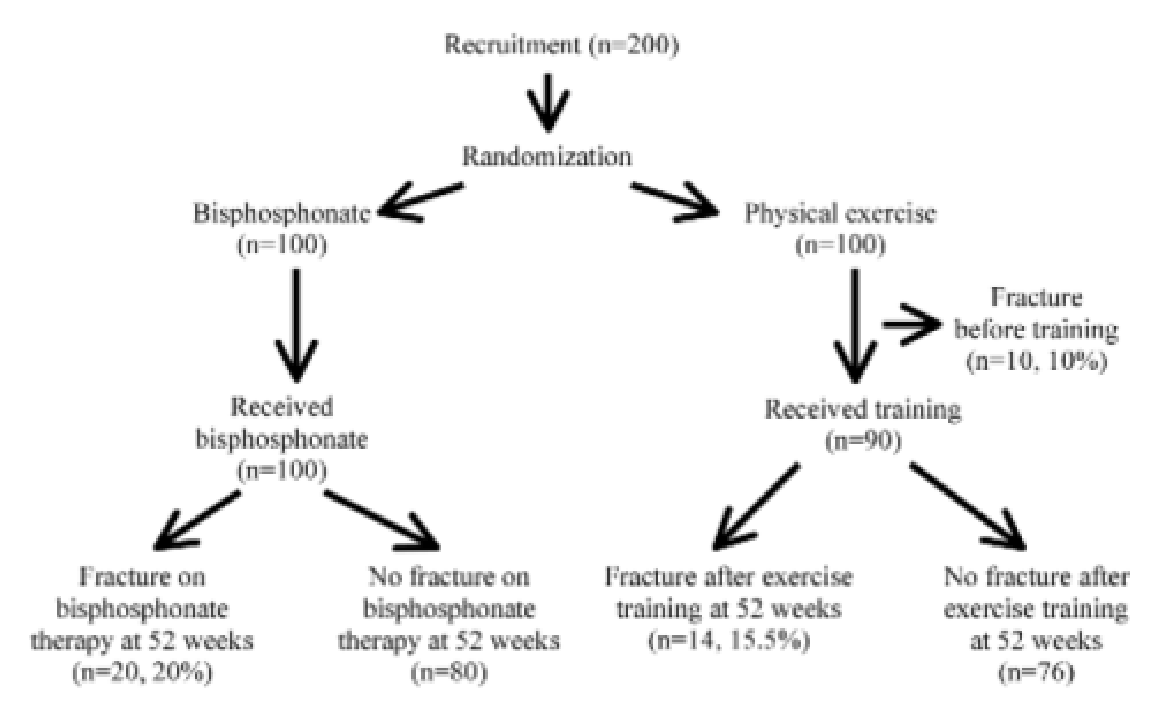
1. Consider a randomized clinical trial in 200 high-risk elderly women studying preventative therapies for hip fracture. The randomized treatments are **medical therapy** (bisphosphonate group, n=100) versus **medical therapy plus weight-bearing physical exercise** (physical exercise group, n=100. For those assigned to the physical exercise plus medical therapy regimen, there is a 6-week delay from the time of randomization to the time they actually commence physical exercise training, and 10% of participants in this arm experience hip fracture before any physical training has been given. Results of the trial are given in the figure below.



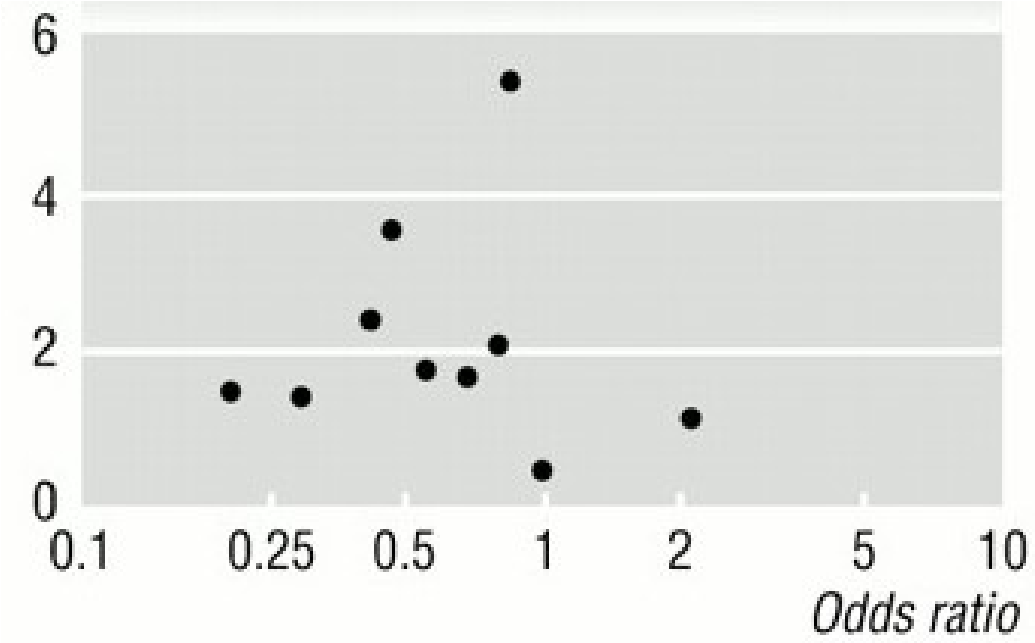
* 1. What proportion of the women experience hip fracture in each of the two randomized groups based on the intent-to-treat principle? I.e., P(fracture | bisphosphonate) and P(fracture | physical exercise) estimated as part of an intent-to-treat analysis.

