. Their belief is that all the new treatments will yield clinically important differences and they insist that the study be powered with that alternative in mind. That is, $\mu_{0A} = 100$, $\mu_{1A} = 115$, $\mu_{2A} = 115$ and $\mu_{3A} = 115$.

a. What test would you use to test $H_0$?

b. If you were to randomize with equal probability to all four arms, then how large a sample size is necessary so that a test at the .05 level of significance would have 90% power to detect the clinically important difference given by the investigators?

c. In contrast, what is the sample size necessary so that a test at the .05 level of significance would be guaranteed to have 90% power if any two treatments had a mean difference of 15 or more?

Regardless of your answers above, a clinical trial was conducted and the results are summarized in the table below.
If we denote by $Y_{ij}$ the response for the $i$-th individual in treatment $j$, where $j = 0, 1, 2, 3$ and $i = 1, \ldots, n_j$, then the treatment-specific sample average is

$$\bar{Y}_j = \frac{\sum_{i=1}^{n_j} Y_{ij}}{n_j}, j = 0, 1, 2, 3,$$

and the sample standard deviation is

$$s_j = \sqrt{\frac{\sum_{i=1}^{n_j} (Y_{ij} - \bar{Y}_j)^2}{n_j - 1}}, j = 0, 1, 2, 3.$$

Looking at the data, it seems that the assumption that the treatment-specific variances are all the same may not be so reasonable. Keep this in mind when constructing the test statistics for parts d. and e.

d. What is the p-value for the data above? (To get credit you must show what test statistic you used) What are your conclusions regarding the null hypothesis?

e. It was always intended to make pairwise comparisons between treatment 1 versus treatment 0 and treatment 2 versus treatment 0 and treatment 3 versus treatment 0. Accounting for multiple comparisons what conclusions would you draw regarding these comparisons? (Show all your calculations including relevant p-values and discuss how you reached your conclusion).

2. There are several treatments that have been proven to be effective in increasing CD4 counts for patients with HIV disease. However, it is well known that such treatments over time become resistant to the HIV virus and lose their effectiveness. Consequently, there is still room for new treatments to be considered that are equivalent in effectiveness to the current treatments. A pharmaceutical company has developed a new drug that they believe is
similar in effectiveness to the drugs currently used and decide to conduct an
equivalency trial. Because the distribution of CD4 counts is right skewed it is
more convenient to work with the logarithm (natural) of CD4 counts as this
will have a distribution that is closer to a normal distribution. Patients with
advanced disease will be recruited for this clinical trial. Based on previous
data the median CD4 counts is roughly about 200 for such patients which
translates to median log CD4 counts of 5.3. Also from past experience the
effective treatment can increase CD4 counts by 50% over a period of one year
or an increase in log CD4 counts of .41. This would correspond to increasing
the median CD4 counts from 200 to 300. Based on these considerations the
primary outcome $Y$ is the difference in log CD4 count for each patient one
year after treatment is initiated.

You are asked to help design this equivalency trial. A randomized clinical
trial will be conducted where patients will be randomized to either a current
effective treatment (positive control) versus the new treatment. As stated
above, the primary endpoint will be the difference in the log CD4 count
one year after treatment. For planning purposes we assume that the mean
log CD4 count difference for patients on positive control will be .41 with a
standard deviation of .20. The FDA has decided that equivalence can be
claimed if the company can prove that the response in CD4 counts is within
10% of the current effective drug. On the log scale this would correspond to a
mean log CD4 count difference for patients on the new drug of .315 or greater
or a tolerable difference of .095 on the log scale. We also assume that the
standard deviation of response (log CD4 count difference) will be the same
as the other treatment; namely, .20. Let $\mu_2$ denote the mean response for
patients if they were treated with positive control and $\mu_1$ the mean response
for patients if they were assigned the new drug.

a. In terms of $\mu_1$ and $\mu_2$ state the null and alternative hypotheses that
will be tested in this equivalency trial.

b. Let $n_1$, $\bar{Y}_1$, and $s_1$ denote the sample size, sample average and sample
standard deviation computed from the patients in the trial that would
be randomized to the new treatment and similarly $n_2$, $\bar{Y}_2$, and $s_2$ for
patients in the trial that would be randomized to positive control. In
terms of these what would you use to compute the test statistic? At
the .05 level of significance when would you reject the null hypothesis?
c. In designing your trial the investigators want to do some additional testing on resistance for the new drug. Therefore in order to get more experience they decide to randomize three times as many patients on the new drug versus positive control; that is, $n_1$ is three times $n_2$. If you wanted 90% or greater power to be able to declare equivalency if, in truth, your new treatment had a population mean response equal to or better than that of the positive control then how large a sample size will be needed?

d. Regardless of your answer to part (c.) a clinical trial was conducted with 202 patients; 152 randomized to the new treatment and 50 to the positive control. The sample average response and sample standard deviation on the new treatment were .40 and .24 respectively and the sample average response and sample standard deviation on the positive control were .39 and .26 respectively. Compute the value of your test statistic and whether or not you will be able to conclude that your new treatment is equivalent to control.