**BIOS668 HW6**

**March 30, 2023**

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Honor code: On my honor, I have neither given nor received unauthorized aid on this assignment. *Sara O’Brien*

**Deng G, et al. Acupuncture for the treatment of post-chemotherapy chronic fatigue: a randomized, blinded, sham-controlled trial.**

1. **What was the research question?**
   1. Does acupuncture reduce post-chemotherapy chronic fatigue more effectively than sham acupuncture, as measured by the Brief Fatigue Inventory (BFI)?
2. **What were the major inclusion and exclusion criteria? (If many are listed, give just the three most important/relevant of each.)** 
   1. Inclusion: Cancer patients reporting significant fatigue persisting for at least 2 months following the completion of chemotherapy
      1. 18-64 years old
      2. Diagnosed with malignancy and completed a course of chemotherapy at least 60 days prior
      3. Fatigue following but not before chemotherapy
      4. BFI score ≥4
   2. Exclusion
      1. Hemoglobin <9 g/dL
      2. Platelets <50,000/L
      3. Absolute neutrophil count <1,000/L
      4. Baseline depression score on Hospital Anxiety and Depression Scale >11
      5. Thyroid disorder, concurrent surgery, immunotherapy, or radiotherapy
      6. Initiation of hormonal therapy within previous 3 weeks
      7. Acupuncture within previous 6 weeks
      8. Change in use of SSRIs in previous six weeks or change in use of opioids or non-SSRI antidepressants in previous 3 weeks
3. **What was the study design? (Include stating the treatment groups and whether or not placebos were used.)** 
   1. Single-center, randomized (1:1), blinded, sham-controlled trial.
   2. Treatment group: true acupuncture.
   3. Placebo group: sham acupuncture performed exactly the same as true acupuncture with the use of sham acupuncture needles and insertion points a few mm off the meridians.
4. **What were the primary outcome(s) and the statistical test(s) used to analyze the primary outcome(s)?** 
   1. Brief Fatigue Inventory (measure of fatigue before and after treatment). The primary endpoint was the mean of day 42 (with first acupuncture session being day 1) and day 49 BFI scores. The primary analysis was the between-groups comparison of the mean of the two post-treatment BFI scores (days 42 and 49) by analysis of covariance (ANCOVA) with mean baseline BFI scores (days -14 and -7) as covariates.
5. **How were participants recruited?** 
   1. Medical records and clinical databases of patients at Memorial Sloan-Kettering Cancer Center were screened for complaints of fatigue from August 2004 to April 2009. A recruitment letter was mailed to potential participants and eligibility was determined among respondents.
6. **How was compliance monitored?** 
   1. Information not provided in manuscript.
7. **Were investigators and/or participants masked/blinded to the treatment?** 
   1. Patients and evaluators were blinded to treatment assignments.
8. **Were investigators/staff who assessed the primary outcome(s) blinded to the treatment assignments?** 
   1. Investigators were blinded to treatment assignments, but acupuncturists were not.
9. **What was the target sample size? Was this based on a formal sample size calculation? If the actual sample size differed substantially from the target, what is the reason for the difference?** 
   1. Sample size was calculated using pilot study data. A minimum clinically significant different of 1.25 on the BFI, with an estimated 20% relative difference between groups determined that there would be a required 44 patients per treatment group (88 total) to obtain an alpha of 0.05 and power of 0.90. The actual sample size of randomized participants was 101, with 49 in the true acupuncture group and 52 in the sham acupuncture group. However, only 74 were left after a nontrivial number of patients did not complete questionnaires at post-treatment follow-up and others discontinued intervention.
10. **How many participants were randomized and what proportion of randomized participants had primary outcome data?** 
    1. 101 patients were randomized and 74, or 73.3%, were evaluated for the primary outcome data.
11. **Does the trial have an entry in ClinicalTrials.gov? If so, state the ClinicalTrials.gov identifier (such as “NCT012345678”).** 
    1. Yes, NCT00200096.
12. **Did the investigators report a statistically significant result for their primary outcome? If so, summarize the findings in a single sentence.** 
    1. No.
13. **What method was used to generate the randomization to treatments?** 
    1. Randomization was in randomly permuted blocks stratified by baseline BFI>6.
14. **How was the randomization implemented (for instance, numbered envelopes or via a web-based interface)?** 
    1. Patients were randomly assigned to true or sham acupuncture via fax to a central randomization service. Randomization was implemented using a secure, password-protected database, ensuring full allocation concealment.
15. **Please re-evaluate the sample size / power calculation for each trial using both formula, software (e.g., SAS PROC Power), and simulation.**

