1. (10 pts) In a small phase II clinical trial with 24 patients receiving a new therapy, there were 3 complete responders.

(a) Find a 90% CI for the true response rate using the normal approximation.

(b) Find a 90% exact CI for the true response rate using linear interpolation given the following probabilities $P[X \leq 3|\pi]$ and $P[X \leq 2|\pi]$ for $X \sim Bin(n = 24, \pi)$:

\[
\begin{array}{c|ccc}
\pi & 0.25 & 0.30 & 0.35 \\
\hline
P[X \leq 3] & 0.1150 & 0.0424 & 0.0133 \\
\end{array}
\]

\[
\begin{array}{c|ccc}
\pi & 0.02 & 0.03 & 0.04 \\
\hline
P[X \leq 2] & 0.9882 & 0.9659 & 0.9307 \\
\end{array}
\]

2. (10 pts) In a phase II study, we decided after consulting with our clinical investigator that the minimal acceptable response rate is $\pi_0 = 0.25$. We would like the width of the 90% CI of the true response rate using the normal approximation at this minimum acceptable rate $\pi_0$ to be 0.2. We decided to use Gehan’s two-stage design for this purpose. In the first stage we will discard the new treatment if no patient out of some number of patients (say $n_0$) responds to the treatment. Suppose the probability we can tolerate to discard the new treatment is $\alpha_0 = 0.01$ when in fact the actual response rate of this new treatment is greater than the minimum acceptable rate $\pi_0 = 0.25$.

Describe how you would set up this two-stage design; i.e., how many patients would you treat in the first stage? how many patients in the second stage? What are the probability that the trial stops at the first stage and the expected sample size if the actual response rate is $\pi = 0.25$? What are the probability that the trial stops at the first stage and the expected sample size if the actual response rate is $\pi = 0.5$? Show your calculation.

3. (10 pts) You are asked to help design a phase II clinical trial using Simon’s two-stage design to evaluate a new treatment. The investigator decides that if the true response rate $\pi \leq \pi_0 = 0.1$ then the treatment is definitely a failure and if $\pi \geq \pi_1 = 0.25$ then the treatment will be declared effective and considered for further investigation in a phase III trial. The investigator wants to control the probability of falsely declaring the treatment effective when in fact it is ineffective at the level of 0.05 and to have high probability 0.8 to declare the treatment effective when in fact
it is effective. Using the tables provided in class, set up a two-stage design that minimizes the maximum sample size \((n)\) by answering the following questions:

(a) How many patients will be treated at stage 1?

(b) How many patients will be treated at stage 2 if the trial is not stopped at stage 1?

(c) When will the trial stop at stage 1? What is the probability that the trial stops at stage when the true response rate is \(\pi_0 = 0.1\)?

(d) When will the treatment be declared effective?

(e) What is the expected sample size if in fact the true response rate is \(\pi_0 = 0.1\)? Does this design also yield smallest expected sample size (when the true response rate is \(\pi_0 = 0.1\)) among all designs satisfying the type I error probability and power constraint?

4. (10 pts) Under the structure imposed for the 5-FU data presented on slide 145, do the following:

(a) Show that 
\[
E[\pi_i(1 - \pi_i)] = E \left[ \frac{n_ip_i(1-p_i)}{n_i - 1} \right].
\]

(b) Using the variance definition, show that 
\[
\sigma_{\pi}^2 = \text{var}(\pi_i) = E(\pi_i)[1 - E(\pi_i)] - E[\pi_i(1 - \pi_i)].
\]

Find an estimate of \(E[\pi_i(1 - \pi_i)]\) using the data and hence find another estimate for \(\sigma_{\pi}^2\) (Hint: use the results on slide 158). Is it close to the estimate on slide 153?