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Quality Assurance Coordinators: Ensuring Quality at the Site Level

NOTE: The quality assurance coordinator role outlined in this article is based on how such a position has been implemented in real-world settings.

PEER REVIEWED | Bryan A. Moore, MA, CCRP | Olga Pizov, RN, MSN, CCRP

[DOI: 10.14524/CR-16-0025]

Does risk-based monitoring (RBM) always provide the highest quality in data, compliance, and subject safety? The short answer is no. In 2013, the U.S. Food and Drug Administration (FDA) published guidance to encourage alternative approaches, such as RBM, to traditional onsite monitoring,[1] and although RBM has become very popular in recent years, some have noted that the approach leaves room for improvement.[2]

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss the role of a quality assurance coordinator and describe clinical quality management plans.

DISCLOSURES
Olga Pizov, RN, MSN, CCRP: *Employee of ClinicalRM*
Bryan A. Moore, MA, CCRP: *Nothing to disclose*

In essence, the RBM approach focuses on maximizing efficiency and effectiveness in monitoring in an attempt to save resources (e.g., time and money). Some have claimed that, in certain situations, RBM can reduce costs over traditional monitoring approaches by 20% or more.[3,4] RBM relies on the assumption that many risks can be determined before a study begins, and that resources should be directed away from low-risk areas to ones that are of high risk.

Further, one of the primary ways by which RBM plans save money is through reducing onsite monitoring visit duration or frequency. However, although RBM may be a useful approach, our sense is that it doesn't necessarily lead to the highest level of quality.

A common focus within the RBM perspective is a move away from 100% source data review and source data verification. There is also a shift toward a more targeted and centralized monitoring approach. Targeted approaches, by nature, however, can miss the mark and overlook critical data points. Centralized, or remote, monitoring can fall short in the detection of data entry errors.

In addition to quality issues, remote monitoring may even increase costs for sites by increasing the amount of time that study coordinators have to prepare for and deal with monitoring activities.[5] Remote monitoring may increase the cost of study coordinators for a typical study by more than three times the cost seen with traditional monitoring.[5] This increased time burden for coordinators may come from file transfer activities and repeated requests for documents.

Looking Beyond the Challenges to the QAC Solution

Despite some challenges, RBM can be a helpful guide in designing monitoring plans. Cost reduction is a real and valid concern for sponsors, and the risk assessment aspect of RBM is a useful tool in decreasing costs. However, we should also acknowledge that it's impossible to precisely predict the future, and that it's wise to utilize methods that help safeguard against situations where RBM might miss the target.

With the above in mind, one way to enact safeguards and increase quality is for sites to employ onsite quality assurance coordinators (QACs) as part of their clinical quality management plans (CQMPs). QACs, also known as quality coordinators

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or quality management coordinators, perform a variety of monitoring and quality-related functions, including source document review, source data verification, pharmacy and lab audits, staff training, and regulatory file review, but they work at the site for the investigator.

QACs also focus on process improvement. They might conduct walkthroughs, or "dry runs," with site staff to address risks and procedural issues in advance of initiating the protocol. They can help with developing source documents to not only capture the protocol-required data, but also to assure data are documented using good documentation practice.

QACs also work on developing tools and checklists to assist the site in collecting data and following the tenets of Good Clinical Practice (GCP); may develop plans for conducting regular and current assessments of subject charts; and maintain standard operating procedures (SOPs) that reflect the site's initiatives for maintaining quality standards.

The QAC role can be filled by various types of research staff—coordinators, nurses, research managers, and other study team members may act as QACs for one or more studies. However, some sites hire individuals specifically for this role. There appears to be a growing use of QACs, as this position can play an integral role in managing CQMPs for sites.

QACs in Action

One organization that often utilizes QACs as part of its CQMPs is the National Institute of Allergy and Infectious Diseases (NIAID), Division of Microbiology and Infectious Diseases (DMID). NIAID require that sites conducting DMID-funded studies establish a CQMP that encompasses both quality control (QC) and QA processes, which often are supported by the QAC role.

QA is defined as planned, systematic, and periodic actions that are established to ensure that the trials are performed and data are generated, documented, and reported in compliance with GCP and applicable regulatory requirements.[6] QC, on the other hand, is defined as real-time operational techniques and activities undertaken within a QA system to verify that the requirements of trial-related activities have been fulfilled.[6]

CQMPs are detailed documents that include the procedures that encompass QA and QC. They describe who is responsible for conducting the day-to-day activities to ensure that the data collected are accurate and complete, the protocol was followed, principles of good documentation practice are incorporated, and the rights and welfare of human subjects are protected. CQMPs also address plans for periodic assessments to be conducted at scheduled periods during trials.

In addition to QA and QC, plans should include the details of any required training for study team members. Plans can be tailored for each protocol or can be developed as one plan that addresses all clinical trials conducted at an individual site. The goal is to make sure the study team members, including the QACs, continually assess potential trial risks and ensure that the CQMPs address these risks.

