2. (B: Pivotal) Suppose we choose a type I error of $\alpha = 0.025$ and a power of 80.0% (so $\beta = 0.20$) under the alternative hypothesis that the true treatment effect is $\theta = 1$.

   a. What sample size *n* will be used in each RCT? __500__

      $$n = \frac{(1.959964+0.8416212)^2 \times 63.70335}{1^2} = 499.999$$

   b. How many of our ideas will we be able to test? _1000_

      $500{,}000/500 = 1000$

   c. How many of those tested ideas will be truly beneficial drugs? __100__

      $1000 \times 0.10 = 100$

   d. How many of the tested beneficial drugs will have significant results? ___80__

      $100 \times 0.80 = 80$

   e. How many of those tested ideas will be truly ineffective drugs? __900__

      $1000 - 100 = 900$

   f. How many of the tested ineffective drugs will have significant results? __23__

      $900 \times 0.025 = 22.5$

   g. How many of the tested drugs will have significant results? __121__

      $98 + 23 = 121$

   h. What proportion of the drugs with significant results will be truly beneficial? _0.8099__

      $98/121 = 0.8099$

3. (C: Pivotal) Suppose we choose a type I error of $\alpha = 0.05$ and a power of 80.0% (so $\beta = 0.20$) under the alternative hypothesis that the true treatment effect is $\theta = 1$.

   a. What sample size *n* will be used in each RCT? __123__

      $$n = \frac{(1.644854+0.8416212)^2 \times 63.70335}{1^2} = 122.081$$

   b. How many of our ideas will we be able to test? _4065_

      $500{,}000/123 = 4065.04$

   c. How many of those tested ideas will be truly beneficial drugs? __407__

      $4065 \times 0.10 = 406.5$

   d. How many of the tested beneficial drugs will have significant results? __326__

      $407 \times 0.80 = 325.6$

   e. How many of those tested ideas will be truly ineffective drugs? _3658__

      $4065 - 407 = 3658$

   f. How many of the tested ineffective drugs will have significant results? __183__

      $3658 \times 0.05 = 182.9$

   g. How many of the tested drugs will have significant results? __509__

      $326 + 183 = 509$

h. What proportion of the drugs with significant results will be truly beneficial? _0.6405__

$326/509 = 0.64047$

Problems using Strategy 2: Screening pilot RCT, followed by Confirmatory RCT

4. (D: Screening pilot study) Suppose we choose a type I error of α = 0.025 and a sample size of *n* = 100 for each pilot RCT.
   a. Under the alternative hypothesis θ = 1, what is the power? _0.2398__

   $$\beta = \Pr\left(Z \leq 1.959964 - 1 \times \left(\sqrt{\frac{100}{63.70335}}\right)\right) = \Pr(Z \leq 0.7071) = 0.7602478$$

   $$Pwr = 1 - \beta = 1 - 0.7602478 = 0.2397522$$

   b. If we use 350,000 patients in pilot RCT, how many ideas will we test? _3500__

   $350{,}000/100 = 3500$

   c. How many of those tested ideas will be truly beneficial drugs? __350__

   $3500 \times 0.10 = 350$

   d. How many of the tested beneficial drugs will have significant results? ___84__

   $350 \times 0.2398 = 83.93$

   e. How many of those tested ideas will be truly ineffective drugs? _3150__

   $3500 - 350 = 3150$

   f. How many of the tested ineffective drugs will have significant results? ___79__

   $3150 \times 0.025 = 78.75$

   g. How many of the tested drugs will have significant results? __163__

   $84 + 79 = 163$

   h. What proportion of the drugs with significant results will be truly beneficial? _0.5153__

   $84/163 = 0.515337$

5. (D: Confirmatory trials) Suppose we choose a type I error of α = 0.025 and use all remaining patients in the confirmatory trials of each drug that had significant results in problem 4.
   a. How many confirmatory RCT will be performed? _163__
   b. What sample size n will be used in each RCT? __2147__

   $350{,}000/163 = 2147.239$

   c. Under the alternative hypothesis θ = 1, what is the power? _0.9999__

   $$\beta = \Pr\left(Z \leq 1.959964 - 1 \times \left(\sqrt{\frac{2147}{63.70335}}\right)\right) = \Pr(Z \leq -3.845472) = 0.000060$$

