What Am I Missing Here?

Thought-Provoking Questions for the Clinical Research Industry

Norman M. Goldfarb

This paper briefly discusses 22 of the more puzzling practices; ones that appear, at least superficially, to be contrary to the spirit of the regulations or counter to our shared goal of a healthy, efficient, and productive industry.

Clinical research is a complex industry with many uncommon business practices. Many of these practices are driven by regulatory requirements, but the rationale behind others is mysterious, at least to the author. Perhaps they are artifacts from the days when every pharmaceutical street was paved with gold. This paper briefly discusses 22 of the more puzzling practices; ones that appear, at least superficially, to be contrary to the spirit of the regulations or counter to our shared goal of a healthy, efficient, and productive industry.

1

If we care so much about the welfare of the subjects, why don't we give them a voice in the process?

It's great that IRBs look out for the welfare of the subjects, but how often do they actually *talk* to the subjects? How is the IRB or sponsor supposed to know if there is a problem with coercion, cursory medical histories, or sloppy procedures? Why not make it a regulatory requirement that subjects provide confidential feedback to the IRB for every visit? What am I missing here?

2

Do we really need 600 different ways to define confidential information?

Every sponsor has a contract template and they are all different. Contract negotiations may delay the average study by two weeks. At $1.3 million a day in lost revenue while a new drug is in clinical development, we're talking serious money. Why can't we develop some industry-standard contract templates? Perhaps we can settle on only six different ways to define confidential information. What am I missing here?

3

You call this informed consent?

How do we know if a potential subject really understands the contents of the informed consent document? How many of these people have ever read a package insert in their entire lives? We split hairs between "free" and "at no charge" when we don't even know if potential subjects understand the difference between a virus and a vaccine. How many potential subjects just go through the motions because they trust their doctor? How many sponsors test their informed consent documents on focus groups to confirm that the message is getting across? How many sites give potential subjects comprehension quizzes before they sign on the dotted line? What am I missing here?

4

If the FDA wants us to enroll minorities, why aren't we doing anything about it?

Minorities comprise over a third of the U.S. population, but their enrollment in clinical trials averages only 8%. Most everyone agrees that we need more minority participation in clinical trials, but sponsors don't provide minority-oriented materials or push sites to enroll minorities. Very few sites have active minority outreach programs. What training or guidance is available to

sites for minority recruitment? What am I missing here?

5

Why don't we speak the same language for a change?

Physicians use CPT (Current Procedural Terminology) codes to specify the tests and procedures they perform on their patients. They use ICD-9 codes to specify medical conditions. Why not use these codes in research protocols so there is no confusion about what needs to be done and what procedures are non-standard? What am I missing here?

6

If a subject has a problem, who is she supposed to talk to?

Physicians can be intimidating and hard to find. Many subjects don't want to hurt the study coordinator's feelings or get them in trouble. It can be darn awkward. A situation has to get terribly serious before a subject contacts the authorities. So who can a troubled subject talk to? Large sites can appoint a subject advocate (ombudsman). Small sites could hire independent subject advocates if they existed. If we really care so much about the subjects' welfare, why doesn't an independent ombudsman organization exist? Why aren't they a regulatory requirement? What am I missing here?

7

If we're so smart, why can't we solve the problem of slow payments?

Sure, sponsors want to verify work before they pay for it. Sure, they have internal processes that can't be messed with. But there ought to be a way to cut investigative site receivables from maybe 120 days down to something normal like 30 days. It makes no sense for big sponsors with low borrowing costs to avoid paying small sites with high borrowing costs. This is what Wall Street calls an "arbitrage opportunity." A site's cost of capital might range from 8% per year for bank loans to 18% per year for receivables financing, assuming a bank can be found to finance 120-day receivables. On the other hand, a middling-sized pharma may pay a 2% annual rate for 3-month financing. That means the cost to the sponsor of financing 90 days of receivables amounts to a measly $250 on a $50,000 contract. The $250 amounts to 0.5% of the total payments to the site. In other words, the cost of making the sites ecstatically happy by paying them net 30 would cost sponsors pocket change. Why not keep everyone honest by charging sites 1% per month for 60-day-old advances and paying them 1% per month for payment 60 days after billable activities occur? What am I missing here?

8

Is the perfect consent document good enough?

Everyone agrees that proper informed consent is absolutely critical and deserves our full attention. But ancient Babylonians would feel right at home with our informed consent process. Hey, this is the TV generation. A lot of people don't even read the newspaper. Why not supplement the consent document with a video? It wouldn't have to be fancy. Sure, it would cost a few thousand bucks to produce, and take some advance planning, but didn't we just agree that proper informed consent is absolutely critical? What am I missing here?

9

How about we define what we do all day?

CPT (Current Procedural Terminology) codes work well for specifying most medical tests and procedures. But there are no equivalent "Research CPT codes" for numerous research activities such as obtaining informed consent, reviewing concomitant meds, and educating subjects. An industry-standard research activity taxonomy will help sites understand their costs and communicate with sponsors. So why doesn't it exist? What am I missing here?

