Preview: Post-class quiz 5 - Clinical Trials

Question 1 **5 points**

What is meant by "randomization"? (Select the one best answer.)

- A. Selection of subjects at random.
- B. Randomization is a method of allocating treatment such that each subject has an equal chance of receiving any of the possible treatments.
- C. Regression to the mean is a common phenomenon in clinical trials.
- D. Biases introduce random outcomes.

Question 2 **5 points**

What are the TWO main purposes of randomization? (Select TWO.)

- A. To eliminate bias in assignment to a treatment group
- B. To achieve baseline comparability between the intervention and comparison (control) groups, i.e. to make the groups being compared similar with respect to known and unknown confounders.
- C. To avoid the problem of random error.
- D. To enhance the predictive value of the study.

Question 3 **5 points**

Which of the following is/are true about an ideal placebo? (Select all that apply.)

- A. It is inert.
- B. It is indistinguishable from the active treatment.
- C. It allows blinding.
- D. It minimizes bias when evaluating subjective outcomes.

Question 4 **5 points**

What is "blinding" and what is its purpose? (Select one).

- A. Blinding means you begin with the null hypothesis, and base your conclusions totally on a statistical analysis of the data without any preconceived ideas.
- B. Blinding refers to equipoise, i.e. uncertainty regarding whether a new treatment is effective.
- C. Blinding means that the subjects and/or investigators do not know which treatment group the subject is in. The purpose is to prevent bias in assessing the outcome.
- D. Blinding occurs when the results totally disagree with previously published studies. Its purpose is to cause a re-evaluation of the data.

Question 5 **5 points**

What is meant by "compliance" in a randomized clinical trial? (Select one).

- A. Flexibility in assignment to treatment groups.
- B. The degree to which study subjects adhere to an assigned treatment protocol.
- C. An inter-institutional agreement for a multi-center study.
- D. Benefits for people who enroll in the study.

Question 6 **5 points**

What problem results when compliance of subjects is poor in an intervention study? (Select one).

- A. Confounding will be introduced.
- B. There will generally be bias away from the "null".
- C. The effectiveness of blinding will be jeopardized
- D. If compliance is poor, the two groups will become more alike and the ability to detect true differences in outcome is diminished, i.e., the power of the study is reduced.

Question 7 **5 points**

Which of the following is the best explanation regarding the relationship between compliance and "bias toward the null" in a clinical trial?

A. Noncompliance will make the groups appear to be MORE similar, and the apparent strength of association will be diminished.
B. Noncompliance will make the groups appear to be LESS similar, and the apparent strength of association will appear to be stronger than it really is.
C. Noncompliance has no effect (a null effect) on the relative risk.

Question 8 **5 points**

Which statement about blinding in an intervention study is NOT correct? (Select one).

- A. The purpose of blinding is to reduce bias in determining the outcome.
- B. The purpose of blinding is to reduce confounding.
- C. In a double blinded study, neither the subject nor the investigators know which treatment the subject is receiving.
- D. Blinding can be accomplished by using a placebo.

Question 9 **5 points**

Intention-to-Treat analysis of a clinical trial means which of the following? (Select one).

- A. Subjects should not be enrolled unless they really intend to take the treatment being tested. This is usually proven during a "run-in" period where their compliance with taking the study drug is tested before the trial begins.
- B. Anyone randomized into one of the study groups must be included in the final analysis in the group to which they were originally randomized, regardless of whether they adhered to the protocol or not.
- C. Anyone randomized into one of the study groups should be included in the final analysis, only if they actually took the drug they were assigned throughout the entire study period.
- D. All subjects must agree to be randomized and to take the treatment of the group they were assigned to.

Question 10 **5 points**

Very small randomized clinical trials may have which of the following problems? (Select all that apply.)

- A. The statistical power of the study may be limited if there aren't enough subjects who develop the primary outcome that is being measured.
- B. Confounding factors may not be equally distributed between groups.
- C. It is easier to break the blind of smaller trials and figure out which treatment patients are getting.

Question 11 **5 points**

The fact that certain types of people agree to participate in clinical trials may affect which of the following? (Select one).

- A. Validity
- B. Generalizability
- C. Randomization
- D. Sub-group analysis

Question 12 **5 points**

Generalizability is more important to a study than validity.

