Collaboration Between Cooperative Groups and Industry

By Linda R. Bressler, PharmD, and Richard L. Schilsky, MD

The proper relationship between academic investigators and the pharmaceutical industry when conducting large, multicenter, prospective, randomized clinical trials is controversial and can be tense. The potentially conflicting goals of government-funded cooperative groups and pharmaceutical industry sponsors was the subject of a recent commentary in *Nature*[1] by Martine Piccart, current President of the European Organisation for Research and Treatment of Cancer and her colleagues. They expressed particular concern that important features of clinical trials—the design, the duration of patient follow-up, the conduct of any subset analysis, and the adverse event analysis and reporting—may be excessively influenced or controlled by an industry collaborator. They proposed a model for collaboration wherein the clinical trial database is maintained by the academic investigators until the trial end points are met. The data would not be disclosed to the industry collaborator without the approval of an independent data monitoring committee. Once the primary end points of the trial are met (eg, patient survival), the data can be provided to the industry sponsor for an application to regulatory authorities for the new indication. Dr. Piccart suggests that such collaboration is a ". . . win-win situation resulting in commercial registration of products, academic publications, and last but not least, hopefully better outcomes for patient treatments."

Linda R. Bressler, PharmD

The model proposed by these investigators has been the foundation of collaborations between the US cooperative groups and the pharmaceutical industry for many years, though it was not always in place. As recently as 12 years ago, it was uncommon for cooperative groups to work closely with industry in a clinical trial. Few pharmaceutical companies were interested in oncology products. Most of the new anticancer drugs in development were available to the cooperative groups through the National Cancer Institute (NCI). Much has changed in the past decade. Dozens of pharmaceutical and biotechnology companies now have cancer drugs in development and hundreds of novel agents are flooding industry drug-development pipelines. Of necessity, cooperative group investigators increasingly work directly with industry partners to obtain novel clinical compounds. Access to new agents coupled with chronic underfunding of the cooperative groups by NCI has led to the development of much closer relationships between the cooperative groups and the pharmaceutical industry. During the past decade, Cancer and Leukemia Group B (CALGB) studies alone have led to US Food and Drug Administration (FDA) approved indications for paclitaxel as adjuvant therapy for node-positive breast cancer, 5-azacytidine as treatment for myelodysplastic syndrome, and nelarabine as therapy for refractory T cell leukemia and lymphoma. In each case, CALGB was solely responsible for the design, conduct, and analysis of the clinical trial and the clinical trial database was provided to the drug sponsor after the trial was completed and the results were known. There are other examples of recent cooperative group trials that have led to new drug approvals or drug label expansion. More recently, CALGB has begun to work prospectively with many companies in the design and execution of clinical trials. At present, the CALGB holds investigational new drug applications for 20 compounds used in 28 clinical trial protocols in diseases as diverse as acute myeloid leukemia, colorectal cancer, and mesothelioma.

Richard L. Schilsky, MD

As Piccart et al point out, a major challenge whenever a cooperative group and a company collaborate is to align the goals of the organizations. Achieving both sets of goals sometimes creates tension because of the need to develop business relationships between organizations that differ substantially in their organization and resources. There are good reasons, however, to try to make the collaboration work as both sides potentially benefit greatly when it does.

The potential benefit to the cooperative group from the collaboration is clear—access to exciting new drugs, the potential to change medical practice by working with a sponsor that can actually deliver a drug to the market, and supplemental financial support. For the industry collaborator, cooperative groups provide access to an established network of high quality clinical trial sites, expertise in clinical trial design, input from the key opinion leaders who serve on cooperative group committees, and the ability to leverage public funding to extend the scope of the company's clinical development program. A particularly important benefit to industry is the scientific credibility of cooperative group studies, which are carefully reviewed and independently conducted without influence from the industry collaborator.

