Do You “Go the Extra Mile” or Adopt a Minimalist Mindset

George F. Nauyok, Jr.

The article “Minimum Requirements for PIs” (Applied Clinical Trials, July 2000) prompts a consideration of how minimum standards may also be part of the mindset of a sponsor or contract research organization. Certainly the regulations are written in such general, nonspecific terms as to permit wide latitude in the conduct of many aspects of the research process—clinical investigator selection; clinical study initiation, conduct, and monitoring; and data collection, correction, and reporting.

When no regulation specifically requires a particular practice, every sponsor or CRO (contract research organization) must weigh the value of additional training, additional oversight, additional subject safeguards, and additional costs against the time and resources (budgetary, personnel) to complete a study. This article examines some areas in which adopting a mindset for maintaining only minimum standards is counter-productive toward the goal of generating quality data. Specifically, quality data is essential to produce a dossier that can withstand the rigors of review by health authorities—for example, FDA (Food and Drug Administration) and EMEA (European Agency for the Evaluation of Medicinal Products)—and to protect subjects’ rights, welfare, and safety. This article addresses three areas (protocols and case report forms, information provided to the subject, and protocol waivers) where a sponsor’s or CRO’s minimalist mindset can have serious negative effects, and where minor efforts to improve processes can reap great rewards.

Protocols and case report forms

Protocols. A study protocol provides directions and instruction for the conduct of a clinical study and is a valuable reference document for the sponsor, the study staff (principal investigator, subinvestigators, pharmacist, study coordinator) and the institutional review board (IRB). Although protocols often are reviewed with site personnel before the start of a study (for example, during an investigator meeting or at an initiation visit), protocols may be referenced long after study initiation and by study personnel who were not in attendance at the investigator meeting or initiation visit. In most cases, when study staff or an IRB refer to a study protocol for clarification or direction, it will be in the absence of a sponsor representative. Therefore, it is very important that the protocol is clear and understandable, and its interpretation is consistent for all participants.

A sponsor or CRO that adopts a minimalist mindset may write a protocol to meet the needs of the sponsor, with no appreciation of the needs of the other study par-
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protocol regardless of how they conduct the study—for example, the site’s practice is in compliance with a protocol requirement on page 6, but is in violation of a protocol requirement on page 28.

This extra, minor effort to ensure the accuracy and appropriateness of a protocol can reap great rewards in many ways that may not be apparent until the study is initiated, subjects are treated, and data is collected. Poorly or ambiguously worded protocols may result in different interpretations of the protocol’s intent, and these different interpretations could result in a multicenter study being conducted differently at some sites than at others. The collection and pooling of data from a multicenter study may be seriously and significantly influenced by practices conducted at a single site, such as

- collection of different endpoint or safety data (for example, only causally related AEs are recorded on CRFs).
- using a unique tool to calculate dose (for example, using the wrong nomogram to calculate body surface area).
- using different dosing regimens (for example, morning, evening, with meals, in fasted state).
- using an ancillary concomitant medication that affects the adverse experience profile of the study drug.

Protocol amendments. A sponsor or CRO should put extra effort into protocol amendments to ensure that when changes are made to the protocol, they are reflected wherever the action is referenced—for example, the action was amended in the protocol text, but the study flow diagram/table was not updated. Therefore, it is important that the clinical research author pay careful attention to detail and that an adequate quality control or other independent review occur with each version of the protocol. A sponsor or CRO with a minimalist mindset may not appreciate the value of this extra effort—of providing an effective independent review of each protocol amendment to eliminate discrepancies or inconsistencies.

Even with extra attention to these points, however, and in spite of a sponsor’s or CRO’s best efforts, misunderstandings of the protocol’s language or intent may occur. After the study’s initiation, the sponsor’s clinical research personnel should be alert to identify and correct such inconsistencies or errors in study conduct, including the drafting and issuance of protocol amendments or providing additional training to site personnel. These inconsistencies may be identified from information obtained by the CRAs (clinical research associates) in routine monitoring visit reports and by the QA auditors in on-site audits.

Case report forms (CRFs). Although it may seem intuitively obvious, information referenced in the protocol must be accurately and completely collected on appropriate CRFs. A sponsor or CRO that has a minimalist mindset may give minor consideration to this important feature. A review of the CRFs against the protocol by an independent party (for example, QA department) serves to minimize the potential for incorrect or incomplete information being collected on the CRFs.

