Adaptive Methods in Clinical Research

Practical 5: Designing your own adaptive 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 anti-viral treatments, that by themselves, however, have not demonstrate high efficacy (at least, yet). The two treatments are (i) molnupiravir (approved as monotherapy), and (ii) a new experimental agent (referred to as Agent A) for which the dose-escalation FIH trial has just completed.

You are asked to design the Phase II study of the combination of molnupiravir and Agent A in patients with mild and moderate COVID-19 within 5 days of the onset of their symptoms. The objective is to gather enough evidence for the proof of activity of the combination treatment, so it can be then recommended for a bigger Phase 3 trials. The activity is defined in terms of the reduction in the viral load. The measurements of the viral load are taken everyday on Days 1–10.

The current approved dose of molnupiravir is 800mg (4 tablets), and the RP2D of Agent A is 100mg (2 tablets). Each agent is administered bi-daily (one dose in the morning, one dose in the evening) for 5 days. The clinical teams does not expect to see any synergistic effect on the toxicities and the adverse events from each compound are expected to be different. The current standard of care (in the UK where the study will be conducted) is Paxlovid, or (if contraindication to Paxlovid) molnupiravir or remdesevir.

Working in groups of 4–5 people, propose your design for the stated problem. Specifically, answer the following

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

(b) How many treatment arms are you proposing? What are these arms?

(c) What is the primary endpoint that you would consider for this trial?

(d) For the stated problem, write down the design that you propose to use? Discuss whether it is adaptive or not, and what the adaptations are. What assumptions will you need to make to design such a study?

(e) Propose scenarios/configurations and metrics to be used for the evaluation of the design?

(f) If you design can be implemented with one of the designs learned/implemented in this course, find the design parameters and its operating characteristics. If the design is not readily implemented, could you use the practicals of this course to inform a ballpark of the sample size needed in such a trial?

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

Notes:

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