From our practical experience, developing these collaborations is not easy. The multiparty negotiations required to achieve the objectives of the cooperative groups and the sponsors, as well as the approval of the regulatory authorities, are often complex and protracted. They involve not only clinical investigators and statisticians, but regulatory managers, lawyers, and financial officers.

Optimally, the cooperative group poses a question that builds on previous research findings, clinical observations, and medical need, and develops a trial designed to answer the question. At what point should industry input be sought? In our view, this is best done early in the design phase to determine whether the company is in agreement with the question posed, as well as agreement with the trial design, and whether they will provide drug and will have interest in pursuing a regulatory submission if the trial meets its objectives. While it is important to learn early if an industry collaborator won't support an idea, it is also important that the cooperative group maintain their independent research direction. Too often, legal and regulatory staff in companies tend to view the cooperative group like a contract research organization that can be hired to carry out an industry-sponsored trial.

Tension can arise at many points. The company loses control of the clinical trial process and timelines for the start-up of cooperative group trials is often lengthy due, in part, to the multiple reviews (eg, NCI, central institutional review board [IRB], FDA) required before the trial is made available to sites to begin accrual.[2] It is not clear, however, that the overall time from conception to the completion of the trial is longer for studies conducted by cooperative groups than for those sponsored directly by industry, although data on this issue are sparse. The processes of IRB review and of contract development and budget negotiation for an industry-sponsored trial often take a considerable amount of time, especially at academic centers.[3] This has led some industry sponsors to focus less on academic centers when considering potential clinical trial sites and, increasingly, to conduct clinical trials outside the United States, where regulatory burdens are often less. However, perhaps because of the extensive initial review at the federal level, the local IRB process for cooperative group trials is often shorter, even at the academic centers.

The involvement of company attorneys at a point in trial development after scientific issues have been decided is a frequent cause of delay. Company medical and scientific officers may have approved the protocol and budget, only to have contract negotiations stall over issues related to intellectual property, publication rights, and data ownership.

Some steps in the process of trial start-up, however, may actually be shorter when industry collaborates with cooperative groups as compared with placing their own trials at multiple sites. The same contract negotiation that is undertaken by the group and the company would have to be done at dozens, maybe hundreds, of individual institutions in an industry-sponsored trial, potentially delaying the start of patient recruitment at many institutions, and ultimately prolonging the time to completion of the trial.

Participation in cooperative group trials with industry collaboration can also be beneficial from the perspective of the individual institution. For one thing, site reimbursement for such trials is often greater than for cooperative group studies that provide standard federal per case reimbursement rates. Centralized contract negotiation between industry and a cooperative group, rather than between industry and an individual institution, also saves the institution time and effort and prevents the company from selecting institutions on the basis of the ease with which their contract provisions are accepted. Subscription by the institution to the NCI central IRB may also expedite local IRB review.

The shared goal of all who participate in clinical cancer research is better patient outcomes. The cooperative group–industry collaboration represents a vitally important process in meeting this goal. When successful, our patients benefit from broader testing of new agents in more diverse patient populations, greater access to promising new agents, and confidence that cooperative group trials are independently designed and monitored and that the trial results will be completely and accurately reported to the medical community in a timely fashion.

Linda R. Bressler, PharmD, is Regulatory Affairs Director, and Richard L. Schilsky, MD, is Chairman at the Cancer and Leukemia Group B, Chicago, IL.

DOI: 10.1200/JOP.0834601

References

1. Piccart M, Goldhirsch A, Wood W, et al: Keeping faith with trial volunteers. Nature 446:137-138, 2007

2. Dilts DM, Sandler AB, Baker M, et al: Processes to activate phase II clinical trials in a cooperative oncology group: The case of the Cancer and Leukemia Group B. J Clin Oncol 24:4553-4557, 2006

3. Dilts DM, Sandler AB: Invisible barriers to clinical trials: The impact of structural, infrastructural, and procedural barriers to opening oncology clinical trials. J Clin Oncol 24:4545-4552, 2006