In addition, sponsors and CROs must appreciate that the design of the CRFs contributes to a site’s ability to complete them accurately. Sponsor or CROs with a minimalist mindset may disregard a site’s concerns in favor of designs that improve the efficient entry of data by their clinical data management (CDM) departments. When the completion of a CRF is not self-evident because of an ambiguous design, the sponsor or CRO will be forced to provide training every time a new study coordinator is hired. In addition, these ambiguously designed CRFs will be the subject of numerous data queries. Ideally, CRFs should be designed to accommodate the needs of both the site personnel and CDM, and sponsors or CROs should consider allowing one or more potential study sites to review the CRF design before the study begins. This minor, extra effort may improve the way that CRFs are completed and minimize the need for costly and time-consuming follow-up data clarifications and corrections or may reduce the need for extensive training of site personnel.

Information provided to the subject

Many sponsors and CROs provide a draft consent form to aid the site personnel in writing a protocol- and site-specific consent form. Sponsors and CROs may also provide subject instruction/information sheets to serve as an easy reference guide for subjects to explain important study-related issues—for example, when to take meds (once a day, before bed), how to take meds (fasted state, with meals), and important safety considerations. A sponsor or CRO with a minimalist mindset may disregard the importance of these tools and how they may influence the timing of the study’s start or the quality of the data generated.

Consent forms. The regulations require that consent forms contain language that is understandable to the subject. When an English language consent form is being used with a prospective subject who speaks/reads/understands English, this requirement of the regulations pertains to the consent document’s readability (for example, written at the comprehension level of a first-

participants. For example, a protocol may be written that does not reflect “real world” situations or practices, or may contain language that is unclear or ambiguous. To prevent protocols from imposing unrealistic demands and from containing language that is unclear, it may be useful for the sponsor to have study personnel at one or more representative sites review and comment on a draft protocol. This minor, extra effort before preparing the final protocol and initiating the study can yield a protocol that is realistic to execute and is understandable—the considerable reward for going beyond the minimum required.

In addition to a review by study personnel, it may be useful to have an independent party—QA (quality assurance) department, for example—review the draft protocol. This independent review helps to ensure that the protocol language is understandable, clear, and unambiguous and that the protocol does not contain inconsistencies or discrepancies. Inconsistencies within the protocol result in study staff being in violation of the
A sponsor with a minimalist mindset may use paragraphs verbatim from the protocol in the sample consent forms; clearly, many prospective subjects do not have a reading comprehension ability at the level at which most protocols are written. The study site personnel, then, must revise the sample consent form provided by the “minimalist” sponsor or CRO to conform to a more reasonable readability standard. This rewriting of the consent form may delay the start of the study.

Sometimes investigators are faced with prospective subjects whose primary language is not English, yet a sponsor or CRO with a minimalist mindset may provide sites with only an English language consent form. Ideally, a sponsor should make available (or provide the means to make available) a complete and accurate translated consent form to study sites in areas where there is a large population of patients whose primary language is not English (for example, Spanish in parts of the United States, French in parts of Canada). This requires extra effort by a sponsor or CRO, and failure to provide this translated consent language may result in delays in the study initiation or subject enrollment. A worse result is obtaining an invalid consent (asking a subject who does not speak/read/understand English to sign an English consent document, or obtaining oral consent by means that do not meet FDA regulations, 21 CFR 50.27).

Subject tools. A sponsor or CRO may provide study subjects with one or more tools to help them understand or remind them of their obligations in the study. Appointment reminders are one tool that some sites provide to study subjects at every visit to remind them of their next visit and of any other obligations associated with that visit—for example, “Remember to fast for eight (8) hours prior to this visit.”

Another tool is a Subject [Patient] Instruction/Information Sheet (PInS), which is a one- or two-page document that contains important and key information about a study (see example). Although the PInS information may be part of the informed consent, this information may be buried deep within the multipage consent form; a PInS may provide this information in a form that is easily referenced. There is no specific regulation that requires a sponsor or CRO to provide PInSs or subject reminders, and a sponsor or CRO with a minimalist mindset would, most likely, not provide those. Subject reminders or a PInS, however, are helpful tools to ensure that subjects follow the protocol requirements. They are particularly useful when the study population (for example, elderly) may be prone to forget key information, when study requirements are particularly confusing or numerous, or when safety concerns are important to identify immediately.

