

# The Ordinary Miracle of Cancer Clinical Trials

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Isn't it remarkable that so many clinical trials come to fruition? When one considers all the events, or lack of events, that can induce a newly conceived treatment study to abort during its multiyear preactivation gestation, and all the obstacles that a toddling activated study can stumble over and be unable to get up again—not to mention the endless, mindless bureaucratic tedium that every study team must endure to avoid being labeled as deviant protocol guardians by external auditors—it is a genuine marvel that so many bright ideas reach maturity, making their way into the world of journals and conferences and influencing clinical practice. Each successfully activated and fully accrued cancer clinical trial is not just a biomedical research ordinary miracle (with apologies to singer Sarah McLachlan), it is also a testament to the desperate needs of patients, the dedicated stubbornness of resourceful oncologists, and the enormous financial rewards possible for corporations who bring blockbusters like rituximab or trastuzumab to market—as well as the ability of like-minded human beings to cooperate and accomplish great things, even within a cumbersome and confusing system.

Although the brutal development gauntlet that clinical trials undergo could be considered a necessary selection process akin to “nature red in tooth and claw,” ensuring survival of only the fittest studies, it may be just as likely that protocols that successfully endure this merciless winnowing are among those attracting the least attention from predators—the least objectionable, least controversial, and least innovative study designs, destined to yield the least exciting results. The tortuous, twisting trail between an investigator's therapeutic brainstorm and the nervous excitement of a podium presentation at the annual meeting of the American Society of Clinical Oncology is arduous enough for straightforward, single-institution studies that involve only one study sponsor.<sup>1</sup> When the proposed study is instead large and complex—and especially when it can only realistically be conducted through one or several of the National Cancer Institute (NCI) –funded cooperative groups—the glorious, long-awaited day of trial activation can begin to seem like a meeting of Procrastinators Anonymous: perpetually postponed.

For the last several years, David Dilts (who holds a PhD in management science) and Alan Sandler (an oncologist), codirectors of Vanderbilt University's Center for Management Research in Healthcare (Nashville, TN), have been working to develop a more detailed understanding of the processes currently required to conduct a clinical trial for patients with cancer. Dilts et al<sup>1</sup> first looked at the Vanderbilt-Ingram Cancer Center and its affiliates to understand single-institution activation processes more clearly, and then began their study of NCI-funded cooperative groups by assessing the Cancer and Leukemia Group B (CALGB).<sup>2</sup> Disturbingly, but not surprisingly,

they found that the trials that opened in CALGB between 2002 and 2005 required a median of 784 days (range, 295 to 1248 days) from initial conception to activation.<sup>2</sup> The CALGB preactivation sequence was noted to involve 370 distinct processes—317 work steps, 42 decision points, and 29 processing loops—of which 63% were beyond the direct control of the principal investigator (PI) and the cooperative group. A follow-up study of the Eastern Cooperative Oncology Group (ECOG)<sup>3</sup> confirmed that CALGB is not unique; in fact, slightly greater complexity is involved in opening a study in ECOG: 481 processes, which include 420 working steps, 61 major decision points, 26 processing loops, and 13 stopping points. In ECOG, preactivation processes consume 54% of the entire time required to conduct a phase III trial. Screening and enrolling patients, administering protocol therapy, and answering data queries are, apparently, the easy parts.

At a recent semi-annual meeting of ECOG, the cooperative group's leaders arranged for the protocol development process diagram outlined by Dilts and Sandler's team to be printed on large sheets and posted along the wall of a hotel ballroom. Stretching more than 20 feet long, and nearly 4 feet high despite a minuscule font—perhaps aspiring to be the type of environmental installation art that Christo and Jeanne-Claude create—this diagram served as both conversation piece and sobering reminder of the continuing challenges that cooperative groups face. We now know that even when everything proceeds as smoothly as possible—when an experienced investigator has tried to anticipate every imaginable hitch, when it is obvious to all informed observers that the study is asking an important question, when contract lawyers and scientific review committees are feeling particularly genial—still, at least 10 months and nearly 500 individual processes are required to turn a concept into a legitimate clinical experiment. This might satisfy some unimaginative functionaries, but for those of us who care for patients directly, as for our many administrative colleagues who have not forgotten why clinical trials are done—and, most importantly, for suffering patients themselves—these time scales are unacceptable.

I am a member of the ECOG Leukemia Committee, and I attended the meeting where the convoluted process diagram was on display. When I walked past the diagram and realized just what it was, it stopped me cold; reflection on the implications caused a surprisingly emotional reaction. Somewhere along the line, our collective research enterprise seems to have lost a critical sense of urgency, confusing the conduct of oncology clinical trials with less-essential processes, such as the update of an automobile design, when last year's model was just fine for moving passengers from point A to point B in safety and comfort. But there is no comparison: people with cancer are dying of their diseases by the thousands every day (approximately 1,500 daily in

the United States alone), and for many patients the available treatments do not just lack the latest features and styling; they do not run at all.

The September 15, 2008, issue of *Newsweek* included a gloomy feature article, “We Fought Cancer...And Cancer Won.”<sup>4</sup> The writer argued that the Lance Armstrongs of the world are the exception rather than the rule, and that for a variety of reasons, including the NCI’s penchant for funding safe science, our society has been soundly beaten in the famous war on cancer declared by Richard Nixon in 1971. Personally, I am more optimistic, and feel that this war is not necessarily lost; the enemies just turned out to be cleverer and better entrenched than was anticipated 40 years ago, so too many battles have gone in their favor. Still, *Newsweek*-style critiques raise uncomfortable questions: surely the unwieldy process to activate and conduct clinical trials has made our cancer research enterprise less productive and efficient than it might otherwise have been.<sup>5</sup> Adding credence to that idea, I have lost count of the number of colleagues who have mentioned what sounded to me like a creative treatment idea, but followed that with a defeated sigh, stating, “It’s something I would study formally, if it weren’t so painful to open up a trial...I only have so much energy.” Although some such comments are likely just kvetching, if even a few of the grumbles are cries of genuinely deferred aspiration, then much may already have been lost.

