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The slow – but desperately needed – evolution of oncology clinical development designs

Oncology trials now make up more than one-third of today's research pipeline, but conventional oncology development programs often are inefficient and have high failure rates. Of the oncology agents that enter Phase I trials, only about 3% eventually receive U.S. Food and Drug Administration (FDA) approval.[1]

We can do better. The application of appropriate adaptive designs at the early stages of development can not only accelerate timelines and reduce costs, but also can help focus development on the most promising agents at the right doses in the right indications for the right patients.

Adaptive designs potentially allow a trial to answer multiple questions at once, leveraging accumulating data so early findings can inform decisions in a flexible process. In contrast, traditional designs answer only one narrow scientific question at a time on a rigid sequential path in which answers to pivotal research

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questions are often obtained only at the end of the trial.

Our experience in submitting protocols with adaptive designs in early stage oncology trials to U.S. and European regulators is that they not only accept these designs – they actively encourage them.

Given that the methods are more efficient, well established and that regulators encourage their use – both through published guidance and in practice – why has adoption not occurred more quickly? To examine the question, let's explore a specific example.

DEFINING THE MAXIMUM TOLERATED DOSE (MTD)

Defining an accurate dose in early-phase oncology clinical trials is a common challenge. The MTD is estimated to be correct in only about 40% of trials,[2] which may result in patients in subsequent trials being treated at subtherapeutic doses or doses that are too toxic. Selection of the wrong dose can not only disrupt the outcomes of all subsequent phases, it can, without a correction, ultimately lead to the development program's failure.

Most trials still identify MTD using the 3+3 design, a rule-based design that offers simplicity, convenience and familiarity. However, 3+3 has significant limitations. It relies on fixed cohort sizes, ignoring uncertainties, to define an MTD based only on data from the last dose. It also offers no ability to re-escalate or respond when late toxicities emerge. Several improved rule-based dose escalation designs have gained popularity in recent years, including the modified toxicity probability interval (mTPI) design and Bayesian optimal interval (BOIN) design.

The continual reassessment model (CRM), an adaptive Bayesian model-based approach introduced in 1990, efficiently evaluates more doses – using all the data it collects – to estimate the MTD more precisely and with more confidence compared to 3+3 and other rule-based designs. The difference in accuracy becomes more obvious as more dose levels are tested. As a result, the CRM provides an increased chance of treating study patients around the MTD and a decreased chance of exposing patients dosed at levels greater than MTD. Several variants of the CRM have been developed, including the Neuenschwander, et. al., NCRM design with overdose control, which is the most-commonly used one (also referred to as Bayesian Logistic Regression Model [BLRM]).

Even though the CRM has been shown to be more accurate in targeting the MTD than the 3+3 design, uptake has been slow. Lack of familiarity with the model and aversion to perceived risk has deterred adoption. But, in fact, many of the barriers impeding early adoption of the CRM have now been overcome. The following chart details common misconceptions that continue to linger.

THIRTY YEARS OF CRM IN PRACTICE: EARLY BARRIERS TO ADOPTION HAVE NOW BEEN ADDRESSED

Part of the beauty of the CRM design is that simulations can compare the performance of the CRM design to the 3+3 and other designs. In our experiences, simulations typically inspire confidence in the CRM design, and then, in turn, the CRM design in practice inspires adoption. In subsequent trials, the CRM often is selected from the start as the go-to dose escalation design.

In our experience, the key to adopting innovative designs is simple: try them. Once you have made a foray into these new ways of working, traditional methods may strike you as inflexible, slow and unclear compared to the flexibility and efficiency inherent in adaptive designs.

[1] *Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2019;20(2):273-286.*

[2] *North B, Kocher HM, Sasieni P. A new pragmatic design for dose escalation in Phase 1 clinical trials using an adaptive continual reassessment method. BMC Cancer. 2019;19(1):632.*

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