**Homework 1, CPH 675 Clinical Trials Dominic LaRoche**

**Due: 11 Feb 2015**

Please turn in a printed out solution. Your answers should be typed (not handwritten), concise and complete. Include relevant code and output only.

For questions 1- 3, work with a partner (William Degnan).

1. [10 pts] Read the following Wikipedia account of the Guatemala syphilis experiment:

<http://en.wikipedia.org/wiki/Guatemala_syphilis_experiment>

Which of the 7 ethical requirements as outlined in Emanuel et al, 2000 were violated? Explain briefly.

* Value – Enhancements of health or knowledge must be derived from the research: No apparent violation. The purpose of the Guatemala syphilis experiment was to test a hypothesis on the effect of penicillin in the prevention and treatment of venereal disease, which, on the surface, appeared to have some scientific value. Per the article, “bad research methods do not render the question valueless.”
* Scientific validity- The research must be methodologically rigorous: **Violation**. It is unclear whether sufficient funds were available to fully administer treatments and the research was ended (presumably early) partially due to lack of funds for the expensive penicillin treatment. Only 25% of the patients intended for full treatment actually received it.
* Fair subject selection – Scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities as study sites and the inclusion criteria for individual subjects: **Violation**. Those who would benefit from the research (at-risk persons in the United States) did not share in the risks and burdens associated with the experiment because it could not be approved and conducted in the US.
* Favorable risk-benefit ratio – Risks must be minimized and potential benefits enhanced, potential benefits to individuals and knowledge gained for society must outweigh the risks: **Violation**. There was no apparent effort to minimize the risks of the experiment; to the contrary, subjects were deliberately exposed to known serious health threats. Benefits were not enhanced due to only 26% of the subjects completing the prescribed therapy.
* Independent review – Unaffiliated individuals must review the research and approve, amend or terminate it: **Violation**. Although the article did not directly address if or how the experiment’s protocol was reviewed, an independent and effective review likely would have prevented the conduct of the experiment to begin with, or at least would have terminated it early after the adverse effects began to appear.
* Informed consent – individuals should be informed about the research and provide their voluntary consent: **Violation**. Highly vulnerable populations (solders, prostitutes, prisoners and persons with mental disorders) were infected with syphilis involuntarily and without consent. The subjects were not informed of the purpose of the experiment nor did they have control over their participation.
* Respect for enrolled subjects - Subjects should have their privacy protected, the opportunity to withdraw, and their well being monitored: **Violation**. The participants had no apparent opportunity to withdraw from the experiment and not all participants who experienced adverse effects received appropriate treatment. Also, there was no mention that they were told about the results of the experiment.

1. [6 pts] Find an example of an RCT from 2013 reported in the BMJ, the Lancet, the New England Journal of Medicine, or JAMA that uses a composite outcome as the primary outcome. Include a link to this article.

Mohr FW, Morice M-C, Kappetein AP el al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *The Lancet*. 2013;381(9867);629-638. [http://www.sciencedirect.com/science/article/pii/ S0140673613601415](http://www.sciencedirect.com/science/article/pii/%20S0140673613601415). Accessed February 4, 2015.

* 1. Discuss how the outcome satisfies the definition.

For patients with three-vessel disease and left main coronary disease, the primary outcome (or endpoint) analyzed in this non-inferiority, unblinded trial was major adverse cardiac and cerebrovascular events (MACCE) at one year after treatment for two different intervention groups: Percutaneous coronary intervention (PCI) using a drug-eluting stent and the standard of care, Coronary artery bypass surgery (CABG). MACCE was defined in the Methods section as a composite outcome with four components: All-cause mortality, stroke, myocardial infarction, and repeat revascularization. The 5-year follow-up result referenced in the title of the paper was one of four secondary endpoints assessed by the authors.

* 1. Discuss how the paper did, or did not, satisfy the best practice criteria for reporting a composite outcome, as outlined in Cordoba et al., 2010.

An outline of the best practice criteria from Cordoba el al (2010) is found in Figure 3 of the paper:

* Remind readers that the result is based on a composite outcome.
  + The paper reminded the reader several times that the study’s findings were based on the MACCE composite outcome. Examples:
  + In the Findings paragraph of the Summary at the beginning of the article, and in the Results section: “After 5 years’ follow-up, Kaplan-Meier estimates of MACCE were 26·9% in the CABG group and 37·3% in the PCI group (p<0·0001).” Results of analyses stratified by SYNTAX score were also reported as estimates of MACCE.
  + In the Discussion section: “... CABG remains the standard of care for patients with complex coronary lesions, driven by favourable rates of MACCE ...”,
* Pre-specify primary and secondary outcomes and death.
  + The article pre-specified the primary outcome as the composite rate of MACCE at 1 year by documenting this planned outcome in an earlier paper.
  + Secondary outcomes were pre-specified in the current article as the MACCE rates at 1 and 6 months, 3 and 5 years, rates of the individual MACCE components (all-cause mortality, stroke, myocardial infarction, and repeat revascularization), and rates of stent thrombosis or graft occlusion.
  + Death was pre-specified as “all-cause” in an earlier paper.
* Report data for all components. For the three SYNTAX score strata (low, intermediate, high) the composite outcome MACCE and all of its components are reported in Table 1. Table 2 also reported MACCE and its components for PCI-only and CABG-only registries.
* State whether the intervention has a similar effect on all components, or specify on which components there is an effect (specifically mentioning the effect on most important component)
  + For each SYNTAX score strata, the article characterized the effect of the intervention with respect to the MACCE composite outcome and its components.
  + For example, the PCI intervention and CABG standard of care had similar, non-significant effects on MACCE and its components in the low SYNTAX score stratum. However, beginning in the intermediate stratum, departures from similarity were noted in the MACCE composite outcome and its components: ”In patients with an intermediate SYNTAX score, mortality rates were similar between treatment groups, but significantly more patients in the PCI group had MACCE than did those in the CABG group, driven by significantly increased rates of myocardial infarction and repeat revascularisation in the PCI group.”
  + Note: The article did not explicitly identify which component of the MACCE composite was the most important: “In this trial, the primary endpoint components of death, myocardial infarction, stroke, and repeat revascularisation were weighted equally without regard to clinical effect.”
* Highlight inherent problems associated with composite outcomes.
  + In the Discussions section, the article did suggest that using the MACCE composite outcome had shortcomings: “Limitations inherent in the use of an unweighted composite endpoint such as MACCE should also be noted.” However, the authors focused on the equal-weighting issue and did not identify or discuss mitigation of the inherent problems of composite outcomes identified in Cordoba et al (2010) such as the potential for bias and unreasonable combinations of components of dissimilar clinical importance.
  1. In your view, do the components have the same level of importance? Provide a persuasive argument.

The components of MACCE clearly do not have the same level of importance. All-cause mortality has the highest importance, repeat revascularization has the lowest importance, and the importance of stroke and myocardial infarction falls in between. Reason: All-cause mortality involves bodily death but repeat revascularization does not; the latter is a redo of a restorative procedure to reestablish blood flow to the heart. Both stroke and myocardial infarction involve blockage of blood flow that can result in the death of brain and heart tissue, respectively. However, both stroke and myocardial infarction can eventually result in severe disability or bodily death; therefore they can be considered to have similar importance.

1. [6 pts] Find an example of an RCT from 2013 reported in the BMJ, the Lancet, the New England Journal of Medicine, or JAMA that uses a surrogate outcome.

We found the article:

<http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70554-0/abstract>

* 1. What is the clinical outcome and what is the surrogate?

The clinical outcome is complete remission and the surrogate is pathological complete response (pCR). They defined pCR as an absence of invasive cancer in the breast and axillary lymph nodes.

* 1. Does the paper discuss why a surrogate was used? Explain briefly.

Yes. Traditional adjuvant studies require a long time because of the length of follow-up necessary to accumulate enough data to estimate disease free survival and overall survival. The use of the pCR outcome can be reported much more rapidly and, therefore, speed up advances in the treatment of breast cancer.

* 1. Discuss how it may or may not satisfy the two Prentice criteria.

It is very likely that pCR, as defined in this study, is correlated with actually being cancer free. However, the second criteria of capturing the full effect of the intervention is less clear. This fact is clearly acknowledged by the authors in this study. The long-term validity of pCR as a surrogate needs to be investigated with long-term trials. Patients in this trial were followed for a median of 47 months, which may not fully capture the full effect of the treatment as recurrence in possible after 5 years and many treatments have differential 5 and 10 year survival/ DFS rates.

1. Read the following article about losing weight by keeping indoor temperatures cooler:

<http://www.webmd.com/diet/news/20140122/could-turning-down-the-thermostat-help-you-lose-weight>

If you were designing a trial to answer this question

* 1. [1 pt] What would the primary outcome be?

The primary outcome would be a decrease in body fat percentage.

* 1. [2 pts] What would the primary research question be?

Does daily exposure to 7 hours of mildly cold ambient air temperature (63 degrees F) reduce body fat percentage after 6 weeks of exposure as compared to exposure to typical indoor ambient air temperature (72 degrees F)?

* 1. [2 pts] Describe two possible adverse events that may occur.

Adverse effects might include an increase in body fat triggered by increased appetite. It is also possible to induce hypothermia at this temperature for susceptible individuals.