For example, new study team members may require more oversight than seasoned study coordinators. Plans can factor in QC procedures that include an independent assessment by the QAC of the first few subjects that new coordinators enroll. Another example includes the initiation of a new protocol; there is a higher chance for error with the start of new protocols, and QACs may conduct independent assessments after the enrollment of the first few subjects to assess for confusion with following the protocol, randomization issues, errors with investigational product preparation and administration, or study data entry.

Targeted approaches, by nature, can miss the mark and overlook critical data points. Centralized, or remote, monitoring can fall short in the detection of data entry errors.

The goal is to have a systematic plan in place that addresses potential risks of each trial while filling in the gaps where site monitoring might fall short. Outcomes of both QC and QA activities should be regularly reported to the study team, in order to address any findings and possibly the need for corrective and preventive actions.

Eyes on the Prize

The goal is to have a systematic plan in place that addresses potential risks of each trial while filling in the gaps where site monitoring might fall short. Outcomes of both QC and QA activities should be regularly reported to the study team, in order to address any findings and possibly the need for corrective and preventive actions. The CQMP should also be evaluated regularly and updated to make sure it continues to address study risks.

In addition to their various other functions, QACs can play a role in creating, overseeing, and evaluating CQMPs, which makes them an important part of quality-related activities at the site. All of this means that the benefits of QACs touch on areas include the following:

- **Real-time monitoring:** QACs review source documents before any monitors, so safety events, deviations, and other concerns are caught sooner. This can lead to better patient safety outcomes and faster reporting.
- **Better compliance with local regulations, internal organizational policies, and site SOPs:** Because QACs are site staff, they may be more knowledgeable of the local regulations and policies at the site. In order for sites to remain operational, they must comply with rules and regulations that are sometimes outside the purview of sponsors or contract research organizations (CROs).
- **Greater access to data and information:** QACs may have direct access to electronic medical records and institutional review board systems where other monitors or QA associates might not. Having access to these systems may increase QA/QC efficiency. It may also increase the scope of quality/monitoring activities into organization-specific systems of which monitors may not be aware.
- **Improved work flow:** QACs focus efforts on process improvement activities, which can translate into greater efficiency, effectiveness, and compliance for the entire site.

On the other hand, the risks presented by using QACs can include:

- **Cost:** QAC positions may require an additional hire for which the site and/or sponsor will have to pay. However, at this point, QAC positions are often entry-level monitoring and QA positions, so salaries may be lower than those for established monitors and QA auditors.
- **Bias:** Because QACs work under the site investigator, they may not be as objective as would be ideal in their reviews; however, this can be mitigated to some degree by having QACs report findings to the sponsor or CRO as part of the CQMP.

In the long run, the work of QACs can offer a cost-effective approach for both sponsors and sites. It helps to ensure quality at the site in areas where RBM plans may fall short. The process improvement efforts of the QAC, combined with real-time reviews of subject charts, will prevent the site from having to invest additional time in reporting deviations, writing notes to file, or having to make multiple corrections on documents. Lastly, with a focus on delivering accurate data and promoting subject safety, this approach will bolster the site's reputation with sponsors.

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Need Help With Investigational Drug Management?
Five Things Large Research Institutions Should Consider

PEER REVIEWED
Ji-Eun Kim, RPh, PhD | Emmelyn Kim, MA, MPH, CCRA, CHRC
[DOI: 10.14524/CR-16-0024]

Investigational drug management is an area that may present challenges for large and complex research organizations. Clinical research involving investigational drugs inevitably impacts site personnel and pharmacies that provide ancillary services to support such activities. For large organizations spread out geographically, having a central investigational pharmacy may not always be practical or feasible. Moreover, many outpatient clinics where research participants receive investigational drugs are increasingly situated separately from hospital facilities, resulting in potential issues surrounding drug management in these settings.

These changes bring new challenges to rapidly expanding healthcare organizations conducting clinical research. In this article, we will outline practical strategies to consider for enhancing overall investigational drug management for clinical trials occurring at various research sites throughout large organizations.

1 Develop a Centralized Review of Drug Management in Research

Appropriate investigational drug management and drug accountability are key components in clinical research compliance. Both the U.S. Food and Drug Administration's (FDA's) *Code of Federal Regulations* (CFR) and the tenets of Good Clinical Practice (GCP) from the International Conference on Harmonization specify regulatory requirements and industry standards for investigators and their delegated individuals.[1,2] A centralized review system should be considered to evaluate the management of investigational drugs across a large organization.

A dedicated resource can perform the reviews and provide guidance on regulatory requirements, resources, and procedures to both pharmacists at the facilities and to research site personnel handling investigational drugs. This process should optimally be embedded at the level of an institution-specific research approval rather than within the scope of local institututional review board (IRB) review, since research sites may use external IRBs.

Organizations using a centralized process will be able to comprehensively review all studies and

LEARNING OBJECTIVE
After reading this article, participants should be able to define strategies to consider for enhancing overall investigational drug management at large research site organizations.

DISCLOSURES
Ji-Eun Kim, RPh, PhD; Emmelyn Kim, MA, MPH, CCRA, CHRC:
Nothing to disclose

A dedicated resource can perform the reviews and provide guidance on regulatory requirements, resources, and procedures to both pharmacists at the facilities and to research site personnel handling investigational drugs.

sites handling investigational drugs and capture relevant data. Metrics can then be evaluated for a better understanding of overall trends and for identifying sites at higher risk than others, and used to target monitoring activities.

