Early Warning: An Ailing Canary in the Mine

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Historically, numerous industries have used a variety of methods to obtain early warning signs of potential future problems. One of the most well known of these is the canary that miners would bring into the mine with them. The idea was that an ailing canary was an early warning signal of the invisible, but deadly, poisonous fumes. Only at their peril did miners ignore a sick or dead canary. Today, cancer research in the United States has been presented with such an early warning sign with respect to the future of clinical trials.

In this issue of Journal of Clinical Oncology, Wang-Gillam et al offer one such warning through their reporting of disturbing statistics about the differences between US and European lung cancer trials at academic medical centers with respect to time-to-opening and accrual for clinical trials. With phase II industry-sponsored oncology trials, the most homogeneous data set in Wang-Gillam et al, the median calendar time from submission of a proposal to the opening of a trial was more than twice as long in the United States as it was in Italy (239.5 days vs 112.5 days). As a management scientist who has studied the automobile industry for years, this called to my mind an unwelcome comparison. In the 1980s, the US automotive industry, referred to collectively as the Big Three, required 9.5 years to develop a new car versus the 4.5 years required by the Japanese auto industry. Japanese cars were of measurably higher quality and lower cost. Under this threat, the Big Three cut their average new car development time in half, increased their quality even higher, and generally maintained a low-cost position. What was the result of these differences? The US public, indeed the rest of the world, began first to try and then to prefer foreign cars.

It appears that pharmaceutical firms are following the same path with respect to clinical research. A recent study by Glickman et al found that approximately one third of industry-sponsored, phase III clinical trials (157 of 509) are being conducted solely outside the United States and that more than half of study sites (13,521 of 24,206) are located outside the United States. Although there are myriad reasons for this, time and cost are primary among them. Arguments for moving trials outside the United States could be tempered by showing that the longer time to opening of US-based trials results in research that is of demonstratively higher quality or that accrual rates were higher domestically compared with European results. Unfortunately, there is no measure of quality to compare trials, and as clearly shown in the article by Wang-Gillam et al, there is a significantly higher likelihood that a US trial will result in zero accruals than that its European counterpart will. These results are in line with other oncology research. Most recently, Durivage and Bridges reported about results of 2,685 industry and cooperative group-sponsored, therapeutic clinical trials at 14 US cancer centers and showed that 1,455 (54.2%) of these trials did not accrue a single patient.

The time it takes to open a trial and the likelihood of having zero accruals are related. In a forthcoming article by Cheng et al, their research on 5 years of clinical trials that were sponsored by the National Cancer Institute’s Cancer Therapy Evaluation Program showed a significant inverse relationship between the time to bring an idea from letter of intent or concept to trial activation and the final accrual performance of the trial.

Even with these gloomy findings, there are some bright spots. First, the National Cancer Institute’s Operational Efficiency Working Group report released in March set timelines that trials must achieve to be opened; otherwise, the development will automatically be stopped. Second, the Institute of Medicine released a report in April stressing the need for fully funding innovative and promising trials, enhancing collaboration among the various stakeholders, consolidating functions within the cooperative group system, and streamlining oversight. Such recommendations from both reports, if adopted, will make major strides in the much-needed re-engineering of the clinical trial system in the United States.

Despite these promising developments, however, there are still some significant barriers to address. First, some researchers appear to believe that these issues are merely a matter of money, and that, if funds for clinical research were significantly increased, the problems would resolve themselves. Although I agree that the per case reimbursements to many clinical trials, particularly those of cooperative groups, are well below treatment costs, the impact of lack of resources pales in comparison with that of lack of cooperation among the various stakeholders in the US clinical trials process. As demonstrated by Wang-Gillam et al, a major issue contributing to an extended approval time in the United States is regulatory approval, which required more than 7X longer in the United States than in Italy. The Big Three automakers fell into the same trap when they spent decades and billions of dollars attempting to improve internal systems, whereas the Japanese automakers spent the same time, but significantly less money, encouraging suppliers to become partners in the design process.

Second, although Wang-Gillam et al have done an excellent job of documenting the differences between the United States and Europe, theirs is not the first call to change the existing system of clinical
Causal Inference for Definitive Clinical End Points in a Randomized Clinical Trial With Intervening Nonrandomized Treatments

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Advancement of treatment for cancer patients requires evidence that administering a treatment will result in better clinical outcomes. This evidence allows one to make a causal inference—an intervention causes a change in an outcome. A randomized clinical trial (RCT) offers the best ability to make a causal inference concerning treatments. If the patients randomly assigned to the experimental treatment arm do better than the patients randomly assigned to the control arm, then we know (with a certain confidence that depends on the sample sizes) that the experimental treatment caused the better outcomes. When biostatisticians refer to causal inference, however, they are usually not referring to the straightforward case of comparing randomized treatment arms. Instead, they are referring to a comparison of interventions that were not randomized but with the aim of drawing the same inference as if there had been a randomization; this is the meaning we will use here. Examples of causal inference include drawing inferences about the effect of a treatment from epidemiologic/observational data, evaluating the effect of an intervention in an RCT in the presence of competing risks, and estimating the efficacy of an interven-

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