Challenges and Pitfalls for Clinical Research in the 21st Century

I started clinical pharmaceutical research in the 20th century and will finish my career in the 21st century. Straddling the momentous decades as I have, I find myself wondering, “What are the new challenges facing the physician who has decided on a career in this field, or the physician who just entered, as well as those ‘seasoned’ veterans thinking about staying in the field or exiting it altogether?”

The biggest new challenges I see facing the principal investigator (PI) are the following:

“Fair market value”—This term appears “fair” on the surface, but it can be very challenging. For example, if in the field of Alzheimer’s disease, the informed consent process requires one hour of the coordinator’s time and 30 minutes of the PI’s time, how can $75 be considered fair market value? Perhaps it is fair for a very simple “bronchitis in 30–45 year-olds” Phase III study of the safety/efficacy of a “10th generation” cephalosporin.

Serious adverse event (SAE) reporting—Typically, sponsors feel their budget more than covers the cost for completing the initial SAE form and the follow-up SAE form for obtaining and reviewing all the hospital records, and for completing the inevitable queries that come after the initial and subsequent SAE forms are completed and sent to the sponsor. Thus, the site should list the SAE form cost as a line item, and not place it in the “administrative overhead” section.

Collection of money due from sponsor—The latest craze, it seems, is to invoice sponsors for all study-related activities. In the “good old days,” the source of all payments was based on the electronic data captured on the case report forms (CRFs). This way, all data entered are paid for by sponsor. I estimate 40% of my income now must be invoiced, which can first be an invoice sent to the contract research organization (CRO), which then sends it to the sponsor, which then can have up to 60 days to authorize payment. It is not uncommon for sites (including mine) to have work done and data entered into the CRF, but not receive payment for more than six months. This is truly a challenge to the efficiency of, and motivation for doing, clinical research.

Revolving monitors—It was very nice in the olden days when a monitor would be at your site for one, two, or even more years evaluating charts,
CRFs, source documents, etc. Now, the turnover rate with outsourced monitors is becoming quite challenging. For example, I have a study that has been in progress for more than three years and we have not only had four different monitors, but they have come from three different companies. The first monitor came from the sponsor; then the sponsor opted to outsource to a larger CRO, which had some issues with properly training its monitors, and so the sponsor fired it; and now, a new CRO is handling the monitoring, and the jury is still out as to its ability to properly do the job.

_Inexperienced monitors_—In my field of mild cognitive impairment and Alzheimer’s disease, it takes a very experienced monitor to be capable of properly conducting the visits. For example, in this specialized field, often the patient is not capable or competent to understand the benefits, risks, or alternatives to a particular study, and a legally authorized representative (LAR) is then asked to act on the patient’s best interests or previously stated wishes (if known previously). Many times, the monitors are from a state where the laws of what constitutes the LAR might be different from those of my state, New Jersey. An educational process then must ensue from myself as PI, or from legal counsel, or from the institutional review board. This causes the loss of valuable time and costs my site money. If the sponsor simply used very experienced monitors in this field, all parties would be pleased.

**ECGs being outsourced to remote centers**—Although I agree central readings are important to keep all data uniform, I cannot agree with waiting sometimes several days for the central read to come back. If a certain Qtc level is exclusionary, I calculate this interval myself based on the ECG printed from the sponsor’s provided ECG machine. Not uncommonly, the central reader has a slightly different read, and the patient is excluded. Such cardiologists are often very hard to reach, and have little interest in discussing the discrepancies, but say, “It is up to the sponsor to decide if the reading is exclusionary.” Of course, the patient will be excluded, since it is always prudent to take the course of maximum conservatism; thus the challenge of the process falls yet again to the PI. Years ago, it was the local readers’ opinions that trumped all others, and in conjunction with the parameters reported by the ECG machine itself, the proper interpretation of ECG intervals can be best assured.

_Who gets the bill?_—The last is the best. I was just asked by a large sponsoring pharmaceutical company to have the insurance for patients in a particular study billed for study-related procedures, such as a CT or MRI of the head. Yes, I read it several times, and indeed the sponsor wants each patient’s insurance billed first and then, only if his or her insurance company denies it, will I as the PI need to invoice the sponsor for the service. Those of you who have not yet fallen off your chair either laughing and/or shaking your head in disbelief should now take a deep breath and simply believe what I just wrote. Yes, folks, sponsors might now be treading on very thin ice here. The educated and experienced readers in this field know quite well that any/all study-related procedures are always paid for by the sponsor and never, repeat never, should a subject’s insurance or the patient be billed for a study-related test or procedure. Of course, in the case of an emergency room visit, the patient or next of kin might not disclose or realize that the pharmaceutical company would cover the costs of a test or hospitalization if there was a reasonable chance the study drug or study subject’s participation in the study was related to the event (SAE or AE). I have notified the sponsor that this request is entirely unacceptable. It is not even challenging. It is just plain wrong.

In summary, the astute PI (be it a “true” PI or a “practically invisible” PI) will always be on the lookout for better ways to work with sponsors, vendors, and monitors. However, the PI and his/her staff cannot accept lower standards of reimbursements from the sponsors any more than the sponsor would accept anything less than high-quality data from each and every site. _APPI_

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