10

Why not put our money where our mouths are?

Investigative sites can promise the moon and never enroll a single subject. They can foul up the data, skip subject visits, and generally make a mess of things. Sponsors can write ambiguous protocols, cancel trials, add reporting requirements, and generally make a mess of things. Companies in other industries can foul things up just as well as we can, but they stand by their commitments. They offer satisfaction guarantees. They offer money-back guarantees. They repair or replace defective products at no cost to the customer. You can walk into most grocery stores, tell them you bought a bad melon the day before and get a new one for free, without showing a receipt, or even a bad melon. If a grocery store can give a free melon to a perfect stranger, why can't we make good to our business partners when we foul up? What am I missing here?

11

Are you ready for big brother?

Electronic case report forms have their issues, but they are inevitable. Electronic source documents are bit trickier, but pose no problems that can't be solved by wireless tablet computers. Hand-writing recognition would be nice, but if it's not required with paper documents, it's not required with electronic ones. So electronic source documents are inevitable too, which, of course, means the end of separate CRFs. That will eliminate a lot of redundant work. But here's the rub: Every time a principal investigator or study coordinator turns on his/her wireless tablet computer to take a medical history, review concomitant meds, or interview a subject, that activity can be observed in real-time by the sponsor. In other words, big brother will be watching every move. Sites and sponsors will know to the second how long each activity really takes. This technology has been used for years in fast-food restaurants to micromanage field staff. Trucking firms

know exactly where their trucks are and how fast they are moving. Are you ready for this call: "Hello doctor, subject ABC has been waiting ten minutes for his physical. Is there a problem?" On the other hand, negotiating budgets will be a lot simpler when everyone knows how long study activities really take. There's a huge cultural change acoming and no one is talking about it. What am I missing here?

12

Can I have fries with that burger, doctor?

It's a national tragedy how difficult it is for foreign MDs to get licensed to practice medicine in the United States. Many of them are thus pursuing alternative careers as retail clerks and security guards. These highly-trained, intelligent, and ambitious people have many of the skills required for careers in clinical research. There must be a way to tap this huge pool of talent, get them started in our industry, and help them achieve their American dream. What am I missing here?

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How can investigators prove they know what they're doing?

In most industries, customers can check customer references before they purchase a product or service from a supplier. In many industries, customers can review the quality of work that a supplier performs. However, in the clinical research industry, confidentiality requirements with subjects and sponsors prevent sponsors from examining study documents or talking to subjects or previous sponsors. Competitive considerations prevent sponsors from calling previous customers for references. Sponsors have to take the investigator's word for their qualifications and track-record. For example, how does a sponsor really know that an investigator was a top-enroller? As a result, it is very difficult for sponsors to qualify new investigators, which can be a high percentage of all the investigators on many studies. Sponsors thus invest substantial sums initiating and managing underperforming—or completely non-performing—investigators, to say nothing of potentially disastrous GCP issues. On the other side of the coin, how can capable investigators prove their qualifications without having worked with a sponsor on a previous study? This problem could be easily solved if organizations existed to certify investigative sites (in addition to site personnel). They could visit an investigative site, audit anonymous study documents, talk to site personnel, contact IRBs, and call previous clients for references. The investigators could certify their statements under pain of losing their certification. What am I missing here?

14

Where are our ethics?

We talk all the time about ethical conduct in clinical research, and rightly so. The Association of Clinical Research Professionals has a code of ethics. If ethics is so important to us, why doesn't every sponsor, investigator and CRO prominently display *their* Code of Clinical Research Ethics? What am I missing here?

15

Why does this industry eat its young?

The current approach to introducing new investigators to clinical research is akin to drafting baseball players from college and giving them all their own teams to manage. Over 60% of new principal investigators participate in only one clinical study before they realize the grass is not greener on the other side of *that* fence. Everyone could save a lot of time and aggravation if someone would warn new investigators about the realities of clinical research—the onerous paperwork, the hidden costs, the indecipherable contracts, the detailed GCP requirements, the complex regulatory rules, the SAEs, the four-month payment delays, etc. The sponsors couldn't possibly have a "seller beware" attitude, could they? Could they? How can this be smart business? What am I missing here?

16

Foot Shooting 101

By combining marketing with overambitious research objectives, many Phase 4 studies are asking for trouble. Phase 4 studies can give physicians "a taste" of medications they have not prescribed before. They also can generate useful research to support marketing claims. Most Phase 4 investigators have never participated in a study previously and are often attracted by curiosity and the allure of easy money. Because of their lack of training and experience, these investigators often learn too late about all the time-consuming, head-scratching work required by the study, with minimal compensation. And, heaven forbid, they have to deal with an adverse event. As a result, many (most?) Phase 4 investigators satisfy their curiosity with one study and never do another. Phase 4 studies may be a good way to give physicians a taste of medications, but, too often, it's a bad taste. In other words, pharmaceutical companies are spending a lot of time and money to annoy their best potential new customers. What am I missing here?

