On the three-arm non-inferiority trial including placebo with a pre-specified margin

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In many clinical trials, a new experimental drug is compared to an active reference drug to demonstrate non-inferiority of the new drug to the reference in a sense that the new drug is not worse than the reference by more than a small amount $\Delta(>0)$, called *non-inferiority margin*, pre-specified in the protocol. However, there could often be a situation where the reference drug has not reliably demonstrated efficacy over placebo. In this situation, it is recommended to consider a three-arm non-inferiority trial including placebo. This design has been proposed in ICH E10 [1] and CPMP [2]. In three-arm non-inferiority trials, we have to establish the following inequality:

$$\mu_P < \mu_R - \Delta < \mu_E,$$

where μ_P, μ_R and μ_E denote the expected value of treatment outcome (with larger value indicating a greater benefit) under placebo, reference and experimental treatment, respectively. In other words, it can be formulated as the following hypotheses:

$$H_0 : \mu_R \leq \mu_P + \Delta, \qquad H_1 : \mu_R > \mu_P + \Delta,$$
$$K_0 : \mu_E \leq \mu_R - \Delta, \qquad K_1 : \mu_E > \mu_R - \Delta,$$

where two hypotheses H_0 and K_0 must be rejected (Tango [3]). On the other hands, Koch and Tangen [4], Pigeot *al.* [5] and Kieser and Friede [6] considered the following re-formulated hypotheses:

$$H_0' : \mu_R \leq \mu_P, \qquad H_1' : \mu_R > \mu_P,$$
$$K_0' : \frac{\mu_E - \mu_P}{\mu_R - \mu_P} \leq 1 - f, \qquad K_1' : \frac{\mu_E - \mu_P}{\mu_R - \mu_P} > 1 - f,$$

by assuming that 1) margin Δ is unknown and 2) a fraction f is a known pre-specified constant such that $\Delta = f(\mu_R - \mu_P)$. However, from the viewpoint that a non-inferiority margin Δ should be specified in advance, the latter approach has obviously no clinical rational to support it. In this presentation, we argue this matter and examine the power, sample size calculations and the optimal allocation of the total sample size for testing hypothesis H_0 and K_0.

References

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