LETTER TO THE EDITOR


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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.

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In order to “stud[y] the principle of coherence in interval-based dose-finding methods,” Wages et al.1 carry out simulations which by their very construction negate the supposed importance and relevance of the peculiar coherence notion of Cheung2 which motivated them. Yet at the same time, these simulations contain the seeds for a newer precautionary coherence3 concept that addresses modern imperatives of precision medicine and patient-centeredness in dose finding.

To support their single-trial simulation, Wages et al. introduce in Section 2.2 a “latent toxicity tolerance” $u_i \sim U[0, 1]$ that characterizes each individual patient. 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.”1 Yet the very real I-PREDICT trial, where patients “received escalating doses of drugs to tolerance, while being monitored closely by their treating physicians,”4 belies such glib denial of the possibility of clinical titration.

I contend that $u_i$ represents nothing other than the cumulative distribution function (CDF) of the individualized maximum tolerated dose which I have introduced elsewhere, denoted ‘MTD’.5 Indeed, the genealogy of $u_i$ leaves little doubt about this. Nearly 2 decades ago, O’Quigley et al. mooted a uniformly distributed $v_j$, as follows: “To each subject $j$ we can associate a numerical value $v_j$ indicating his/her toxicity tolerance threshold to the treatment under study.”6 A discussion that preceded this definition is worth quoting at length, since it illuminates the realism underlying the authors’ conception:
“A key assumption here is that, for the toxic side effects of interest, the hypothesis of the toxicity increasing with dose results from the fact that a subject who experiences a severe toxicity at a given dose level would have had a severe toxicity at every higher level. In the same way we are leaning on the implicit assumption that a subject tolerating a treatment at some given dose level would have tolerated the treatment at every lower level. This relatively uncontroversial and easily accepted, albeit debatable, restriction, turns out to be central to the main development.”

From their counterfactual language, it seems clear to me that O’Quigley et al. regarded $v_j$ as a real, durable property belonging to individual patient $j$, and defining $j$’s responses to various doses of the drug.

This realism grows even more vivid in Paoletti & Kramar with the introduction of a quantity $s_j$ that, unlike the dimensionless $u_i$ or $v_j$, is denominated in dose units:

“Let $S$ be a random variable that denotes the lowest dose at which a subject has a DLT. Given value $s_j$ for patient $j$ and supposing an increasing dose-toxicity relation, the probability of toxicity at any level is either zero or one.”

Paoletti & Kramar proceed to introduce the CDF of $S$, and remark on its connection with “what we are used to doing when we computationally simulate the response of a patient at a given dose level.” Yet as far as real patients are concerned, Paoletti & Kramar allow themselves only to note in passing that “$S$ is not far from a latent variable,” and neglect entirely the patient-centered interpretation of $s_j$ as an individualized ‘MTD.$j$’.

In the context of early-phase oncology dose-finding studies pursued with therapeutic intent, our interpretation of these various subscripted quantities establishes the very foundation for all meaningful discussion of coherence. Cheung’s formulation of coherence begins “[f]rom an ethical and practical viewpoint,” and depends vitally upon his appeal to our instinctive sense of what is “counter-intuitive.” Ethical, practical and intuitive considerations necessarily implicate meaning and interpretation. What becomes of Cheung’s coherence, reinterpreted in light of a realistic MTD.$i$ conception?

Most remarkably, we see that the very context which Cheung sets out for his discussion is itself intrinsically incoherent. Cheung’s context, “where the objective is to estimate a targeted quantile of the unknown dose-toxicity curve,” translates as seeking an arbitrarily selected quantile of the population distribution of MTD.$i$. From an ethical, practical and intuitive perspective that acknowledges the real individuals in that population, we may see that treating all patients at ‘the’ MTD (thus defined) necessarily underdoses those for whom MTD.$i$ > MTD.the and overdoses those for whom MTD.$i$ < MTD.the. (In presumptively identifying MTD.$i$ with individually optimal dosing, I adopt a heuristic of long standing which in the setting of severe oncologic disease and curative intent enjoys even some degree of formal justification. These underdosing and overdosing errors expose an in-built incoherence in dose-escalation designs that “escalate or de-escalate doses for future patients based on previous observations.” Such designs routinely enroll new subjects who leapfrog earlier cohorts into never-before-tried doses, placing
these new subjects at unnecessary risk of severe and fatal toxicities, while leaving earlier-enrolled subjects to languish at possibly subtherapeutic low doses.\textsuperscript{12} To treat enrolling persons not as ‘subjects’ but truly as patients—i.e., with therapeutic intent—demands a \textit{precautionary coherence}\textsuperscript{3} under which drug-naive patients enroll at low quantiles of population MTD\textsubscript{i}, whereas never-before-tried doses are attempted preferentially in those who have already demonstrated tolerance of an adjacent, lower dose level.

It is in this distinction between \textit{subjects} and \textit{patients} that we should seek a broader perspective on the criticism Wages et al.\textsuperscript{1} advance against interval-based dose finding. All dose-escalation designs, whether of the CRM family, interval-based, or algorithmic, evaluate \textit{doses} as their primary objects of interest, and for this purpose typically exploit \textit{subjects} for the Bernoulli random variates which they yield in binary DLT assessments. By contrast, the person-centered orientation of dose-titration designs aims to treat \textit{patients} at individually optimal dosing. A primary 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.”\textsuperscript{13} Wages et al. appear to endorse this motivation by pointing to a similar benefit that the newer dose transition pathways\textsuperscript{14} confer on CRM designs, and indeed by identifying Cheung’s coherence as “a property that ensures clinical acceptability of the [dose-finding] method used.”\textsuperscript{1} But this kind of marketing badly misunderstands the core motivations of physician-investigators, whose highest 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. Thus Wages et al.\textsuperscript{1} develop their argument entirely within a dose-centered universe—under dose-centered presumptions, according to dose-centered principles and, most absurdly, \textit{dose-centered ethics}. Ironically, this is all done in a problem context ostensibly driven by efforts at outreach to clinician-collaborators, to whom such principles and ethics are necessarily and forever foreign.

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

\textbf{References}