2 Provide a Risk-Based Framework

For large organizations that are comprised of multiple hospitals and pharmacies, facilities, and ambulatory sites, the provision of investigational drug services needs to be operationally feasible. Such organizations should consider providing the option to either utilize pharmacy services at a local facility or to manage investigational drugs at principal investigators' (PIs') offices, depending at the very least on the nature of the investigational drug, storage and preparation requirements, and the experience of the research team.

This operational flexibility may reduce drug transport costs and patient waiting times, but should be evaluated based on overall risks presented by the proposed research. If the risks are high where the drug preparation is complex and adequate resources are not available at the site level, then use of a pharmacy should be required. If a PI opts to manage an investigational drug at his or her own site, there should be a process to gauge the PI's study-related knowledge and ability to operationalize the following:

1. Ensure that an adequate number of qualified staff and resources are available to handle the investigational drugs properly and safely;
2. Appropriately maintain records, including qualified individuals to whom the PI has delegated investigational drug handling and drug accountability;
3. Adequately supervise delegated individuals to ensure that they are informed about the protocol, the investigational drugs, and their responsibilities, and are adequately trained in handling the investigational drugs; and
4. If applicable, obtain written approval from the sponsor for onsite storing and dispensing of the investigational drugs and meet any additional federal or state level requirements.

Management of investigational drugs within outpatient sites often comes with certain risks and means that an increased level of checks and balances through monitoring by the quality assurance (QA) or risk management groups is needed. It further, and most importantly, requires ongoing staff training and education. Institutions that are decentralized or that have a greater risk tolerance will need to invest in development of tools and resources to support individuals involved in drug management; this includes guidance documents and tools to promote site compliance with regulatory requirements, GCP standards, and institutional policies.

Such tools and resources should be developed based on ongoing reviews of current practices, internal and external audit findings, and updates in regulatory requirements and industry standards. Examples of guidance documents include those pertaining to investigational drug management, current Good Manufacturing Practice (cGMP) requirements for investigational products, initial submission and maintenance of Investigational New Drug (IND) applications, and use of controlled substances in clinical research. Templates can be developed for a manual of operating procedures (MOPs), standard operating procedures (SOPs), drug accountability record forms (DARFs), disposal records, temperature logs, and more.

3 Get Involved Early by Providing Support

Poorly designed protocols that have not been carefully planned with regard to investigational drug handling and management can lead to a variety of downstream issues. These can include delays in IRB or institutional approvals, issues with study initiation or conduct, and unanticipated costs.

Consider offering drug management consultation services before or during the centralized review process. Proactively guiding research teams and pointing them to existing resources will more likely ensure implementation of effective processes and systems and compliance with regulatory requirements. This will also prevent delayed study initiation and help to avoid unforeseen issues and costs during study conduct.

Management of investigational drugs within outpatient sites often comes with certain risks and means that an increased level of checks and balances through monitoring by the quality assurance or risk management groups is needed.

Depending on the proposed research, the following are areas deserving special attention due to the additional regulatory layers or processes associated with them:

- **Investigational drug quality:** For investigator-initiated studies, the PI may be using a commercially available product or may be developing a new drug product. If the PI is purchasing commercially available products (e.g., drugs, dietary supplements) or their blinded versions, including a placebo for a clinical study, the PI must ensure the quality of these investigational products. If the PI is developing a product, which requires an IND, the PI should be familiar with the chemistry, manufacturing, and controls (CMC) information; the current Good Laboratory Practice (cGLP) requirements; and the cGMP requirements for the IND submission. Provision of regulatory guidance on drug QA and other related regulatory requirements (e.g., Food, Drug, and Cosmetic Act section 503A for compounding) may be beneficial.
- **IND applications:** Assistance in evaluating whether a research study requires submission of an IND to the FDA may expedite IRB and institutional approval processes. Provision of guidance on sponsor-investigator responsibilities for investigator INDs can help to facilitate IND submission and maintenance, and can promote compliance with additional regulatory requirements. This includes expanded access INDs for both emergency and non-emergency uses.
- **Controlled substances:** Another category requiring additional support and close monitoring is the use of controlled substances in clinical research. Clinical research investigators may not be aware of additional federal and state requirements beyond their existing Drug Enforcement Administration (DEA) registration obtained for clinical practice. Acquiring a DEA registration and a state research license or authorization is a time-consuming, but mandatory, step to take. Security measures and adequate storage conditions for the designated schedule of an investigational drug are other considerations that need to be attended to before DEA and state inspections occur at the site. Such details should optimally be discussed during the study feasibility stage, as coordinated efforts among facilities, pharmacy, security, safety, compliance, and legal department may be needed and fulfillment of the requirements may impact the study budget due to increased costs for DEA registration, state licensure, security set up, etc.