$\text{Pwr} = 1 - \beta = 1 - 0.000060 = 0.99994$

d. How many confirmatory RCTs will be for truly beneficial drugs? ___84__

e. How many of the tested beneficial drugs will have significant results? ___84__

$84 \times 0.9999 = 83.99$

f. How many confirmatory RCTs will be for truly ineffective drugs? ___79__

g. How many of the tested ineffective drugs will have significant results? ____2__

$79 \times 0.025 = 1.975$

h. How many of the tested drugs will have significant results? ___86__

$84 + 2 = 86$

i. What proportion of the drugs with significant results will be truly beneficial? _0.9767__

$84/86 = 0.9767$

6. (E: Screening pilot study) Suppose we choose a type I error of α = 0.10 and a power of 85.0% (so β = 0.15) under the alternative hypothesis that the true treatment effect is θ = 1.

a. What sample size *n* will be used in each RCT? __342__

$n = \frac{(1.281552+1.036433)^2 \times 63.70335}{1^2} = 342.28$

b. If we use 350,000 patients in pilot RCT, how many ideas will we test? _1023__

$350{,}000/342 = 1023.39$

c. How many of those tested ideas will be truly beneficial drugs? __102__

$1023 \times 0.10 = 102.3$

d. How many of the tested beneficial drugs will have significant results? ___87__

$102 \times 0.85 = 86.7$

e. How many of those tested ideas will be truly ineffective drugs? __921__

$1023 \times 0.90 = 920.7$

f. How many of the tested ineffective drugs will have significant results? __92__

$921 \times 0.10 = 92.1$

g. How many of the tested drugs will have significant results? __179__

$87 + 92 = 179$

h. What proportion of the drugs with significant results will be truly beneficial? _0.4860__

$87/179 = 0.4860$

7. (E: Confirmatory trials) Suppose we choose a type I error of α = 0.025 and use all remaining patients in the confirmatory trials of each drug that had significant results in problem 6.

a. How many confirmatory RCT will be performed? __179__

b. What sample size n will be used in each RCT? _1955__

$350{,}000/179 = 1955.3$

c. Under the alternative hypothesis θ = 1, what is the power? __0.9998__

$$\beta = \Pr\left(Z \leq 1.959964 - 1 \times \left(\sqrt{\frac{1955}{63.70335}}\right)\right) = \Pr(Z \leq -3.579804) = 0.000172$$

$Pwr = 1 - \beta = 1 - 0.000172 = 0.999828$

d. How many confirmatory RCTs will be for truly beneficial drugs? ___18__

$179 \times 0.10 = 17.9$

e. How many of the tested beneficial drugs will have significant results? ___18__

$18 \times 0.9998 = 17.9964$

f. How many confirmatory RCTs will be for truly ineffective drugs? __161__

$179 \times 0.90 = 161.1$

g. How many of the tested ineffective drugs will have significant results? ____4__

$161 \times 0.025 = 4.025$

h. How many of the tested drugs will have significant results? ___22__

$18 + 4 = 22$

i. What proportion of the drugs with significant results will be truly beneficial? __0.82__

$18/22 = 0.8181$

Comparisons

8. Of the 5 different strategies considered (problems 1, 2, 3, 4 and 5, or 6 and 7) which do you think best and why?

The strategy D used in problems 4 and 5 has the best outcome using the same resources and is, therefore, to be preferred. This strategy results in a very high proportion (~98%) of truly beneficial drugs being adopted. And, of the strategies resulting in a similarly high proportions of beneficial drugs adopted, it results in a greater number of adopted drugs.

9. The above exercises considered "drug discovery" with randomized clinical trials. What additional issues have to be considered when we are using observational data to explore and try to confirm risk factors for particular diseases?

Because observational studies are more prone to confounding and bias, the number of confirmatory studies may need to be greater before a conclusion can be trusted than in the RCT setting. In addition, it can be very tempting to change important aspects of the study design and analysis such as subject population or outcome between the exploratory and confirmatory phases of investigation, however this should be considered carefully as it can lead to inflation of the Type I error.