We can use the stated power of 0.90, alpha level of 0.05, estimated mean difference of 1.25, and 1:1 randomization ratio in our sample size calculations. Additionally, we can pull the standard deviation of 1.88 from the post-treatment BFI scores reported in Table 4. Using these values and the formula that we derived in Homework 4, we get a calculated sample size of 48 for each treatment group, for a total target sample size of 96. Of note, this value is larger than the sample size stated in the paper, as we had to work around the absence of some measures in the sample size calculation.

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Similarly, we can use a PROC POWER to re-evaluate the sample size and power calculations. We will use the aforementioned parameters and the target sample size from the paper, 88 to yield a calculated sample size of 98 and calculated power of 0.896. As with the formula, these values do not exactly match what we expect due to slight differences in estimators used.

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Lastly, we can run a simulation to check the power and type I error produced when using the sample size determined in the paper. To do so, we generate random values to test if the treatment groups are significantly different using a PROC ttest. We check power at N(1.25,1.88) and type I error at N(0,1.88). This simulation, for 1000 iterations, produces a power of 0.865 and type I error of 0.037. Again, these values are less than expected based on the paper but sufficient in our re-evaluation of sample size given restrictions in our knowledge of all estimates used.

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Turkova A., et al. Shorter treatment for non-severe tuberculosis in African and Indian children.

