Sample size and sequential trials

1) An investigator is planning a placebo-controlled randomized clinical trial to assess the effects of a new drug on mild intermittent claudication (a cardiovascular disease which affects the flow of blood to the legs). She has come to you for advice on the design of the clinical trial which she plans to undertake at her clinic. After some discussion, you have finalized with her that the primary outcome measure to be used in the study is the time until the onset of leg pain during an exercise test (involving walking up a gradient on a treadmill). All patients with this disease do experience such leg pain fairly quickly. The test will be conducted after three months on study treatment.

In order to help with the derivation of the size of her study, the investigator has reviewed the clinical records of all 25 patients who have attended her clinic in the past year and who would fit the eligibility criteria for the planned trial. She has found that the mean time to the onset of pain for the exercise test of interest is 15 minutes with standard deviation 7 minutes. Based on her experience, she anticipates that a relative increase in time to pain of about 5 minutes would produce a significant improvement in a patient's quality of life (notably in their ability to lead a reasonably normal life in their own home without nursing support).

(a) Produce a table with columns displaying effect sizes of 3 minute, 5 minute and 7 minute increases in time to pain and rows with assumed standard deviations of 5, 7 and 9 minutes. Aiming for a 90% powered study with type I error of 5%, fill in the table with sample sizes required by each of the design parameter combinations in the table. You may use any software package used in class or your may work by hand. If you use SAS, then please provide your SAS code.

What size trial would you recommend?

(b) The power of a study to detect a treatment difference of size, Δ, when the outcome is normally distributed within a treatment group with standard deviation σ is given by:

$$\text{power} = \Phi\left\{(\Delta^2 n/2\sigma^2)^{1/2} - z_{1-\alpha/2}\right\} \tag{1}$$

where α is the two-sided level of significance to be used in the test, n is the sample size per treatment group, and Φ is the standard normal cumulative distribution function. Using this formula, or the software package of your choice, construct a table to show what power you would have using the sample size that you suggested in part (a) if the standard deviation was 5, 7, or 9 minutes, and the effect sizes were 3, 5 or 7 minute increases. Again, assume that the type I error is 5%.

(c) Which table do you prefer?, the table constructed in part (a) or in part (b)?

(d) Do you foresee any potential problems with her planned study
in terms of the size/power issue? If so, briefly discuss what alternatives might be considered.

2) The same investigator is also considering a trial with the same agent for the treatment of advanced intermittent claudication in those at highest risk for requiring surgery within 2 years. In this higher risk population, she estimates that roughly 50% of patients will require major surgery within two years. She is interested in assessing whether treatment would delay the time until surgery is necessary. After discussion with some colleagues who might participate in a multi-center randomized controlled trial with her, she concludes that a reduction in the two-year rate of surgery from 50% to 37% would be clinically worthwhile (this corresponds to increasing the median time to major surgery from 2 to very close to 3 years if times are exponentially distributed).

(a) What size of trial would be required if patients participating in the trial were all followed for exactly two years? Assume type I error of 5% and power of 90%. You may use hand calculations or the software package of your choice. If you use SAS, please provide code and output.

(b) Instead of undertaking a trial with a fixed length of follow-up for each patient, you suggest allowing a variable length of follow-up depending, in part, on how long it takes to accrue sufficient patients. If you are willing to assume that the time to surgery is exponentially distributed, how many surgical interventions would be required to give a study with 90% power? Show how you derived the number.

(c) The 12 main centers in the U.S. who see about 30 new patients each per year have already agreed to participate. She wonders if it is possible to complete the study within three years just at these centers by having an accrual period of one year with further follow-up of all patients for a further two years after accrual has closed. By evaluating the size of trial required for this design (assuming 5% type I error and 90% power), determine whether her proposal is reasonable. Justify your answer. If you use SAS, please provide code and output.

(d) If the 12 centers in the U.S. are not sufficient, then she would have to extend the trial to include centers in Europe though this would raise many practical difficulties and so would be willing to consider a trial of four years duration in the U.S. as an alternative to doing this. Explore different accrual and follow-up times to see if this is feasible. What would you recommend? Justify your answer. If you use SAS, please provide code and output.

(e) You present your best design from part (d) to your colleagues and they recommend adding an interim analysis plan to the design with 3 planned analysis times. Use PROC SEQDESIGN in SAS and an O'Brien-Fleming style error spending approach to provide the required information below:

(i) The new accrual rate per year that accounts for the interim analyses to be performed

(ii) The type I error to be spent at each interim analysis.

(iii) The critical values associated with these type I errors (labeled boundary values by SAS)

(iv) The probability of stopping at the first, second and third analyses if the alternative hypothesis used in the design is true.

Please provide relevant SAS Code and Output with your responses.