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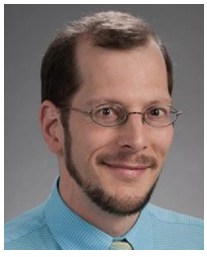

David C. Norris

One-size-fits-all dosing in oncology wastes money, innovation and lives

Executive summary

Failure to individualize drug dosing may waste 50% of the value of pharmaceutical innovation coming off the bench, driving the unacceptable failure rates of drug development programs and unsustainable drug costs. An immense opportunity is thus presented to investors in pharmaceutical innovation who are willing to develop and field innovative Phase 1 trial methodologies that solve this problem. The principle of Dose Titration Algorithm Tuning (DTAT) offers a reasoned strategy for accomplishing this.

The cost of 1-size-fits-all dosing

In oncology drug development, it has become a commonplace to cite *inadequate dose selection* as an important cause of program failure, and thus of the unsustainable cost of drug development generally [1]. These complaints usually focus on technical inefficiencies in the 3 + 3 and similar 'algorithmic' dose finding methods, relative to newer 'model-based' methods as employed in CRM, EWOC and MCP-Mod designs. Yet however much these latter methods may improve *formally* upon the 3 + 3 design, they do nothing to right its fundamental error.

All these designs chase the mirage of 'the' maximum tolerated dose ('the' MTD) of the investigational drug, as if there could possibly be one single right dose for everyone. It is a matter of simple common sense, of course, that each patient has his or her own *individual* MTD—or MTD_i if you will. And in the face of such common sense, it should seem grossly unethical to define 'the' MTD in terms of some target whole-cohort frequency of dose-limiting toxicities (DLTs), and to seek to achieve this DLT rate in Phase 1 study cohorts. Nevertheless, this practice persists. Worse, this pattern of dose-finding activity gets carried forward unthinkingly into oncology *practice*, where one-size-fits-all dosing remains pervasive despite the steady accumulation of evidence dating back two decades [2] demonstrating that hematologic and other toxicities augur better outcomes from chemotherapy—and now from targeted therapies [3] as well. (For a fuller bibliography on this point, with several dozen citations, please see https://www.zotero.org/groups/1150255/the_mtd_kills.)

From the perspective of patients, this practice exacts one of two possible costs. Except for the rare few who happen to have an MDT_i exactly equal to 'the' MTD (or 'the' dose on the label of a marketed drug), and who therefore get treated at their optimal dose, everyone else either gets *undertreated* (MDT_i > 'the' MTD) or experiences a DLT (MDT_i < 'the' MTD) and *discontinues* the drug. Thus, under one-size-fits-all dosing, nearly everyone derives either suboptimal or zero benefit from the drug. (To explore these principles interactively, please visit this online application: https://precision-methodologies.shinyapps.io/thecost/.)

In a recent bioRxiv preprint [4], I have situated these costs within a population-level pharmacoeconomic context, demonstrating plausibly—and with a rigorous sensitivity analysis—that *failure to individualize dosing may waste 50% or more of the potential value of pharmaceutical innovation.* The essential story is contained in Fig. 1, which shows that the more patients' MTD_i's vary across

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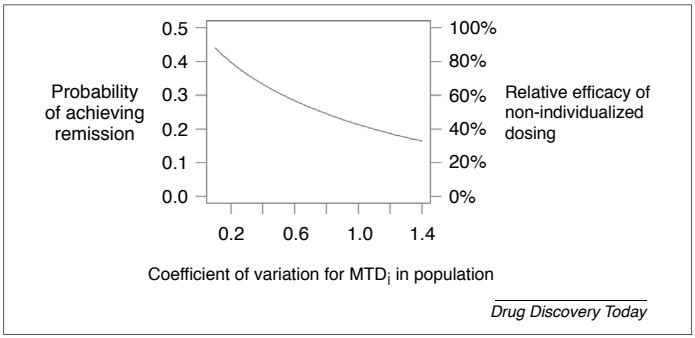

FIGURE 1

Population-level efficiency of one-size-fits-all dosing, relative to individualized dosing.

the population, the less efficient (and more untenable) one-size-fits-all dosing becomes. Recapturing the wasted value depicted in Fig. 1 creates a powerful financial incentive for pharmaceutical firms and the CROs that serve them, to design and implement Phase 1 studies capable of supporting *dose individualization*.

The DTAT principle

Dose Titration Algorithm Tuning (DTAT) [5] makes dose individualization possible by directly attacking two fallacious abstractions that have mired drug development in its one-size-fits-all mindset. First, DTAT abandons the conception of 'a' dose-limiting toxicity ('a' DLT) as some discrete, unitary event occurring with a catastrophic unpredictability, the way a glass rod fractures abruptly under strain. Rather, DTAT appreciates drug adverse effects as graded, continuous and—to some extent, at least—*predictable* phenomena subject to rational control. Under this more realistic notion of toxicity, *titration* becomes conceivable; and the fallacious abstraction of 'the' MTD yields to a *dose titration algorithm* (DTA) with its associated *tuning parameters*.

