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How to Solve the Quality Problem in Clinical Research

By Norman M. Goldfarb

Ask anyone in the clinical research industry if high-quality data is important, and you almost certainly will get a positive answer. However, if you focus on the industry's actions rather than its words, you may conclude otherwise. For example, data query rates in the United States average 14 per 100 CRF pages, about triple the rate in some developing countries.[1] Armies of clinical research associates roam the land, but Six Sigma quality – 1 error per 3.5 million items – is an amusing fantasy, even ignoring errors that do not appear in data queries because they are undetectable by site monitoring and data management.

Before we can solve the industry's quality problems, we need to answer some very basic questions:

- Do sponsors care about quality?
- Should research sites care about quality?
- Should sponsors pay for quality?

Do Sponsors Care about Quality?

High-quality data is obviously of great value to clinical research sponsors: It increases the statistical power of study databases and reduces site monitoring and data management costs.

FDA guidances and ICH guidelines place the burden for data quality on both sites and sponsors and sites:

- ICH Guideline E6 § 4.9.1 (which is also an FDA guidance) states that "the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports."
- ICH Guideline E6 § 5.18.4 states that the sponsor's "monitor specifically should verify that… the data required by the protocol are reported accurately on the CRFs and are consistent with the source data/documents."
- The FDA's "Guideline for the Monitoring of Clinical Investigations" states that the sponsor "is responsible for assuring that the data submitted to FDA… are accurate and complete."

If the FDA perceives problems with data quality, it may delay or reject an NDA marketing application.

Nevertheless, many sponsors appear to have limited interest in data quality. This is not to say that they do not prefer high-quality data, just that it is a lower priority than, for example, recruiting research sites, enrolling subjects, and staying within budget. These sponsors may say they want quality data, but do not back their words up with action:

- They do not explicitly set standards for data quality in clinical trial agreements.
- They do not pay extra for high-quality data or site attributes, such as certified personnel and internal quality assurance programs, correlated with high quality.
- They do not provide sites with reports on their quality performance.

- They do not give awards or provide other recognition to sites that generate high-quality data.
- They do not explain to unsatisfactory sites why they do not call them again for future studies.

The most likely explanation for this conflict between words and actions is that sponsors are willing to settle for data from research sites that is "good enough," but far from perfect.

Should Research Sites Care about Quality?

Regardless of the quality message that sponsors think they are sending, the message that research sites are receiving is that data quality is a relatively low priority. Most research sites do not perceive a business advantage from generating high-quality data. The proof of this statement is simple: How many research site websites include metrics on high data quality?

Research sites cannot obtain payment for the full value of high-quality work from sponsors that place a low value on quality, but, over time, it will pay off with sponsors that do appreciate good work: High-quality work creates satisfied sponsors, leading to repeat business and reducing marketing and training costs. With proper documentation, high-quality data can be an effective marketing and budget negotiation tool. Because many research sponsors have deficient institutional memories, sites may have to remind them of the good work they have done in the past, but it is worth the effort.

It would be a sad world if research sites cared about quality only to the extent that they can charge higher prices for it. Regardless of any actions or statements by the sponsor, when a site signs a clinical trial agreement, it accepts a regulatory and ethical obligation to the sponsor to do good work. Even more importantly, the site accepts an ethical obligation to the study subjects who are donating their time and risking their health on the presumption that the data collected will be accurate.

High-quality work incurs extra costs, e.g., in training. However, if lessons from other industries apply, it saves more than it costs. For example:

- High-quality work minimizes the cost of inspection and rework, e.g., resolving monitoring visit "stickies" and data queries.
- High-quality work minimizes the risk of negative findings in an FDA inspection.
- High-quality work improves employee morale, thereby aiding hiring, retention and productivity.

A commitment to quality benefits sites in indirect ways that are difficult to measure. Sites that operate with high quality spend less time fixing errors, freeing up time to do things right the first time. For example, one measure of quality in subject recruiting is how long it takes the site to return telephone calls from potential subjects. Losing potential subjects because of slow return telephone calls is a real waste.

If a site has aspirations to become a top-enroller, the benefits of high quality increase: Sponsors are more sensitive to quality problems at high-enrolling sites because they could jeopardize the entire study. Also, the FDA is more likely to inspect sites that are top enrollers.

Should Sponsors Pay for Quality?

Many sites believe that study sponsors should pay a premium for high-quality data because "quality costs money." However, as discussed above, it is not clear that quality does cost money; in most industries, it makes money. More importantly, supplier cost is a poor

argument for higher prices – customers do not care what it costs to grow an apple; they care how the apple tastes.

The better argument is that high-quality data is more valuable to sponsors than low-quality data – it "tastes" better. Not every customer will pay more for tasty apples, but many will. Similarly, high-quality sites attract sponsors that care about quality and are willing to pay more for it. Sponsors that care about quality at research sites are also more likely to care about quality in their own operations saving sites times and money. For example, they may write higher-quality protocols, conduct monitoring visits more efficiently, and not waste site time with spurious data queries.