4 Ensure Reviews are Meaningful While Setting Expectations

During the aforementioned centralized review process for institutional approval, the reviewer with expertise in investigational drug management or services should identify the necessary resources and procedures for investigational drug management and provide feedback to the research team on standards required to effectively facilitate the research. Communication with the pharmacy department, if utilized, as a checkback can be beneficial during this process. Securing the necessary resources and establishing pertinent procedures prior to study initiation should be emphasized to set expectations for best practices.

Below are examples of key resources and procedures to look for during the review process:

- **Written procedures:** External sponsors typically include written procedures in the protocol and investigational product manual (or pharmacy manual) to describe investigational products and their management. However, for investigator-initiated studies, investigators must proactively establish written procedures either in their protocols or MOPs to promote consistent protocol implementation by delegated individuals at a site or across sites. Pharmacies and sites should ensure that written procedures provided in MOPs or SOPs describe key elements in drug management (i.e., procurement, transport, storage, randomization, preparation, dispensation, disposal, accountability, and documentation) and set expectations.

Investigators and individuals delegated to handle investigational drug management may not always receive adequate training and education prior to study start-up.

- **Procurement:** For investigator-initiated studies, the PI may need to procure an investigational drug; however, discussion of the process and costs associated with drug procurement may not necessarily be considered a high priority during the feasibility stage. Without timely procurement of an investigational drug and other resources, study initiation may be delayed. Therefore, timely coordination and discussion among the research team, drug distributor, and pharmacy (if applicable) is needed and should be evaluated during reviews, particularly if there are any additional processes required, such as drug export and import and controlled substances procurement.
- **Receipt and transport:** In large organizations, a research study may be conducted at multiple sites. Therefore, research teams must establish procedures starting with receipt of a drug by a central location and subsequent distribution to other sites, or direct drug delivery to each involved site. In the former case, securing resources and establishing procedures for drug transport and tracking between the central depot and local sites are important. If applicable, resources and procedures for transporting prepared drugs to a dispensing or administering location also need to be established.
- **Storage and dispensation:** An investigational drug may require certain storage temperatures (e.g., for being refrigerated or frozen) or may require off-hour dispensation during nights or weekends. Research teams must discuss any resources needed to store and dispense the drug. This includes details on the personnel who will be delegated such responsibilities by the PI (e.g., ambulatory practice staff or pharmacist) and on staff availability during potential research participant visit schedules.
- **Preparation:** If an investigational drug requires aseptic manipulations, the PI also must ensure that the site has 1) adequate space, equipment, and environmental monitoring; 2) adequate procedures and practices, including disinfecting aseptic preparation area, personnel cleansing, and garbing; and 3) adequate periodic trainings and evaluation for delegated staff involved in aseptic preparations, as applicable to each investigational drug. If the site does not have adequate resources and procedures, the research team should utilize pharmacy services.
- **Delegation:** PIs must consider staff expertise and qualifications when delegating drug handling and administration. For example, if licensed individuals must carry out delegated tasks, such as drug preparation, dispensation and administration, the PI must have their licenses and any pertinent training records on file. When opting to manage an investigational drug at the site, the PI must assess the need for unblinded personnel delegated to handle an open-labeled drug and placebo for a double-blinded study. Lastly, the PI must ensure that unblinded and blinded personnel perform their tasks as delegated to maintain study blinding.

Routine reviews by a central compliance or QA office should occur to check documentation, management practices, and overall drug accountability focusing on the key areas above. Reviews should ensure that high-risk sites are reviewed at a minimum and that a diversity of sites, departments, and research teams are included in the sampling. Findings from the reviews can then be used to bolster training and education or policy development in drug management for research.

5 Offer Flexible Training and Education

Investigators and individuals delegated to handle investigational drug management may not always receive adequate training and education prior to study start-up. Personnel delegated to manage investigational drugs may gain their knowledge from "hitting the ground running" or through trial and error.

Typically, industry sponsors provide protocol-specific trainings for investigational drug management via an onsite visit, web-based conference, or teleconference during study initiation. For investigator-initiated studies, you may want to consider offering role-based training, which may be optional or mandatory, depending on a study team member's role, experience level, and related study requirements.

Consider tailoring the training for the various individuals who touch the process. For example, providing an overview for pharmacists on research and regulatory requirements may be beneficial, especially if they do not have a high level of experience with drug trials. Conversely, site staff may need an overview of drug accountability, management, and documentation basics. Training should embed GCP standards, and may include protocol-specific information (i.e., investigational drug description, drug ordering and receiving procedures, drug storage conditions, subject randomization, drug dispensing and disposal procedures, drug accountability records, and documentation).

Training and education can be offered in a variety of formats. Didactic, in-person training can be offered regularly at the organizational level in a central location that is conducive to learning. However, attending an in-person course may still be a burden for research personnel working at different facilities across a large organization. Alternatively, *ad hoc* in-services can be provided when new studies are initiated or for remedial purposes, based on audit findings. Developing web-based electronic courses is a more flexible approach that can reach more individuals throughout the organization, particularly those who are busy with clinical responsibilities during the day or who work non-regular shift hours. Consider developing educational courses through a learning management system to better facilitate assignment and tracking of training, reminders, and running reports.