Non-English-speaking subjects. Even if the FDA requirements for obtaining oral consent are met for non-English-speaking subjects, the needs of these subjects can be neglected by a sponsor with a minimalist approach to clinical research. For example, an English-speaking subject takes home an English consent form to read at his/her leisure, to discuss with family members, and to reference after the day it is signed. An English-speaking subject may also take home an English-language PInS that addresses specific issues not necessarily mentioned on a consent form (for example, study drug storage conditions). Moreover, that subject benefits from the added information on the second label that is often affixed by the pharmacy. The label may contain (in English) instructions for use (for example, take with meals) and cautionary statements (such as, do not take other medications within two hours). For sponsors and CROs that take a minimalist approach, subjects whose primary language is not English may have none of these tools to help them understand their obligations regarding the study and pertinent safety issues. As stated earlier, there is no specific regulation that requires a sponsor to provide this supplemental information to a subject.

A sponsor with a minimalist mindset may fail to appreciate that subjects who understand their obligations in a study are more apt to follow the dosing regimen, alert the investigator to important AEs, and, generally, provide more complete and accu-
rate data than subjects who have no information other than that which was shared (verbally) at the first visit. Providing this extra information to subjects whose primary language is not English takes foresight and requires more time, cost, and effort than failing to provide this information. If subjects whose primary language is not English are enrolled, a sponsor must weigh those extra commitments against the potential and real benefits to subject safety and data quality.

**Protocol waivers**

**Waivers for enrollment.** Sponsors often provide waivers to investigators to enroll subjects into a study when the subject does not meet one or more protocol requirements (for example, inclusion/exclusion). An investigator may decide that if a sponsor approves enrollment of an ineligible subject, there is no reason to obtain IRB approval before the subject is enrolled or no reason to alert the IRB to this protocol violation. And a sponsor or CRO with a minimalist mindset may consider that their providing a waiver absolves the investigator of the requirement to obtain IRB approval of this change to the study design and of the increased risk to the study subject that may be inherent in the protocol deviation. Some potential problems are missed in this minimalist thinking.

**Investigator.** An IRB’s responsibility is to assess risk/benefit and ensure subject safety (to the greatest extent possible). The IRB has approved the study given a certain set of criteria—namely, the inclusion and exclusion criteria. If the investigator deviates from these criteria, the IRB must be made aware of the deviation. Also, the investigator must receive IRB approval before enrolling a subject who fails to meet the criteria, since the risk/benefit profile of the study (and its associated safety issues) have been altered from the original approval. The sponsor or CRO with a minimalist mindset, then, must weigh the legal and ethical ramifications of enrolling an ineligible subject into the study without the prior approval of the IRB. The FDA considers enrolling ineligible subjects into a clinical study a serious protocol deviation, and has issued Warning Letters to principal investigators for this practice.

**Sponsor.** Every waiver is, by definition, a protocol violation. The FDA may disallow from New Drug Application (NDA) efficacy considerations all the data associated with a subject who was ineligible to enroll by the protocol criteria. In this case, the data for subjects who were enrolled via waivers could be used only to support safety assessments. A sponsor must assess the value (and ethics) of enrolling ineligible subjects into a clinical study when the data associated with efficacy parameters may be disallowed in an NDA submission.

**“Show me the regulations”**

Clinical studies are expensive to conduct, analyze, and submit for approval, and there will always be a focus on identifying time-and-cost-saving measures. The adage “penny wise, pound foolish” is particularly germane, however, to the conduct of clinical research. A mindset that adopts the minimum standards required by the regulations or guidelines is a misguided stance and, typically, is characteristic of a sponsor or CRO that is more concerned with rapid subject enrollment than with obtaining...
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or 25 years or more, pharmaceutical executives have been inundated with promises of the latest technological breakthroughs that will speed up the clinical trial process. It would be a safe bet that, if you polled a group of them, any one of them would have heard this enough times to recite it from memory:

“Our new [fill in the blank with your favorite new technology] will help you speed up the clinical trial process. By increasing the speed at which you currently process data, this new technology will move your trials to NDA faster, thereby maximizing the marketing time under patent.

Given the fact that blockbuster new drugs can earn $1 million to $5 million per day, our new technology could generate tens of millions of dollars in increased revenue.