DTAT goes further, however, than merely rejecting these two problematic abstractions. DTAT commits to a learn-as-you-go concept of pharmaceutical development that departs radically from the received view of a rigorously staged sequence of tightly constrained estimation and hypothesis-testing activities. To be sure, developments such as accelerated approvals and other expedited programs represent an *implicit* acknowledgement of fundamental flaws in this received view. But DTAT rejects this view explicitly, on principle, *as a methodologic tenet*. The 'DTAT principle' conceives dose individualization as a continuous *learning task* that recursively adjusts a DTA's tuning parameters, gradually improving its performance. The traditional scoping of 'dose finding' to a single phase is thus seen to be arbitrary and unnecessary. (A concrete illustration and fuller details are provided in the DTAT paper itself [5], its code supplement, and a lay explainer provided on the GrowKudos platform: https://www.growkudos.com/publications/10.12688%25252Ff1000research.10624.2/reader.)

Even such hallowed notions as 'the dose' on 'the label' crumble in the face of dose individualization. Apparently, in place of 'the dose' we may expect to find instead 'the URL' linking to the most up-to-date DTA, distributed as web application—or, better yet, integrated into electronic health record systems [6].

Demands of implementing a DTAT study

To paraphrase Stephen Senn: *Just about anybody can design and implement a 3 + 3 dose escalation study—and frequently does.* This cannot be said of the newer dose-finding designs, but only because of their added *technical* complexities. As already noted, none of these 'new' designs departs *conceptually* from the fallacy of targeting whole-cohort frequencies of dose-limiting toxicities (DLTs), in pursuit of the mirage of *a single recommended dose*.

To make this departure, as DTAT does, will demand a coordinated effort drawing on several disciplines. On a purely scientific level, the design of a DTAT study will require intensive collaborations between biostatistics and pharmacometrics functions, of a kind long thought to be as problematic as they are desirable [7].

Beyond the challenges of managing collaboration across historically separate functions within pharma, DTAT also presents *novelty*—and therefore risks—in the regulatory arena. Early engagement and regular consultation with regulatory authorities may prove nearly as important to successful design and fielding of a DTAT trial as will effective biostatistics-pharmacometrics collaboration. Such engagements must be expertly managed on both institutional and personal levels. Notwithstanding bitter disappointments related by others, it has been my own impression that some forward-thinking regulators are acutely aware of harms done by poor dose selection, and are hungry for methodological advances in this area.

Developing DTAT to its full potential, as an industry-leading capability, will require a pharmaceutical firm or CRO to invest in specialized expertise and capabilities in simulation and high-performance computing. However, as I demonstrate in the Epilogue to my pharmacoeconomic treatment of DTAT [4], even relatively modest steps toward dose individualization may recapture substantial value relative to one-size-fits-all dosing. Thus, a mature DTAT program need not be in place to achieve early gains. A DTAT program can grow organically, and develop incrementally.

In full bloom, a DTAT program may look like nothing less than a 'world city', drawing on a cosmopolitan variety of advanced pharmaceutical development capabilities and practices. One particularly exciting opportunity is the potential—anticipated in DTAT from the outset—for ''bringing into view *objectively* the important matter of patients' heterogeneity with respect to values and goals of care" [5]. Achieving such humanistic aims in early-phase oncology development will require essential contributions from the fields of Psychometrics, Medical Decision-Making, and other human and behavioral sciences. Most rewarding, perhaps, will be the rich opportunities to engage *patients and their advocates* in the design and fielding of a new generation of methodologically enterprising and ethically enlightened early-phase trials.

References

1 Sacks, L.V. *et al.* (2014) Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000–2012. *JAMA* 311, 378–384
2 Saarto, T. *et al.* (1997) Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. *Br. J. Cancer* 75, 301–305
3 Osorio, J.C. *et al.* (2017) Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann. Oncol.* 28, 583–589
4 Norris, D.C. (2017) Costing 'the' MTD. *bioRxiv* http://dx.doi.org/10.1101/150821 http://www.biorxiv.org

5 Norris, D.C. (2017) Dose Titration Algorithm Tuning (DTAT) should supersede 'the' Maximum Tolerated Dose (MTD) in oncology dose-finding trials. *F1000Research* http://dx.doi.org/10.12688/f1000research.10624.3 https://f1000research.com
6 Neely, M. (2017) Scalpels not hammers: the way forward for precision drug prescription. *Clin. Pharmacol. Ther.* 101, 368–372
7 Sheiner, L.B. (1991) The intellectual health of clinical drug evaluation. *Clin. Pharmacol. Ther.* 50, 4–9

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