Conclusion

Taking a more proactive, upstream approach to initiating investigational drug trials will increase the likelihood of successful implementation and reduce the potential for unanticipated problems and costs. Employing a centralized institutional review will allow for an up-front evaluation of the proposed study, while using a risk-based framework provides greater flexibility for sites with adequate resources and procedures.

A key component for a centralized review process is to get involved early by assessing regulatory requirements as a whole for the study; this will allow sites to set strategic priorities to reduce potential delays and avoid other implementation issues. However, reviews should be made meaningful by asking standard key questions regarding management of the investigational drug throughout the life cycle of the study.

Finally, using an alternative approach to training and education that is flexible and tailored to delegated staff will increase engagement and knowledge for the enhancement of the overall quality of drug management and study conduct.

In large organizations, a research study may be conducted at multiple sites. Therefore, research teams must establish procedures starting with receipt of a drug by a central location and subsequent distribution to other sites, or direct drug delivery to each involved site.

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OPINION:

Is Bias Inherent in the Current Reporting Practices for Adverse Events?

PEER REVIEWED | Robert Jeanfreau, MD

[DOI: 10.14524/CR-16-0012]

In clinical research, the collection of adverse events (AEs)—not the scientific method—is how safety is demonstrated. The U.S. Food and Drug Administration (FDA) defines an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

There are two sources for the collection of AEs—the first is the subject and the second is the principal investigator (PI), who will identify changes in the examination of the subject and in laboratory tests.

At the outset, the term "adverse event" in and of itself bespeaks a certain prejudice. An unintended and unrecognized effect of using the term is the introduction of a subtle source of error. The term springs from the unfounded assumption that every event not directly planned to be among the results of a treatment will be adverse.

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss the cause and effects of potential bias in the reporting of adverse events in clinical trials.

DISCLOSURES
Robert Jeanfreau, MD:
Nothing to disclose

Although the informed consent generally instructs the patient to report changes in health, the data on unexpected effects that are actually sought and captured are almost entirely about AEs. This bias is reflected in the mindset of the clinical researchers, and tends to be communicated to potential subjects during the consent process.

This is to say, there is no specific mechanism in place for capturing "positive side effects." (It should be noted that these observations are not the result of a formal review of the literature, but are based upon personal experience from conducting clinical trials over the last 10 years.)

The Scientific Method in Clinical Research

The framework for modern clinical research is formed by the principles of the scientific method, along with codified principles of human protection, including regulations of the FDA and the tenets of Good Clinical Practice (GCP) from the International Conference on Harmonization. The boundary at which these two sets of principles meet is the collection of AEs. The gathering of such data plays a critical role in insuring not only the safety of study subjects, but also the safety of future consumers.

At the outset, the term "adverse event" in and of itself bespeaks a certain prejudice. An unintended and unrecognized effect of using the term is the introduction of a subtle source of error.

Considering the historical development of clinical research as an area of specialty in healthcare, it should not be surprising that the role of bias in the field has been studied extensively with regard to how experiments are managed in human subjects; however, the effect of bias in the collection of AEs has received scant attention. Beyond the sound statistical treatment of AEs, there has been surprisingly little critical attention paid to how they are collected.

To more fully understand and to even improve clinical trials, it is instructive to examine the evolution of clinical research from an historical perspective. The philosophical bedrock common to all fields of modern science is the concept of the scientific method. *The Oxford English Dictionary* defines the scientific method as "a method or procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses."[1] This is a rational process that gradually draws our understanding of the universe into an ever more clear focus.

This somewhat dry definition does not convey the initial excitement and enthusiasm that first ignites the process. Curiosity and wonderment of an observed natural phenomenon are frequently captured within the first step. The initial observation is followed, sometimes quickly and sometimes slowly, by an intuition or insight that imparts meaning to some aspect of the phenomenon. This is called the hypothesis.

The next step is an attempt to prove veracity; the hypothesis is tested in an experiment designed to yield certain results if the hypothesis is true. The experiment stands at the very heart of the scientific method—it may be defined as a process of testing, under controlled conditions, the validity of a hypothesis as determined by an evaluation of the measurements obtained during the testing. The final step brings the collection and interpretation of the data.

Applying What We Know

Humankind's strivings to understand the greater world around it have co-existed for millennia with attempts to understand the human diseases within. Both of these aspects of understanding have evolved over time, but it only a relatively recent development that the scientific method has been applied to the study of human disease. In 1943, the patulin study for the treatment of the common cold was the first double-blind, controlled study, and in 1946, the trial of streptomycin was the first randomized, controlled study.[2]

Meanwhile, utilizing the scientific method in the study of human disease has introduced an unprecedented challenge in terms of the protection of the involved human subjects. Efforts to ensure the safety of human subjects begin long before a drug or device reaches the stage of clinical research. Most compounds are eliminated during extensive preclinical trials; ideally, only the most promising, in terms of both effectiveness and safety, ever make it to clinical trials.