Thirty years ago, the high-tech breakthrough was the popularization of mainframe computers and centralized computing. Then came the first commercial software packages for advanced project management. Then the PC revolution decentralized systems and empowered workers to perform more efficiently, which started the first great “gold rush” to electronic data capture. This was followed by more commercial software from imaging to document management. Then we all jumped on the Internet and World Wide Web bandwagon, returning to the concept of centralized systems.

Now we have the latest, and potentially the most powerful, breakthrough: “e.” This new advance is so big that it is hard to define. “eBusiness” is used to describe many different things: application service providers (ASPs), the Internet, a browser, wireless, or whatever you want it to describe. As long as it has an “e” in front of it, it must be good.

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quality data or addressing subject’s rights and welfare. Minimum standards have the potential to negatively affect the data or the ability to pool data in a multicenter study when some sites (or some personnel at a single site) interpret the protocol differently and conduct the study in unique ways. Data integrity is also affected if subjects do not have the tools to understand the protocol requirements. The adoption of a minimalist mindset may result in data being withdrawn from an NDA because ineligible subjects were enrolled into a study.

Subject safety is affected when subjects are not provided the tools to identify or know how or when to report important adverse experiences.

All of these activities have the potential to negatively affect the quality of a sponsor’s NDA submission (see Consequence Table). For all these reasons, sponsors and CROs must abandon a “show me the regulations” philosophy when extra efforts are identified that have the real or potential benefit of improving subject safety and data integrity, particularly when the regulations are nonspecific on these practices. Following the regulations to the minimum extent possible is the wrong focus for a sponsor or CRO. Rather, sponsors and CROs should conduct clinical studies in a fashion that balances their budgetary/personnel resources with the need to protect subjects’ safety and rights and to maximize the quality of their clinical data.

George Nauyok, Jr. is president of Quality Auditing & Research, 5388 Wilshire Drive, San Diego, CA 92116, (619) 280-0509, qualityauditingandresearch@yahoo.com.

Launching Taratec Development Corporation (Bridgewater, NJ), a provider of integrated e-technology and regulatory solutions for the life sciences industry, launched Taratec University, an educational environment designed to help pharmaceutical, medical device, and biotechnology companies improve corporate training programs and to comply with FDA regulations.

BBK Healthcare, Inc. (Newton, MA) released a guide for providing information on recruiting and retaining subjects for clinical trials. The resource, A Guide to Patient Recruitment: Today’s Best Practices and Proven Strategies, covers such topics as budgeting and contracting, ethics and confidentiality, media strategies and tactics, recruiting subjects on the Internet, retention and subject satisfaction, and recruiting pediatric subjects.

Aventor (Washington, DC), a consulting company, has entered the medical technology industry. The company provides integrated, single-source solutions for regulatory, reimbursement, and political challenges that influence the introduction of new drugs, medical devices, and biologics into global markets.

The Coalition of National Cancer Cooperative Groups, Inc. (Philadelphia, PA) launched the Web site www.cancertrialshelp.org to help increase the number of adult subjects participating in cancer clinical trials. The site offers a list of available cancer trials being conducted by the seven cooperative groups in the coalition, basic information on clinical trials for potential subjects, and information on patient advocate groups.

Research Triangle Institute (Research Triangle Park, NC) released version 8 of its statistical analysis software SUDAAN. The new version features expanded analytical functions and improvements in the ability to coordinate with other packages such as SAS and SPSS.

QED Solutions, Inc. (McLean, VA), a provider of drug safety management products, and Relsys International, Inc. (Irvine, CA), a provider of fully validated software solutions for the pharmaceutical and medical device industries, entered into a strategic alliance to make QED’s Qscan and Relsys’ Argus Safety and EasyTrak software available to biopharmaceutical companies for monitoring adverse events and for worldwide regulatory reporting in real time.

CDC Solutions, Inc. (Cincinnati, PA) and First Consulting Group (Long Beach, CA) formed an alliance to provide an integrated content management solution designed to meet the business needs of submission assembly and publishing in the life sciences industry and to meet the regulatory guidelines for electronic submissions, including 21 CFR 11 compliance. The solution will combine the former company’s EZsubs for submission publishing with the latter’s FirstDocs for research and development.

Phase Forward Incorporated (Waltham, MA) and Relsys International, Inc. (Irvine, CA) entered into an agreement to integrate the former company’s InForm Web-based clinical trial management platform with the latter’s Argus Safety surveillance software for pharmacovigilance.

QUMAS, Ltd. (Cork, Ireland) and Liquent, Inc. (Fort Washington, PA)