17

Is that a CDA on the fax machine?

Almost every time we talk to a sponsor about a new study, the sponsor requires us to execute a Confidential Disclosure Agreement (CDA). Completing the form is seldom a problem, although it sometimes takes a few days to obtain a principal investigator signature. It would save time and paperwork for everyone if sponsors were to write all their CDAs as master agreements. Sites shouldn't object and many probably won't even notice. Then, for subsequent studies, a sponsor could just remind the investiga-

tor of the existing agreement. What am I missing here?

18

Why do sponsors make sites reinvent source documents?

Sponsors seldom provide source documents to sites. Many sites have their own forms for common activities such as medical histories and physical exams, but most source documents are unique for each study. Creating source documents takes each site perhaps a day of uncompensated coordinator time. Sponsors could create draft source documents in electronic form and provide them to the sites for any necessary modifications. If a sponsor doesn't want to do it, it could commission one of the sites to draft the forms for the other sites at a modest cost. Instead, months of coordinator time are wasted. If sites were to charge sponsors $1,000 each to draft the forms, how long do you think the current system would last? What am I missing here?

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What do you know?

When we interview candidates for study coordinator positions, we give them a quiz. The first three questions are: "What does 'GCP' stand for?", "What does 'CRF' stand for?", and "What does 'SOP' stand for?" We wanted to start out with some easy questions to make the candidates feel comfortable, but over half of the candidates with over one year of CRC experience miss at least one of these questions. Some miss all three. Considering the complexity of the job requirements, there are a *lot* of untrained people in clinical research. If sponsors insisted today on formal training and/or certification for their principal investigators and study coordinators, they probably wouldn't get many studies done. But, if sponsors started offering trained and/or certified study personnel a bonus of a couple of hundred dollars per study, the potential income would motivate a lot of people to get trained and certified. If sponsors really want trained study personnel, perhaps it's time to move beyond the 45-minute GCP primers at investigator meetings. What am I missing here?

20

Is that your elephant in the corner?

Site/sponsor budget negotiations primarily focus on the budget line items, which mostly relate to study visits. There may be a negotiation of overhead costs. But the "hidden costs" (not overhead), by definition, are seldom budgeted, reimbursed, negotiated, or even discussed. So, what are hidden costs? In general, they are the labor costs incurred between study visits. How big are they? Well, they are *huge*: 75% to 90% of study-related activities occur between visits. In other words, 75% to 90% of a site's costs are hidden! So when sponsors are negotiating budgets, it's like they are negotiating to buy the freezer and get the refrigerator for free. No wonder it's tough for sites to make a buck giving away refrigerators, even when sponsors think they are paying top dollar for the freezers. Has anyone developed metrics on hidden costs? What am I missing here?

21

Is it a big secret that investigators often conduct multiple studies?

Our investigative site receives faxes and mail every day that do not clearly indicate the sponsor's name, the study name, the protocol number, or the study coordinator's name. Sometimes all four are missing. We thus have to spend extra time routing the communication to the appropriate study coordinator. Some sponsors, CROs, and central labs have a hard time understanding that our research center and coordinator offices have different addresses, further delaying communications. Few electronic documents include the sponsor's name. If we forget to rename these, they can be very difficult to locate later. We appreciate business partners who make an effort to understand how our business operates and make our lives a bit easier. These are just three small examples, but addressing them seems like good business to me. How hard can it be? What am I missing here?

22

Blue pens not welcome here.

The use of black pens is fundamental to Good Clinical Practice. But why? Perhaps it's because early photocopiers did not duplicate blue ink, or perhaps blue ink was not archival. Technology solved those problems years ago. If you have ever copied pages and lost track of which pages were the originals and which the duplicates, you understand one serious disadvantage of black ink. How many copies are inadvertently mailed off every day instead of originals? With blue ink, the identity of the originals is obvious. Perhaps it is time to rethink at least one GCP fundamental. And why in the world do exhibitors at clinical research meetings give away blue pens? What am I missing here?

The Monitor is pleased to announce that this article will initiate a new column starting with the next issue, titled "What Am I Missing Here?" Author Norman Goldfarb will present more thought-provoking ideas, including those of our readers. Your input, elaboration, argument, and outrage are encouraged for a vigorous discussion. Mr. Goldfarb does not claim to have all the answers, but he is not afraid to ask the questions and neither should you. Please send your comments to the author at ngoldfarb@firstclinical.com or editor@acrpnet.org.

Norman M. Goldfarb is President and CEO of First Clinical Research, a multi-specialty investigative site, in San Francisco, CA. He can be reached by tel (415) 681-4657; fax (415) 681-1428; or e-mail ngoldfarb@firstclinical.com.