* 1. [2 pts] What would a good control group be?

A control group could go undergo an artificial treatment at typical room temperature.

* 1. [2 pts] What are some of the issues that may threaten the validity of this study?

Blinding would be difficult since it is hard to mask temperature exposure to both participants and investigators. Also, the generalizability of this study might be called into question since it seems reasonable that people will have different physiological reactions to cold exposure depending on their ancestry.

* 1. [2 pts] How might you address the above issues?

Using minimization or stratification to balance the ancestry of the participants could alleviate the generalizability problem. Masking could be partially achieved by not revealing the true treatment to the participants. E.g. participants could be told that they are getting one of two treatments with enriched oxygen. Participants might then think that the cold temperature is just a side effect of the treatment apparatus and not specific to the treatment.

1. [10 pts] Use statistical software (SAS, Stata, or R) to create a randomization list for a 3-arm RCT with n = 600 that uses simple randomization. Start from first principles, by using a statistical distribution, and ensure that you have equal numbers in each of the groups. Include your code, and appropriate tabulation(s) that indicate that you have achieved balance across the arms.

trtA<-trtB<-trtC<-vector()

trtGroup<-character()

i<-0

set.seed(37)

while(length(trtGroup)<600 ){

u<-runif(1)

if(u < (1/3) & length(trtA)<200){

i<-i+1

trtGroup[i]<-"Treatment A"

trtA<-c(trtA,1)

}

if(u > (1/3) & u < (2/3) & length(trtB)<200){

i<-i+1

trtGroup[i]<-"Treatment B"

trtB<-c(trtB,1)

}

if(u > (2/3) & length(trtC)<200){

i<-i+1

trtGroup[i]<-"Treatment C"

trtC<-c(trtC,1)

}

}

summary(factor(trtGroup))

Treatment A Treatment B Treatment C

200 200 200

1. [2 pts] Write a sentence that is appropriate for a journal where the results of the above RCT are being reported.

We randomly allocated 200 participants to each of the three arms for a total of 600 participants.

1. [8 pts] Use statistical software to create a randomization list for a 2-arm RCT with n = 1000 that is stratified by sex and by treatment center, assuming that there are 4 centers, and with a random block size. You do NOT have to program this from first principles, but please reference appropriately (ie, if you used code from a website to get an idea of where to get started). You may use built-in procedures or user contributed modules/libraries. Include your code, and appropriate tabulation(s) that indicate that you have achieved balance.

library(blockrand)

dat<-list()

m<-c("Male","Female")

center<-c(1,2,3,4)

strat<-expand.grid(m,center)

for(i in 1:8){

set.seed(i)

dat[[i]]<-blockrand(n=125,num.levels=2,levels=c("Treatment","Control"))

dat[[i]]$Sex<-strat[i,1]

dat[[i]]$Center<-strat[i,2]

dat[[i]]<-dat[[i]][1:125,]

}

data<-do.call(rbind,dat)

sum(data$treatment=="Treatment")

[1] 501

table(data$Center,data$treatment)

Control Treatment

1 126 124

2 126 124

3 125 125

4 125 125

table(data$Sex,data$treatment)

Control Treatment

1 125 125

2 123 127

3 126 124

4 125 125

1. [2 pts] Write a sentence that is appropriate for a journal where the results of the above RCT are being reported.

We used a permuted block design stratifying by sex and treatment center, with randomly selected block sizes of 2, 4, 6 and 8 participants, to assign each of the 1000 participants to either the treatment or control arm.

1. [10 pts] Consider a trial in which 80 participants have already been randomized, as shown in the table. A). Use Tave’s minimization to decide the allocation of the 81st individual given that she is 52 years of age with late stage breast cancer.

Intervention = 9+20+20 = 49

Control = 8 + 21 + 21 = 50

So she would be randomized to the intervention arm

B). Use Pocock and Simon’s method using an unweighted sum and p1 = 1.

First calculate the imbalance generated by assigning to either treatment or control.

Intervention = 10-8 + 21-21 + 21-21 = 2

Control = 9-9 + 22-20 + 22-20 = 4

So assignment to the intervention arm would generate less imbalance. This is exactly what we would expect given the equivalence between the Tayes method and the Pocock and Simon method with p= 1 and equal variables weights.

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| --- | --- | --- |
| Prognostic Factor | Intervention | Control |
| Cancer stage |  |  |
| Early | 31 | 32 |
| Late | 9 | 8 |
| Cancer type |  |  |
| Colorectal | 20 | 19 |
| Breast | 20 | 21 |
| Age group |  |  |
| 18-30 | 6 | 7 |
| 31-50 | 10 | 8 |
| 51-70 | 20 | 21 |
| >70 | 4 | 4 |