1. To begin, we will finish our discussion of the proposed heroin trial from Tutorial 1.

2. The role of circulating *catecholamines* in the serum of patients with essential hypertension has been an area of intense medical research. In this study, researchers want to compare the heart rate in patients with essential hypertension and high catecholamine levels to the heart rate in patients with essential hypertension and low catecholamine levels.

The investigators have determined that a difference of 10 or more beats per minute represents a clinically significant difference, and assume that the (common) standard deviation in heart rate is 15 beats per minute. If the Type-I error rate is fixed at 5% then find the minimum number of patients required in each group to attain 80% power when the true difference is 10 beats per minute.

3. In the above problem, we were interested in determining the study size for a specified power and given magnitude of the effect to be detected. However, given the values of any two of these items, we can find the third. This is known as the *inverse problem* and is useful when the trial size is limited by other considerations such as cost or availability of patients.

In the following trial, the effects of two interventions on forced expiratory volume (FEV) are to be compared in two groups of men; the group sizes are to be fixed at 50 men per group. Assume that the standard deviation in FEV is known to be 0.5, and that a two-sided test with significance level 0.05 is to be used.

(a) Calculate the power against the clinically significant alternative hypothesis \( H_A : \delta = 0.25 \).

(b) Find the value \( \delta_0 > 0 \) for which we will have 80% power against the alternative \( H_A : \delta = \delta_0 \).

4. * Consider a trial designed to compare two methods of helping smokers give up smoking. One group is to be given nicotine patches and the other group will receive advice from their doctor and a booklet. On the basis of published evidence, it is expected that in the advice group, 15% of the subjects will remain non-smokers at 6 months. An improvement to 30% in the group given patches would be considered to be of clinical importance.

A two-sided test with significance level 5% is to be used in the analysis of the results. Find the minimum number of smokers required per group in order to have an 85% chance of detecting a difference of this magnitude.

5. Sample size calculations for clinical trials depend on the endpoint to be used in the final analysis. The choice of endpoint is clearly important, but may not be straightforward, as the following example illustrates.

The Physicians’ Health Study was a $2 \times 2$ factorial randomized controlled trial of aspirin and beta-carotene. A total of 22,000 men aged 40-84 years were randomized onto aspirin or placebo, resulting in 11,000 in each of the aspirin and control groups. Patients within each group were then randomized onto beta-carotene or placebo, but it is the first randomization onto aspirin or placebo which concerns us
here. The primary aim of the trial was to assess the effects of aspirin in reducing both total mortality (i.e. deaths from all causes) and cardiovascular (CV) mortality (i.e. deaths from heart attack or stroke) among men. At the planning stage of the trial, there was some debate about whether to use total mortality or CV mortality as the major endpoint for analysis. A 20% reduction in CV mortality due to aspirin was expected, with a corresponding reduction of 10% for total mortality. It was anticipated that approximately half of all deaths would result from non-CV causes, and it was assumed that aspirin would have no effect on these.

(a) The number of CV deaths in the control group was anticipated to be 500. How many CV deaths were anticipated in the aspirin group?

Construct a test of the null hypothesis of no difference between the groups, and comment on the outcome.

(b) The researchers were concerned that using total mortality alone as the endpoint for analysis could seriously reduce the power of the study to detect a true aspirin effect on CV mortality. They expected to observe 500 non-CV deaths in each group. Suppose that by chance however, the non-CV deaths actually distributed themselves as shown in the table on page 113 of the article from *Statistics in Medicine*. Suppose also that total mortality was used as the major endpoint for analysis in each case. Reproduce the chi-squared statistics (or the equivalent $z$-statistics) and comment on the possibility of losing evidence of a real benefit of aspirin on cardiovascular mortality.

Assignment 2 is due by 4pm on Friday 5 September (end of Week 6).

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