- True
- False

Question 13 **5 points**

Is Low Dose Aspirin Beneficial? The Physician's Health Study was conducted to test the hypothesis that 325 mg. of aspirin taken every other day would reduce mortality from cardiovascular disease (N. Engl. J. Med. 320:1238, 1989). Male physicians 40 to 84 years of age living in the US in 1980 were eligible to participate. Physicians were excluded if they had a personal history of myocardial infarction, stroke or transient ischemic attack; cancer; current gout; liver, renal or peptic ulcer disease; contraindication to aspirin consumption; current use of aspirin, platelet-active drugs or non-steroidal anti-inflammatory agents; intolerance to aspirin; or inability to comply with the protocol. Eligible subjects who met the inclusion criteria and who successfully completed a run-in phase were randomly assigned to receive aspirin or a placebo. Eventually 22,071 physicians were enrolled; 11,037 were assigned to aspirin, and 11,034 were assigned to placebo. The agents (aspirin and placebo) were identical in appearance and were mailed to the subjects. The recipient's treatment was coded, and neither the subject nor the investigators knew which treatment group a given subject was in. Table 1 below shows the frequency of some risk factors of the subjects at the beginning of the study (baseline). RR is the relative risk of having the risk factor, comparing those who received aspirin to those who received placebo. The p-values that were computed were based on a comparison of the frequency of having the risk factor (or not) among the two treatment groups.

Table 1	Aspirin group(N=11,037)	Placebo group(N=11,034)	RR	p-value
Cigarette smoking				
Past	4373	4301	1.02	0.33
Current	1213	1225	0.99	0.79
Diabetes mellitus	275	258	1.07	0.46
Parental history of MI	1420	1432	0.99	0.80
Cholesterol>260 mg/dl	582	570	1.02	0.72
Exercise <1/week	2997	3060	0.98	0.34

Which of the following is an appropriate conclusion that can be drawn from these data? (Select the one best answer.)

- A. Aspirin did not reduce the risk of diabetes.
- B. The sample size was too small.
- C. Based on these data, randomization appears to have been successfully in controlling confounding.
- D. The frequency of diabetes differed significantly between the two groups since the p-value was less than 0.5.

Question 14 **5 points**

Table 2 below summarizes adverse outcomes in the Physicians Health Study. Use the Cohort Studies worksheet in the "Epi_Tools" Excel spreadsheet to compute the missing risk ratios and p-values for the association between aspirin use and fatal, non-fatal, and total myocardial infarctions. After computing the missing values, which of the following is the most appropriate conclusion?

Table 2

End-Points	Aspirin Group	Placebo Group		
	(N=11,037)	(N=11,034)	RR	P value
Myocardial infarction				
Fatal	10	26		
Non-Fatal	129	213		
Total	139	239		
Stroke				
Fatal	9	6	1.50	0.44
Non-Fatal	110	92	1.20	0.20
Total	119	98	1.24	0.12
Type of stroke				
Ischemic	91	82	1.11	0.49
Hemorrhagic	23	12	1.92	0.06
Upper GI ulcer	169	138	1.22	0.08
with hemorrhage	38	22	1.73	0.04
Bleeding problems	2,979	2,248	1.32	<.001
Bleeding requiring transfusion	48	28	1.71	0.02

A. The frequency of stroke and upper GI ulcer was significantly greater in the aspirin-treated group.

B. Aspirin should be recommended to all adults, because it was associated with a significantly reduced risk of fatal and non-fatal myocardial infarctions no adverse effects.

C. Aspirin was associated with a significantly reduced risk of fatal and non-fatal myocardial infarctions, but aspirin users had significantly more bleeding ulcers and other bleeding problems and a borderline significant increase in hemorrhagic strokes.

D. Aspirin users had significantly more strokes.

Question 15 **5 points**

Since the Physicians Health Study was conducted in men, there were questions about the efficacy of aspirin in women. As a result, the question about efficacy in women was addressed in another large randomized clinical trial published in 2005 (Ridker PM, et al.: A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N. Engl. J. Med. 2005;352:1293-304.) "Methods: We randomly assigned 39,876 initially healthy women 45 years of age or older to receive 100 mg of aspirin on alternate days or placebo and then monitored them for 10 years for a first major cardiovascular event (i.e., nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). Results: During follow-up, 477 major cardiovascular events were confirmed in the aspirin group, as compared with 522 in the placebo group, for a non-significant reduction in risk with aspirin of 9 percent (relative risk, 0.91; 95 percent confidence interval, 0.80 to 1.03; P=0.13). With regard to individual end points, there was a 17 percent reduction in the risk of stroke in the aspirin group, as compared with the placebo group (relative risk, 0.83; 95 percent confidence interval, 0.69 to 0.99; P=0.04), owing to a 24 percent reduction in the risk of ischemic stroke (relative risk, 0.76; 95 percent confidence interval, 0.63 to 0.93; P=0.009) and a non-significant increase in the risk of hemorrhagic stroke (relative risk, 1.24; 95 percent confidence interval, 0.82 to 1.87; P=0.31). As compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25; P=0.83) or death from cardiovascular causes (relative risk, 0.95; 95 percent confidence interval, 0.74 to 1.22; P=0.68). Gastrointestinal

bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group (relative risk, 1.40; 95 percent confidence interval, 1.07 to 1.83; P=0.02). Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women 65 years of age or older." **Based on the information in this abstract, which of the following is true?**

- A. The benefits and risks of low dose aspirin are similar in males and females.
- B. Unlike male physicians, the women in this study experienced a significant decrease in ischemic strokes, with no significant reduction in myocardial infarction, except in women over age 65.
- C. The study in women is inconclusive, because it lacked sufficient sample size.
- D. Women on low dose aspirin did not have a significant increase in gastrointestinal bleeding.