1. **What was the research question?**
   1. Is a shorter 4-month regimen not worse than/as good as the standard 6-month regimen of first-line antituberculosis treatment in children with nonsevere, smear-negative, presumably drug-susceptible tuberculosis?
2. **What were the major inclusion and exclusion criteria? (If many are listed, give just the three most important/relevant of each.)** 
   1. Inclusion:
      1. Children younger than 16 years of age
      2. Symptomatic nonsevere tuberculosis that was smear-negative on a respiratory sample (including respiratory tuberculosis confined to one lobe with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph-node tuberculosis)
      3. Due to start first-line antituberculosis treatment
   2. Exclusion:
      1. Children with confirmed drug resistance or known exposure to an adult with any drug-resistant tuberculosis.
3. **What was the study design? (Include stating the treatment groups and whether or not placebos were used.)** 
   1. International, open-label, parallel-group, randomized (1:1), controlled, noninferiority trial.
   2. Treatment group: 4 months (16 weeks) of antituberculosis treatment using WHO-recommended pediatric doses.
   3. Control group: 6 months (24 weeks) of antituberculosis treatment using WHO-recommended pediatric doses.
   4. No placebo used.
4. **What were the primary outcome(s) and the statistical test(s) used to analyze the primary outcome(s)?** 
   1. The primary efficacy outcome was unfavorable status, which was a composite of treatment failure (extension, change, or restart of treatment or tuberculosis recurrence), loss to follow-up during treatment, or death) by 72 weeks. The analysis was based on the absolute difference between 4-month and 6-month groups in the percentage of participants with an unfavorable status in the modified intention-to-treat population, with adjustment for minimization factors with Cochran-Mantel-Haenszel weights. Time-to-event analyses of unfavorable status and death were also run with log-rank tests and Cox proportional-hazards models.
   2. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment. This outcome was monitored using standard summary statistics of counts and percentages affected throughout the study.
5. **How were participants recruited?** 
   1. Information not provided in manuscript. Although there is no information on recruitment, there is information on screening, including the history taking used to identify contacts with persons with tuberculosis and an evaluation of symptoms associated with tuberculosis.
6. **How was compliance monitored?** 
   1. Adherence was assessed by means of pill counts at each visit during treatment and by the administration of adherence questionnaires at the end of the intensive phase and at the end of treatment.
7. **Were investigators and/or participants masked/blinded to the treatment?** 
   1. No.
8. **Were investigators/staff who assessed the primary outcome(s) blinded to the treatment assignments?** 
   1. They were not blinded for the primary outcome, but the radiographic image review was conducted in a blinded manner using a standardized approach. An end-point review committee was also blinded to treatment assignments and reviewed clinical events suggestive of treatment failure or tuberculosis recurrence and all deaths.
9. **What was the target sample size? Was this based on a formal sample size calculation? If the actual sample size differed substantially from the target, what is the reason for the difference?** 
   1. Assuming a 10% loss to follow-up, an unfavorable status by 72 weeks in 8% of participants in the control group, and a non-inferiority margin of 6 percentage points, the target sample size was calculated to be 1200 children to achieve 90% power at a two-sided significance level of 5%. Statistical power of the trial was determined on the basis of key subgroup analysis involving children found to have tuberculosis at enrollment during independent adjudication. 1204 patients underwent randomization, but due to exclusions and non-adherence, the actual sample size for primary outcome analyses was 1121.
10. **How many participants were randomized and what proportion of randomized participants had primary outcome data?** 
    1. 1204 children underwent randomization, with 563 participants in the 4-month group and 558 participants in the 6-month group having primary-outcome data, so 93.11% of randomized participants had primary outcome data.
11. **Does the trial have an entry in ClinicalTrials.gov? If so, state the ClinicalTrials.gov identifier (such as “NCT012345678”).** 
    1. No.
12. **Did the investigators report a statistically significant result for their primary outcome? If so, summarize the findings in a single sentence.** 
    1. Yes, the difference between groups for an unfavorable status was an adjusted -0.4 percentage points and the trial showed noninferiority of 4 months as compared with the standard 6 months.
13. **What method was used to generate the randomization to treatments?** 
    1. Eligible children were randomly assigned in a 1:1 ratio to the treatment groups. Randomization was conducted with use of minimization with a random element according to trial center, age (<3 years or ≥3 years), HIV status, and ethambutol use.
14. **How was the randomization implemented (for instance, numbered envelopes or via a web-based interface)?** 
    1. All available information provided in manuscript regarding randomization is included in part (m).
15. **Please re-evaluate the sample size / power calculation for each trial using both formula, software (e.g., SAS PROC Power), and simulation.**

We can use the stated power of 0.90, alpha level of 0.05, and 1:1 randomization ratio in our sample size calculations. We can approximate for the estimated mean difference, since the value used by the investigators for the estimated mean difference is not stated. Using an estimated mean difference of -0.4 (based on findings from Table 2), we can use a PROC POWER to get a measure of standard deviation by plugging in available parameters, including a total sample size of 1200. Using this method, we determine the standard deviation for future use in formula, PROC POWER, and simulations to be 2.46.

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Then, using the formula derived in Homework 4, we get a calculated sample size of 648 for each treatment group, for a total target sample size of 1296. Of note, this value is larger than the sample size stated in the paper, as we had to work around the absence of some measures in the sample size calculation.

Similarly, we can use a PROC POWER to re-evaluate the sample size and power calculations. We will use the aforementioned parameters and the target sample size from the paper, 1200, to yield a calculated sample size of 1204 and calculated power of 0.899. These values align quite well with what we would expect based on the values presented in the paper.

SAS Code for sample size and power calculation using PROC POWER:

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Lastly, we can run a simulation to check the power and type I error produced when using the sample size determined in the paper. To do so, we generate random values to test if the treatment groups are significantly different using a PROC ttest. We check power at N(-0.4,2.46) and type I error at N(0,2.46). This simulation, for 1000 iterations, produces a power of 0.804 and type I error of 0.039. Again, these values are less than expected based on the paper given restrictions in our knowledge of all estimates used.

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SAS Output for simulation:

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