When experimentation involves the use of investigational drugs or devices in human subjects, both efficacy and safety must be demonstrated. Since safety is such an important issue, it is not only reasonable, but appropriate, that the reporting of AEs has attained such a prominent role in clinical trials. These two goals are the very essence of the FDA's mission statement:

"FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation."[3]

Therefore, it is understandable that the current system has been purposely designed to protect consumers from the consequences of approving a drug with unrecognized health hazards.

The effect of bias in the collection of AEs has received scant attention. Beyond the sound statistical treatment of AEs, there has been surprisingly little critical attention paid to how they are collected.

Since safety is such an important issue, it is not only reasonable, but appropriate, that the reporting of AEs has attained such a prominent role in clinical trials.

Standing the Test of Time

The scientific method is the means by which efficacy is shown; it has stood the test of time and led to an explosion of information, a well-founded understanding of how the world around us works, and breathtaking advancements in applied science. It has also become clear that, even in the most carefully designed experiments, errors can occur. Most of the refinements in the scientific method have been advanced as a direct result of the relentless pursuit of identifying and eliminating, or mitigating, such errors.

Error is broadly defined as "the difference between the true value of a measurement and the recorded value of a measurement."[4] Error can be divided into two broad categories—random error and systematic error, as described further below:

- There are a number of sources of **random error.** For example, variation in how measurements are obtained is a common problem and is addressed by rigorous standardization procedures. Furthermore, because random error is, in fact, random and not directional, the net effect of this type of error tends toward zero when the sample size is large enough.
- **Systematic error,** also known as bias, is not the result of variations due to chance. Bias is the tendency, either intentional or unintentional, to over- or under-estimate the effects of an intervention. Since bias (as opposed to random error) is directional, increasing the sample size or the number of observations does not ameliorate the effect. According to one source, "In fact, bias can be large enough to invalidate any conclusions. In human studies, bias can be subtle and difficult to detect. Even the suspicion of bias can render judgment that a study is invalid. Thus, the design of clinical trials focuses on removing known biases."[4]

Clearly, establishing the validity of clinical trials by ensuring that they are free from as much bias as possible is the major focus of evidence-based medicine. To this end, the authoritative *Cochrane Handbook for Systematic Reviews of Interventions* provides guidelines for evaluating the quality of clinical research and identifies six subclasses of bias: selection, performance, detection, attrition, reporting, and miscellaneous.[5]

Consequences of Bias in the Reporting of Adverse Events

"Does it really matter if only AEs are collected?" is a reasonable question. After all, there are postapproval processes (e.g., Phase IV studies, registries, annual reports, postmarketing surveillance) in place that could capture these data. The problem is that all of these processes focus on the collection of AEs only. One can find on the FDA website a statement that, "Because all possible side effects of a drug can't be anticipated based on preapproval studies involving only several hundred to several thousand patients, FDA maintains a system of postmarketing surveillance and risk assessment programs to identify [AEs] that did not appear during the drug approval process."[6]

Therefore, the answer to the above question is a resounding yes, for several reasons:

- **Subjectivity—**Asking subjects to report "adverse events" as opposed to "changes in health" introduces a greater degree of subjectivity. Some subjects may interpret the exact same symptom in two diametrically opposed ways. For example, suppose a drug in a clinical trial causes mild anorexia. An obese subject may not report this symptom as an AE since the subject may actually view it as a positive effect, whereas an underweight subject may report it as an AE. If subjects were counseled to report all changes in health—both positive and negative—then this particular symptom would have been captured in both subjects. The same sort of problem could be encountered in the assessment of lab results. The PI may interpret a slight decrease in the hematocrit as an AE, but not an increase in the hematocrit of similar magnitude.

Asking subjects to report "adverse events" as opposed to "changes in health" introduces a greater degree of subjectivity. Some subjects may interpret the exact same symptom in two diametrically opposed ways.

- **Greater Understanding—**Positive changes in the subject's symptoms, physical findings (the lowering of blood pressure, for example), and labs (such as the lowering of cholesterol) could provide scientists with a greater understanding of a drug's mechanism of action.
- **Overlooking Benefits—**By ignoring positive changes in health, researchers could potentially overlook important, as-yet unrecognized, uses for the drug under study. Amantadine is only one such example; the FDA first approved its use in 1966 for seasonal influenza, yet three years later approved it for the treatment of Parkinsonism because a positive change in health was observed.
- **Innovation—**This bias toward negative AEs is so ingrained and pervasive that it can blind researchers to a potential positive use suggested by the negative effect. For example, Neucardin™ is a fragment peptide of human neuregulin-1 that binds to the epidermal growth factor ErbB4 receptor tyrosine kinase on cardiac myocytes. When inhibition of NRG-1 was first studied as a possible treatment for breast cancer, a serious, attributable AE occurred in the form of congestive heart failure. A less inquisitive investigator would have stopped there and relegated the compound to the dust bin. Undeterred, this researcher reasoned that if inhibition caused heart failure, then stimulation may improve heart failure. Such reasoning has led to a very promising new avenue in the treatment of congestive heart failure.
- **Negative Perception—**Although not proven, subjects who are instructed to report only "side effects" may be more likely to report a greater number of AEs than subjects instructed to report any changes in health.
- **Evidence-Based Medicine—**Finally, a dispassionate search for all effects—both positive and negative—fosters a sense of objectivity that is a hallmark of all scientific endeavors.