* 1. What proportion of the women experience hip fracture in the two treatment groups when those in the physical exercise group are restricted to the 90 patients who actually received training (n=90)?

* 1. Circle the correct response. As the time it takes to initiate physical therapy in the physical exercise group increases, power for the intent-to-treat analysis
     + 1. increases
       2. stays the same
       3. decreases

* 1. What analytical concerns, if any, result from the comparison of hip fracture probabilities as calculated in part (b)? Please summarize in **no more than 3 sentences**.

1. A meta-analysis of the effect of intravenous nitrate therapy on mortality in acute myocardial infarction was published in May 1988 (Yusef et al, Lancet). This article reported an overall OR that nitrate use was significantly protective (OR=0.65; 95% CI 0.51-0.82). The following funnel plot was not included in the original article, but was summarized later in follow-up articles.



Precision

a. Circle the correct response. Based on this funnel plot, the meta-analysis is likely

* + - * 1. underestimating the benefit of nitrate use (i.e., overall OR should be smaller)
        2. estimating the benefit of nitrate use reasonably well
        3. overestimating the benefit of nitrate use (i.e., overall OR should be bigger)

b. Explain your reasoning behind your response in part (a).

1. You are asked to collaborate in designing an investigation to study a new treatment for COVID-19. Assume the patients are eligible if they are over 18 years old, and hospitalized for covid-19 but not on a respirator at enrollment. The outcome of interest is if they are intubated (yes or no) at some point. Assume this treatment has never been studied for these patients, but has been used for other illness and we know dosage levels that are safe. Please describe how you would proceed to investigate this treatment. State any assumptions you would make. This should be an open ended question and you can describe your plan in no more than a page or two at most of text. You can use anything you have learned in this course so far for clinical trials. I’m interested to see how you take what you have learned and apply it.

1. 24 Healthy volunteers participated in a randomized crossover study comparing the bioavailability of two formulations of a drug product. The two formulations were either 5 50mg tablets (test formulation) or 5mL or an oral suspension (50 mg/mL; reference formulation). Blood samples were obtained from 0 to 32 hours from dosing and corresponding AUC values were calculated; AUC values during each dosing period are given below according to randomization sequence. For a subject randomized to sequence 1, the order of formulations was the reference formulation followed by the test formulation. For a subject randomized to sequence 2, the order of formulations was the test formulation followed by the reference formulation.

Sequence Period 1 Period 2

1 74.675 73.675

1 96.400 93.250

1 101.950 102.125

1 79.050 69.450

1 79.050 69.025

1 85.950 68.700

1 69.725 59.425

1 86.275 76.125

1 112.675 114.875

1 99.525 116.250

1 89.425 64.175

* 1. 55.175 74.575
  2. 74.825 37.350

2 86.875 51.925

2 81.675 72.175

2 92.700 77.500

2 50.450 71.875

2 66.125 94.025

2 122.450 124.975

2 99.075 85.225

2 86.350 95.925

2 49.925 67.100

2 42.700 59.425

2 91.725 114.050

* 1. Plot the AUC values using PROC TTEST. The vertical axis should be the AUC and the horizontal axis should show the reference formulation on the left and test formulation on the right. The plot should distinguish between sequence 1 and sequence 2 subjects. Overall means should also be superimposed.

* 1. Perform a statistical test assessing whether there are any period effects in this crossover trial. Calculations either by hand or via SAS PROC TTEST are acceptable as long as relevant code and output are shown. Summarize your results in a sentence.

* 1. How much power was available for detecting a 5 unit period effect in this study? (You may use STPLAN and report the parameters you used as well as your result.)

* 1. Assuming no carryover effects, estimate the overall treatment difference adjusted for period.

* 1. Is this treatment difference statistically significant? Perform the appropriate statistical test and summarize results. Calculations either by hand or software such as via SAS PROC TTEST are acceptable as long as relevant code and output are shown.

* 1. How much power was available for detecting a 5 unit treatment effect in this study? Is it bigger, smaller or the same as the power available for detecting a period effect of 5 units? Explain why it is considered harder to detect period effects than the overall treatment effect in a crossover study.

* 1. Was there statistical evidence of a carryover effect? Perform an appropriate statistical test and report results. (Not automatically included as output from PROC TTEST crossover analysis).