Dose-escalation designs for combination & dose-schedule studies

MRC Biostatistics Unit

Practical 5: Setting up your own adaptive combination trial

Although, there has been an incredible progress with vaccines development protecting from the COVID-19, there is still a lack of a promising antiviral treatments for people already sick with the COVID-19. To tackle this problem, there is a clinical interest in combining two existing (and already approved) anti-viral treatments, that by themselves, however, did not have high efficacy. The two treatment are molnupiravir and Paxlovid. However, these two drug has never been given in combination.

You are asked to design the Phase I dose-escalation study of molnupiravir and Paxlovid in patients with mild and moderate COVID-19 within 5 days of the onset of their symptoms. The current approved dose of molnupiravir is 800mg (4 tablets), and the current approved dose of Paxlovid is 100mg of ritovir (1 tablet) + 300mg (2 tablets) of nirmatrelvir. Each agent is administered bi-daily (one dose in the morning, one dose in the evening) for 5 days. Given the current clinical evidence on the efficacy and toxicity of these drugs, the clinical team believes that there is little point in having the final approved combination with dose of each drug lower than these approved dosages.

Working in groups of 3-4 people, propose your design for the stated problem. Specifically, answer the following

(a) How have you formally formulated the objective of the trial?

(b) What is the dose/combination grid you are proposing?

(c) For the stated problem, write down the mathematically the model (if any) that you propose to use for this trial?

(d) For the stated problem, write down the design that you propose to use?

(e) Propose simulation scenarios to be used for the calibration and evaluation of the design?

(f) Propose a calibration plan for your design. How have you decided on the parameters? If you have the code for the proposed design, conduct a small calibration exercise.

(g) For the calibrated parameters, plot a dose-transition pathways on what happens after 0 DLTs in the first cohort, and 0/1/2/3 DLTs in the second cohort

(h) Propose the performance metrics for the simulation study for this trial.

(i) Prepare a 5-minute presentation with the proposed design and the scheme to set up such a design.

Notes:

i) If you have further questions, you can ask imposter/Twitter clinical experts present in the room.

ii) Once you have agreed on the model, you have a chance to approach a statistical methodologist that *might* be able to provide you with the code implementing the model you have chosen. Just ask!