Working Toward Bias Elimination

The first step before undertaking any change in reporting practices is to verify the nature and scope of the suspected problem described here. If it should be determined that shortcomings due to typical AE reporting practice are pervasive, then the next step would be to determine how to address them.

It will take a groundswell of interest to eliminate biased reporting language from clinical trial data. While researchers, scientists, and pharmaceutical companies may take the initial step in creating an industry-wide dialogue and awareness on this issue, it will ultimately require the support and collaborative involvement of the FDA to eliminate biased reporting language.

This brief discussion of biased reporting language should be sufficient for the FDA and the pharmaceutical and medical device industries to recognize that similar events may not be interpreted and reported the same (or at all) by every subject, or be viewed by every investigator in every trial as "adverse." The informed consent instructs subjects to report all "changes in health"; therefore, all changes in health observed during the course of a clinical trial, including both "positive side effects" and "adverse events," should be sought and captured under the more neutral, unbiased term of "changes in health."

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HOME STUDY HS

Make Your Studies Smarter

OPEN BOOK TEST

This test expires on February 28, 2018

(original release date: 2/1/2017)

Quality Assurance Coordinators: Ensuring Quality at the Site Level

1. **Risk-based monitoring (RBM) approaches attempt to:**
- **A.** Decrease the number of data points
- **B.** Save resources
- **C.** Increase risk
- **D.** Shorten monitoring plans

2. **Some have claimed that RBM can reduce costs over traditional monitoring approaches by at least:**
- **A.** 10%
- **B.** 20%
- **C.** 25%
- **D.** 30%

3. **One way to enact safeguards and increase quality is for sites to:**
- **A.** Conduct new clinical trials
- **B.** Increase study team members' salaries
- **C.** Employ onsite quality assurance coordinators (QACs)
- **D.** Ignore RBM plans

4. **QACs may perform function like:**
1. Source data verification
2. Pharmacy and lab audits
3. Obtaining informed consent
4. Staff training
   - **A.** 1, 2, and 3 only
   - **B.** 1, 2, and 4 only
   - **C.** 1, 3, and 4 only
   - **D.** 2, 3, and 4 only

5. **Incorporating the QAC role will assist sites in the delivery of accurate clinical data, and encourage the focus on subject safety during the conduct of a clinical trial by:**
1. Developing quality assurance and quality control procedures
2. Focusing on process improvement
3. Having the QAC be part of the study team
4. Relying on an RBM approach
   - **A.** 1, 2, and 3 only
   - **B.** 1, 2, and 4 only
   - **C.** 1, 3, and 4 only
   - **D.** 2, 3, and 4 only

6. **The QAC may perform the following:**
1. Provide real-time monitoring of study data
2. Conduct study procedures
3. Conduct a dry run prior to study initiation
4. Ensure written procedures are in place that reflect study activity
   - **A.** 1, 2, and 3 only
   - **B.** 1, 2, and 4 only
   - **C.** 1, 3, and 4 only
   - **D.** 2, 3, and 4 only

7. **The QAC responsibilities are defined by:**
- **A.** The protocol
- **B.** U.S. Food and Drug Administration (FDA) regulations
- **C.** A clinical quality management plan
- **D.** An RBM plan

8. **Quality management plans:**
1. Take into account potential risks specific to each study
2. Include quality assurance activities
3. Include quality control activities
4. May not be amended after the initiation of the study
   - **A.** 1, 2, and 3 only
   - **B.** 1, 2, and 4 only
   - **C.** 1, 3, and 4 only
   - **D.** 2, 3, and 4 only

9. **QACs may have direct access to:**
1. FDA systems
2. Institutional review board systems
3. U.S. Department of Health and Human Services systems
4. Electronic medical records
   - **A.** 1 and 3 only
   - **B.** 1 and 4 only
   - **C.** 2 and 3 only
   - **D.** 2 and 4 only

10. **Benefits of the QAC role include:**
1. Real-time monitoring
2. Greater access to data and information
3. Increase in study budget
4. Better compliance with regulations
   - **A.** 1, 2, and 3 only
   - **B.** 1, 2, and 4 only
   - **C.** 1, 3, and 4 only
   - **D.** 2, 3, and 4 only

Need Help With Investigational Drug Management? Five Things Large Research Institutions Should Consider

11. **Based on the article, which of the following scenarios presents the greatest challenge for investigational drug management?**
- **A.** A central investigational pharmacy providing services for a single hospital campus
- **B.** Many outpatient clinics situated separately from hospital facilities, spread out across multiple regions, and individually providing investigational drugs to research participants
- **C.** Research drug trials primarily occurring in one geographical location
- **D.** A large organization that provides investigational drug management services through a central investigational pharmacy

12. **At what level should a centralized review of investigational drug management optimally be embedded?**
- **A.** Local institutional review board (IRB)
- **B.** External IRB
- **C.** Central IRB
- **D.** Institution-specific research approval process

13. **A centralized review of investigational drug management will be able to:**
- **A.** Resolve operational issues at each research site
- **B.** Comprehensively review all studies and sites handling investigational drugs and capture relevant data
- **C.** Bypass IRB approval
- **D.** Increase subject enrollment