Question 16 **5 points**

Statins are a class of drugs that have been demonstrated to be effective in lowering blood levels of cholesterol and significantly reducing the incidence of major cardiac events (heart attack, stroke, severe angina) in patients with elevated cholesterol levels. However, certain groups of people who do not have elevated cholesterol levels are still at increased risk of having a major cardiac event, including people who have elevations in an inflammatory marker called C-reactive protein. In Nov. 2008 the New England Journal of Medicine published the results of a study in which the investigators enrolled 17,802 subjects who had no history of heart disease. All subjects had elevated levels of C-reactive protein, but they all had normal cholesterol levels. Subjects were randomly assigned to receive either the statin Rosuvastatin (Crestor) 20 mg. per day or a placebo that looked identical to the active agent. The drugs were coded, and neither the investigators nor the subjects know who was receiving the active drug. Subjects were followed for an average duration of about two years.

Several points from the Methods section of the paper:

> "Follow-up visits were scheduled to occur at 13 weeks and then 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after randomization. Follow-up assessments included laboratory evaluations, pill counts, and structured interviews assessing outcomes and potential adverse events."
> "The primary outcome was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes."
> "All reported primary end points that occurred through March 30, 2008, were adjudicated on the basis of standardized criteria by an independent end-point committee unaware of the randomized treatment assignments. Only deaths classified as clearly due to cardiovascular or cerebrovascular causes by the end-point committee were included in the analysis of the primary end point."

The following table summarizes the main findings of the study.

Group	Subjects	Major Cardiac Events	Person-years
Crestor (statin)	8,901	142	18,442
Placebo	8,901	251	18,529

Using the data from the table above, calculate the rate ratio for the overall effect of Crestor compared to placebo. Round your answer to two decimal places (e.g., if your answer is 1.2345, the rounded answer would be 1.23; if your answer is 1.2365, the rounded answer would be 1.24), and submit your numeric answer.

Question 17 **5 points**

For the clinical trial on Crestor in the previous question the authors reported that 75% of the study subjects were taking their assigned medications by the end of the study (i.e., 75% compliance), and the primary analysis was an “intention to treat” analysis. Assuming that Crestor was truly beneficial, which of the following is true about the true effectiveness of Crestor (i.e., if all subjects had complied and taken the pills they were given) compared to the effect that was observed in the intention to treat analysis?

- A. If compliance had been 100%, Crestor would have been even more effective than it appeared in the intention to treat analysis, since non-compliance would cause an underestimate.
- B. If compliance had been 100%, Crestor would have appeared to be less effective, because non-compliance causes an overestimate.
- C. If compliance had been 100%, Crestor would have had the same rate ratio as the rate ratio measured with 75% compliance.
- D. It is impossible to say without more information.

Question 18 **5 points**

Using the data from the table above from the Crestor trial, *calculate* the incidence rate difference for daily use of Crestor compared to placebo. To the nearest whole person, how many fewer major cardiac events would there be in persons using Crestor for a total of 10,000 person-years. Enter just the number of people without units.

Question 19 **5 points**

CanadianDrugs.com was selling 20 mg. of Crestor for about $2.00 (US) per pill.

First, compute the cost of treating 10,000 persons with a 20 mg. Crestor pill each day for one year. Then, using your answer for the previous question, what would be the *annual cost to prevent one* (1) major heart attack in a group of 10,000 people with elevated C-reactive protein? Round off your answer to the nearest $1,000 and submit just the number of dollars (*without* the $ sign or any commas).

Question 20 **5 points**

What is meant by a "run-in period" for a clinical trial?

- A. A period before the real trial begins when subjects are screened to ensure that they are committed to the trial and likely to be compliant.
- B. The period during which the subjects receive their medication packages, in contrast to a "run-out" period, which refers to when they run out of medications.
- C. The same thing as a "wash-out period."
- D. When trying to obtain Institutional Review Board (IRB) approve for a study, the investigators sometimes have major differences with the IRB regarding the conduct of the trial. The run-in period is the critical period during which these differences are resolved, usually just before IRB approval is finally obtained.

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