When sponsors develop clinical trial budgets, they want the numbers to be "fair," in part because of potential problems with anti-kickback laws when they pay higher prices to some sites than others without justification. Paying a low-quality, high-prescribing research site more than a high-quality, low-prescribing research site suggests chicanery. However, it is perfectly legitimate to pay a high-quality site more than a low-quality site. There is no reason why research sponsors cannot pay for the value they receive from high-quality sites.

The term "fair market value" often comes up in discussion of clinical research pricing. "Fair market value" does not mean price equals cost, or even relates to cost; it means customers are willing to pay that price for the services provided. According to Merriam-Webster's Dictionary of Law, "fair market value" is "a price at which buyers and sellers both having reasonable knowledge of the property and being under no compulsion are willing to do business."

It is often assumed that the fair market value for clinical research services is determined by the prices charged to regular clinical patients. However, this assumption is false because a service provided to a clinical patient is usually not the same as that service provided to a clinical research subject. For example, in clinical research, processing lab specimens and dispensing study drugs often require additional training, paperwork and attention from management. Clinical research is notorious for hidden costs that must be compensated somehow if the site is to sustain its research business.[2] There are enough such factors that it is perfectly reasonable for a site to develop a price list ("ChargeMaster") specifically for clinical research. Healthcare providers already have multiple price lists for Medicare, Medicaid, different insurers, and uninsured patients, so the existence of another price list is no cause for alarm.

The pertinent language in MAGI's Model Clinical Trial Agreement makes no reference to fees charged for regular clinical services:

> "Compensation under this Agreement is consistent with fees charged for similar research in Site's geographical area, has been negotiated at arms-length, and is unrelated to the volume or value of any referrals or other business otherwise generated between Sponsor and Institution." [3]

Many research sites price their services based on their costs, but that doesn't mean research sponsors care about site costs. Sponsors may inquire about costs as a negotiating tactic or to understand why a particular price is high. However, they determine the fairness of clinical trial budgets based not on what it costs sites to conduct the research, but on what sites are willing to accept. Many sponsors use industry databases to determine fair market value; these databases include price, not cost, data.

Research sponsors prefer to pay a consistent price across all the sites in a study. By doing so, they minimize problems with anti-kickback laws, sites that complain about other sites getting paid more, administrative hassles, and the challenge of developing a more rational value-based fee structure. If a sponsor wants to pay fairly, one might think that it would pay all sites the highest price (within a narrow range) it has to pay any similar site. In

practice, however, sponsors tend to pay all sites the lowest price (within a narrow range) it is able to negotiate with any similar site. The burden is thus on the research site to demonstrate convincingly the extra value it provides, not an easy task, but often possible. Metrics that demonstrate high-quality data help make the case.

As mentioned above, in a free market, customers pay for value and care nothing about the supplier's costs. For example, if the research site's landlord raises the rent to pay for an improved ventilation system that reduces sample contamination, the sponsor benefits from lower contamination rates, not the higher rental rate. There is, of course, a relationship between cost and price – for one thing, pricing below cost is a sure road to ruin. Stable commodity markets tend to price based on cost, with the lowest-cost suppliers setting the market price and higher-cost suppliers accepting lower profit margins, differentiating their products to have higher value (think perfume), or leaving the market. Largely missing from the clinical research market are active efforts by research sites to differentiate their services based on quality, and pricing messages from research sponsors that encourage such differentiation.

Although clinical research is what economists call an "inefficient" market, with limited information about buyers, sellers and prices, sponsors clearly prefer sites with lower prices. Sites with high prices stay in business because they provide high value, be it rapid subject enrollment, high-quality data, key opinion leaders, attentive customer service, or geographical convenience. At the other end of the spectrum, many research sites that charge low prices unknowingly subsidize unprofitable clinical research activities because they do not know their costs.

In other industries, there is the concept of "total cost of ownership" – automobile companies charge more for reliable cars that require fewer costly repairs; artificial plants often cost more than real ones, because you don't have to water them or buy new ones when they die.

The total-cost-of-ownership concept is largely lacking in the clinical research market. For example, by far the lowest-cost source of good data is a research site that generates high-quality data and requires very little site monitoring and data management.[4] Clearly, therefore, sites that can demonstrate high-quality should not be shy about attempting to price their services to reflect the high value they deliver. Similarly, sponsors should have no qualms about paying higher prices for the higher value they receive. Even with a substantial premium, the total cost of ownership is much lower than for low-quality research sites.

Conclusion

In a marketplace, the most effective way to communicate that high quality is a desirable product attribute is to pay a higher price for it. In the clinical research marketplace today, the price of high-quality data reflects little or none of the premium value of that data. As a result, there is a huge competitive opportunity for research sponsors to pay a bit more for high-quality data and keep most of the value for themselves.

If paying more for high quality becomes more common in the clinical research marketplace, more research sites will improve their quality to obtain the higher prices. As the supply of high quality research increases, competition "at the top end" will increase, and the cost of high quality will decline. Until then, research sponsors that make it known that they pay for high quality will attract the best sites and the best service from those sites, major competitive advantages. High-quality research sites may capture only a fraction of extra value they deliver, but they will capture enough of the revenue increase – and all of the cost savings – to give them a competitive advantage as well.

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Author

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.