LETTER TO THE EDITOR


David C. Norris*

**Summary**

Simulation experiments conducted by Wages et al. formally utilize a variance reduction device that, when given a realistic interpretation, entails an unraveling of the very coherence concept which motivated those simulations.

**KEYWORDS:**

dose finding, oncology, coherence, ethics, dose individualization

To “stud[y] the principle of coherence in interval-based dose-finding methods,” Wages et al. carry out simulations which by their very construction negate the supposed importance of the peculiar coherence notion of Cheung which motivated them. Yet at the same time, these simulations contain the seeds for a newer precautionary coherence concept that addresses modern imperatives of precision medicine and patient-centeredness in dose finding.

To construct their single-trial simulation, Wages et al. introduce a “latent toxicity tolerance” $u_i \sim U[0, 1]$ that characterizes individual patients. Perhaps recognizing the dangerousness of this idea, however, the authors immediately dismiss $u_i$ as mere technical artifice: “Of course, in a real trial, it is impossible to observe a patient’s latent tolerance, but it is a useful tool in simulation.” Yet the very real I-PREDICT trial, where patients “received escalating doses of drugs to tolerance, while being monitored closely by their treating physicians,” belies such glib denial of the possibility of clinical titration.

I contend that $u_i$ is best understood as the cumulative distribution function of a titration-based concept: the individualized maximum tolerated dose (MTD$_i$). If Wages et al. allow that their $u_i$ admits this realistic interpretation, what becomes of the coherence principle they sought to study? Cheung’s problem, “where the objective is to estimate a targeted quantile of the unknown dose-toxicity curve,” now translates as seeking an arbitrarily selected quantile of the population distribution of MTD$_i$.

But treating all patients at ‘the’ MTD (thus defined) necessarily underdoses those with MTD$_i > MTD_{\text{the}}$, and overdoses those
with \( M_{TD_i} < M_{TD_{\text{the}}} \). These dosing errors entail a form of incoherence peculiar to dose-escalation designs which “escalate or de-escalate doses for future patients based on previous observations.” Such designs routinely enroll drug-naive subjects who leapfrog earlier cohorts into never-before-tried doses, placing new subjects at unnecessary risk of severe and fatal toxicities whilst consigning earlier-enrolled subjects to possibly subtherapeutic low doses. To treat enrolling persons not as ‘subjects’ but truly as patients—i.e., with therapeutic intent—demands a precautionary coherence under which drug-naive patients enroll at low quantiles of population \( M_{TD_i} \), whereas never-before-tried doses are attempted preferentially in those already demonstrating tolerance of an adjacent dose level.

This distinction between subjects and patients helps us to gauge what actual importance the studies by Wages et al attain, relative to the supposedly clinical motivations they adduce. All dose-escalation designs, whether of the CRM family, interval-based, or algorithmic, evaluate doses as their primary objects of interest, and for this purpose typically exploit subjects for the Bernoulli random variates they yield in dose-limiting toxicity (DLT) assessments. By contrast, the person-centered orientation of dose-titration designs aims to treat patients at individually optimal dosing. A prime motivation cited for interval-based designs is that they are “transparent in the sense that physicians can see all the possible dose-finding decisions before the trial starts.” Wages et al. endorse this motivation by pointing to similar benefits the newer dose transition pathways confer on CRM designs, and by identifying Cheung’s coherence as “a property that ensures clinical acceptability of the [dose-finding] method used.” But this kind of marketing badly misreads the core motivations of physician-investigators, whose truest values will be served not by neater repackaging of dose-centered designs, but by innovative advances toward practicable, patient-centered designs that support clinical dose titration.

Financial disclosure

This work received no external funding.

Conflict of interest

The author operates a scientific and statistical consultancy focused on precision-medicine methods such as those advanced in this Letter.

References