14. **Which of the following should be considered when a principal investigator (PI) opts to manage investigational drugs at his or her own practice?**
- **A.** Convenience for the research team
- **B.** The experience of the research team with investigational drug handling
- **C.** The PI's academic rank
- **D.** The size of the practice and its office space

15. **Which of the following will decentralized institutions have a greater need to provide?**
- **A.** Centralized investigational pharmacy services
- **B.** Outsourced research staff
- **C.** Guidance documents, tools, and training based on ongoing reviews and audits
- **D.** Single IRB review

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

16. **Poorly designed protocols without specific instructions or plans for investigational drug handling and management will likely lead to:**
- **A.** Expedited IRB approval
- **B.** Accelerated study initiation
- **C.** Compliance with regulatory requirements
- **D.** Inconsistent investigational drug management

17. **For investigator-initiated studies, who is responsible for ensuring the quality of investigational drugs?**
- **A.** The local IRB
- **B.** The PI
- **C.** A central reviewer
- **D.** The U.S. Food and Drug Administration

18. **What is the function of a centralized reviewer with expertise in investigational drug management during the institutional approval review process?**
- **A.** Identify the necessary resources and procedures for investigational drug management to promote compliance with regulatory requirements and to facilitate research
- **B.** Write investigational drug handling procedures for individual sites
- **C.** Develop the study budget
- **D.** Purchase resources for drug management

19. **If a central research location receives and distributes an investigational product to multiple sites within a large organization, which of the following must be established in addition to other drug handling procedures?**
- **A.** Drug randomization
- **B.** Drug administration
- **C.** Subject enrollment
- **D.** Drug transport and tracking

20. **Which of the following formats will provide a more flexible and efficient approach for training and education within a large organization?**
- **A.** Face-to-face lectures
- **B.** On-the-job training
- **C.** Web-based courses
- **D.** Individualized coaching

OPINION: Is Bias Inherent in the Current Reporting Practices for Adverse Events?

21. **An adverse event is:**
- **A.** Any side effect directly attributable to a drug or device
- **B.** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
- **C.** Any negative symptom identified by a subject during the course of a clinical trial
- **D.** Any negative symptom or lab abnormality identified as a result of the drug under investigation

22. **The scientific method is:**
- **A.** Ultimately flawed, as evidenced by Heisenberg's principle of uncertainty
- **B.** Not utilized in human research because it would place human subjects at unacceptable risk
- **C.** A process of testing, under controlled conditions, the validity of a hypothesis as determined by the evaluation of measurements obtained during testing
- **D.** Only utilized in the laboratory setting where every possible variable can be controlled

23. **The first double-blind, controlled study in humans:**
- **A.** Yielded the first and only effective treatment for the common cold
- **B.** Was conducted on prisoners without their consent
- **C.** Was the streptomycin trial in 1946
- **D.** Was the patulin study in 1943

24. **Efforts to ensure the safety of human subjects in clinical trials:**
- **A.** Begin before a drug or device is first used by or on a volunteer study participant
- **B.** Are likely to be fully characterized only as Phase III studies are conducted
- **C.** Are of concern only when the U.S. Food and Drug Administration (FDA) is more interested in a product's safety vs. its efficacy
- **D.** Begin through the conduct of unofficial studies by researchers who are independent of the product's manufacturer

25. **The FDA's mission is to:**
- **A.** Protect the public health by assuring the quality of food and effectiveness of investigational drugs only
- **B.** Protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation
- **C.** Protect the public health by assuring the safety of medical devices only in response to consumer complaints
- **D.** Protect the public health by preventing foreign food and medical products from being used in the U.S.

26. **Error, as defined in the scientific method:**
- **A.** Will always invalidate the conclusions of a study
- **B.** Is readily detectable
- **C.** Is the difference between the true value of a measurement and the recorded value
- **D.** Can always be uncovered by careful statistical analysis

27. **Systematic error is:**
- **A.** An unintentional error due to chance
- **B.** Always intentional
- **C.** Due to faulty systems
- **D.** Also known as bias

28. **The publication that provides guidelines for evaluating the quality of clinical research is:**
- **A.** Cochrane Handbook for Systematic Reviews of Interventions
- **B.** Code of Federal Regulations
- **C.** Guidelines for Good Clinical Practice
- **D.** Cochrane Guide to Reputable Research

29. **"Positive" adverse events are:**
- **A.** Only discovered in Phase IV studies
- **B.** Tracked through patient registries
- **C.** The reason postmarketing surveillance is conducted
- **D.** Subjective in nature

30. **Possible benefits of identifying "positive" adverse events include:**
1. A greater understanding of a drug's mechanism of action
2. Identification of other possible uses for the drug under investigation
3. Fostering a sense of objectivity that is a hallmark of all scientific endeavors
4. Simplification of warning labels for prescription drugs

- **A.** 1, 2, and 3 only
- **B.** 1, 2, and 4 only
- **C.** 1, 3, and 4 only
- **D.** 2, 3, and 4 only