

## EDITORIAL

# Predicting Low Trial Accrual Mathematically: Is That the Right Emphasis?

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The paper by Bennette et al. (1), creating a mathematical predictive algorithm for low accrual to National Cancer Institute cooperative group trials, is the first of its type to my knowledge. As such, it is well-crafted, important, mathematically sound, and cautious, given the authors' correct preference to allow validation before crying "Victory!" This team extracted data from 787 phase II/III trials, launched between 2000 and 2011, to identify parameters that predict low accrual (defined as less than 50% of target). Their candidate predictors were drawn from an extensive literature review and interviews with clinical trial experts, with stepwise regression defining their final list.

The candidate list makes pretty good sense, and intuitively one might have predicted that low incidence of the target tumor type, number of competing trials, absence of metastatic disease, and focus on established agents were likely to be contributors to low accrual. Thus this passes the common sense "sniff test." It is possible that other factors dropped out simply because of a numbers issue, with nonsignificant *P* values that reflected the numbers of trials analyzed or the low proportion of patients with the specific parameters rather than an absolute lack of statistical significance. I was a little surprised that the authors didn't incorporate specific patient-based factors, such as age, ethnicity, and socio-economic status, but they reported that their selection of factors reflected the experience and beliefs of their interviewed experts and the literature that they reviewed. Presumably these specific factors didn't appear or might not have been measurable via their trial design. That said, a potential nonrandom variable that was not considered was the issue of time to lift-off, the extraordinarily long gestation period for many trials, with its downstream implications (2). Their final list of important factors seems very reasonable, and the implications for future trial design are obvious and should be considered carefully.

Given that this is a well-conceived and executed body of work, why would I question whether it is a step in the wrong direction? Clearly we do need a mechanism to avoid the profligate

waste associated with the design, implementation, regulation, and oversight of incomplete trials, and this mathematical predictive approach should certainly help to achieve that laudable goal if implemented by the cooperative groups.

However, the real issue is still the lack of patients involved in cancer trials, irrespective of whether they are conducted by cooperative groups, private or single-institution entities, or the pharmaceutical industry. Different aspects of the problem have been addressed as part of our national angst about the paucity of patients, usually estimated to be less than 10%, who actually are involved in clinical trials (3–6). Thus, in addition to the predictors of low accrual that relate to specifics of design (1), there are barriers to enrollment, such as unavailability of appropriate protocols (4), performance status and comorbidities (4,5), insurance and fiscal issues (4), disparities of cancer care (4), and distance from cancer center (4,5). The administrivia associated with trial initiation and oversight will frequently contribute to delays that may make the trials uninteresting or less relevant by the time they are opened (6).

It seems to me that we need to focus on a much more creative strategy than merely trying to avoid the initiation of trials with risk factors that portend failure to complete. It is well documented that patients on clinical trials have better outcomes than those who do not participate. Nonetheless, as oncologists who wish the best for our patients, we should strive to improve trial enrollment, giving the associated potential for improved results. Whether the basis is incidental, because of case selection bias, or reflects the support available to trial patients has not been determined, but the fact remains that outcomes are better.

However, it isn't that easy. As noted above, the health care system is burdened by inequities and heterogeneity, variable levels of access (both geographical and fiscal), and lack of time and resources to allow the average practice oncologist access to cancer trials, and the health insurance and payment system frequently disincentivizes participation in trials by patients and their

physicians. What I find to be most puzzling is the frequent willingness of the health insurance industry to support the use of agents that are known to be unlikely to work in first-line or salvage treatment, such as reimbursement for multiple iterations of fluoropyrimidine therapy in resistant gastro-intestinal cancers, while being unwilling to financially support hypothesis-driven cancer trials based on strong preclinical models.

In the broad context of health care delivery, there has been a dramatic shift from volume-driven to value-driven constructs (7), and this movement has found its way into oncology, with the genesis of programs to reduce profligate waste (8,9) and structured attempts to place mathematical algorithms into the definition of value (10,11). It is time to apply these concepts to trial design and to conceive studies that focus on real value with substantial increments in outcome, rather than focusing solely on P values, Forest plots, and waterfall plots as (false?) measures of progress.

There are now in play some bold experiments designed to overcome some of the problems above, integrating improved access, fiscal support for the conduct of cancer trials, and extending trial availability irrespective of insurance status or geographical/fiscal isolation. For example, the Levine Cancer Institute, North Carolina and South Carolina, has developed a 25-site integrated cancer institute under the control of a single institutional review board and data center, with evidence-based electronic cancer management pathways that incorporate best-practice clinical paradigms, open cancer clinical and translational trials and the use of palliative and supportive medicine, computerized applications that allow daily electronic patient self-reporting of toxicity, a system-wide biorepository that supports molecular prognostication, and an extensive patient navigation system. In its first years of function, this approach has quadrupled accrual to investigator-initiated and early-phase cancer trials. Memorial Sloan Kettering Cancer Institute, Fox Chase Cancer Center, and MD Anderson Cancer Institute have evolved networks that improve access to institutional standard treatment paradigms and offer selected clinical and translational trials. Integral to all these efforts is the detailed and serious attention focused on establishment and maintenance of

high-quality, symmetrical, system-wide standards, thus facilitating access without loss of rigor.

However, all these programs face serious challenges from a top-heavy regulatory environment that is not sufficiently nimble to recognize, incorporate, and set specific standards to allow these new models to flourish as single-entity research engines. If our federal authorities wish to match rhetoric to outcome, they will have to set new standards and to develop a consensus approach to the change from Ivory Tower to academic community-based research engines. Hopefully at that time we will not have to focus only on avoiding risk factors for poor accrual because the climate for patient access to clinical cancer research will have changed.

## References

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