In this issue of *Journal of Clinical Oncology*, Dilts et al<sup>6</sup> turn their attention to a set of processes they treated as black boxes in their previous reports on CALGB and ECOG, but which are in fact processes with an iPod-like internal complexity that rivals that of the preactivation steps. The intricate organizations involved are the nine offices and branches of the NCI’s Cancer Therapy Evaluation Program (CTEP), tasked with supporting and coordinating more than 1,000 clinical trials at any given time,<sup>7</sup> and the NCI Central Institutional Review Board (CIRB), which was founded in 2001 with a goal of reducing the administrative burden on local IRBs.

The results of the new process analysis echo the earlier findings for cooperative groups: from the time of phase III trial concept submission to CTEP until protocol activation, at least 296 distinct CTEP-/CIRB-related processes are required, including 239 working steps, 52 major decision points, 20 processing loops, and 11 stopping points. Because most clinical trials require revision and resubmission and then re-enter the processing queue at an earlier stage than where they ran into problems, the number of steps is, in reality, much greater. In fact, during the time period reviewed by the investigators, not one of the 167 trials submitted to CIRB was approved on the first submission. This startlingly protracted slump raises a number of questions, such as how the clarity of instructions to investigators about CIRB expectations might be improved to diminish wasted time and effort. Furthermore, although CIRB review may indeed streamline local protocol evaluation, it does not exempt a protocol from institutional IRB scrutiny. In practice, local IRBs routinely delay CIRB-approved protocols because of concerns about institution-specific consent forms or other idiosyncrasies.

A key finding of the new CTEP/CIRB analysis is that no one particular process or agency is to blame for the lengthy protocol activation process; rather, the sum is much greater than the parts, and it is the systemic complexity and issues of coordination or synchronization that result in extensive delays. It is not that many of these steps

are unnecessary (although some likely are—not everyone who desires input into a process deserves it, because only some add enough value to justify the delays they cause). Instead, the problem is that the important components of the long processing chain are poorly linked.

Like the duckbill platypus, the contemporary clinical trial development process is an organism that no rational person would have designed a priori. Its awkward present form evolved because of decades of tinkering with administrative structures at NCI and the National Institutes of Health, reactions to specific events or perceived risks, and changing needs of various governmental and nongovernmental stakeholders. Just as one alteration in platypus anatomy would inevitably affect other parts of the animal, these protocol process changes can upset trial development homeostasis, creating endless loops or Catch-22s that then require special intervention to resolve. Committee A may need the approval of Committee B to move a protocol forward to Committee C, but Committee B may be silent because it is waiting on something from Committee A—a Dilbertian impasse. For example, some protocols have been delayed because study sponsors are reluctant to sign contracts until IRBs approve the protocol, yet some IRBs have been hesitant to approve protocols until contract language is agreed. Administrative streamlining can resolve these dilemmas (eg, by limiting the number of persons or committees permitted to demand review of only a finalized version of the protocol that everyone else has already seen and approved; only one person can be the anchorman in a tug-of-war). But when these roadblocks are either opaque to the PI or out of the PI’s control, they can impede study activation considerably. When dozens of committees, processes, and stakeholders are involved, the potential for an impasse or endless loop greatly increases.

The current clinical trial process is like a sick patient—one who is still alive, but has a dramatically reduced performance status—and Dilts et al,<sup>6</sup> along with others of like mind, are performing a series of imaging studies to diagnose where the trouble originates. As with many sick patients, the past medical history is complex, so there is more than one ailment involving several organ systems. While there are common themes, each problem requires unique evaluation and treatment.

The best consultants do not stop with merely identifying a set of problems; they also propose some solutions. What sorts of remedies might get this ailing patient back to health? First, technology can help. Real-time electronic tracking of protocol steps, now that they have been more clearly outlined by the Vanderbilt group, will enable PIs and other stakeholders to know exactly where a trial is in the preactivation process. This knowledge will allow investigators and administrators to diagnose problems more quickly, anticipate approaching obstacles, and expedite advancement of protocols through the processing queue. Electronic tracking has an encouraging precedent: it has dramatically reduced manuscript submission-to-acceptance time at many medical journals. Second, more processes could follow the model of the US Food and Drug Administration’s investigational new drug application process. Once a trial protocol has been acknowledged as received by the US Food and Drug Administration’s investigational new drug office, if no specific objections are raised within a certain time period, the protocol is considered approved by default and can move on. Finally, expectations for each of the many hundreds of processes need to be made explicit, so that Catch-22s become obvious

and can be resolved by senior administrators, and redundant or low-value reviews can be eliminated.

John Godfrey Saxe, a 19th-century Vermont poet best known for the metaphor of the blind men and the elephant, once quipped, “Laws, like sausages, cease to inspire respect in proportion as we know how they are made”<sup>8</sup> (the quote is often attributed to German Chancellor Otto von Bismarck, who paraphrased it). Yet Upton Sinclair’s famous muckraking novel *The Jungle* exposed the horrors of sausage-making, which led to the Federal Meat Inspection Amendments of 1906 and resulted in removal of some of the nastier bits from processed meat (lawmaking has yet to undergo such bold reform). It is my hope that as light is shed into the darker corners of the clinical trial development process by the important work of Dilts, Sandler, and the Vanderbilt group, the revelations will prompt urgent action, with similar salutary effects on public health.

#### AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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