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[DOI: 10.14524/CR-17-0020]

The Hidden Value of **Onsite Monitoring**

PEER REVIEWED
Jerry Stein, PhD
Elham Einolhayat, RN

Electronic data capture (EDC), central monitoring, and risk-based monitoring (RBM) have been disruptive to the entire clinical research enterprise. These new technologies and processes offer the potential to increase efficiency while reducing onsite monitoring and data management costs. Sponsors and contract research organizations (CROs) are crafting standard operating procedures (SOPs) which will allow these changes to occur in their organizations, and they have been discussed extensively at professional meetings and in publications

Rarely discussed, however, is the role onsite monitoring plays in detecting high-level problems with the design of investigational test products, with the clinical protocol, and with site noncompliance or fraud.

Given recent and ongoing developments in monitoring practices, is traditional study site monitoring an historical anachronism? Would it be better if onsite monitoring were only applied to a few unique situations? These provocative questions are being discussed throughout the clinical trial enterprise. Indeed, with the growing adoption of EDC in conjunction with the increase in computer-assisted centralized monitoring and RBM processes, one might logically raise the question whether onsite monitoring should be significantly scaled back or totally abandoned.

Our view is that clinical monitoring operations have been significantly disrupted by the acceptance of these new and partially automated processes by regulatory bodies and their growing adoption by sponsors, CROs, and sites. In this article, we describe aspects of the overall topic that are rarely discussed, with special focus on the risks that accompany these trends and the underestimated value provided by onsite monitoring.

Purpose of Traditional Monitoring

Traditionally, a significant proportion of onsite monitoring has been devoted to ensuring that central site study files and source documentation are in place to safeguard human rights and verifying that all study information is accurate and properly documented.[1] Checking every datapoint in the sponsor's database against patient charts and other records is a major activity of traditional monitoring models representing a large proportion of the work done during most site visits.

In addition, monitors perform verification and accountability of study drugs or devices to confirm protocol adherence. Ultimate goals include confirming that the study was conducted per protocol, gaining an increased assurance that the safety and human rights of subjects were protected, and ensuring a diminished likelihood that auditors will find deficiencies in the study conduct.

Onsite monitoring is often responsible for identifying high-level issues that impact the outcome of entire projects, and which often are only discussed behind closed doors.

Evolution of the New Processes

Given the intentions stated above, what are the key advantages offered by the new processes and technologies impacting monitoring styles? The Clinical Trials Transformation Initiative (CTTI) has addressed many of these factors with one key conclusion from this source being that the amount of effort required in traditional onsite monitoring did not justify the resources applied to this activity. Part of this conclusion was based on economic and statistical arguments. Specifically, it was asserted that the occasional random error that occurs during a large clinical study should not make an appreciable or statistical significant difference to bottom line determinations of safety and efficacy.[2–5]

These conclusions, along with public comment, were incorporated into the 2011 U.S. Food and Drug Administration (FDA) guidance on RBM.[6,7] The guidance states that there are "a variety of acceptable approaches to fulfill monitoring responsibilities," and that monitoring should be focused on critical, higher risk clinical sites and data that impact subject safety and data reliability. Also, it emphasizes that monitoring plans should be dynamic and reflect the discovery of new information.

The implications of the guidance on monitoring, as well as those of similar International Council for Harmonization and International Organization for Standardization documents, have been published extensively in this journal and elsewhere.[1,8–17] Sponsors are slowly implementing changes that have the potential to significantly impact long-held practices, and monitoring organizations are carefully adjusting their SOPs and (hopefully) watching out for unintended consequences.

We are in the midst of a "formative" period—one in which sponsor/CRO processes can be influenced; therefore, before the new monitoring practices become standardized across the industry, it is important to raise concerns, some of which have hardly ever been discussed or published.

This new paradigm envisions a monitoring and database validation process with a higher level of efficiency and reduced cost, as well as the following advantages:

- If site personnel are responsible for entering data directly into electronic systems, transcription errors will be reduced significantly, compared to the process of using paper case report forms (CRFs) and other hard copy study documents as source documentation.
- Out of range or inconsistent data values can be proactively rejected prior to data being saved, as they would be identified by automated, pre-identified edit checks and/or centralized data reviews.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.

- Essential study documents can be stored in central repositories that provide site personnel, monitors, and sponsors with remote electronic access.

Since clinical monitoring is one of the most time-consuming and expensive product development activities, even a small change in the amount of onsite monitoring will have a large impact on product development costs.[1,18,19] Monitors will have more time to concentrate on problematic subjects or entire sites identified remotely by the new systems. On a higher level, RBM and properly applied centralized monitoring has the potential to identify anomalies at both the site and study levels that might not be apparent without automated processes.

Benefit of Onsite Monitoring

While the new processes have several important advantages, those already provided by traditional onsite monitoring models must be addressed. The following sections expound on these advantages, which are summarized in Table 1.

PROBLEMS TO BE DISCRETE ABOUT

Onsite monitoring is often responsible for identifying high-level issues that impact the outcome of entire projects, and which often are only discussed behind closed doors. Frequently, these tales concern inadvertent noncompliance, known but uncorrected errors, or outright fraud by site personnel. These incidents are not often discussed publicly for obvious reasons, as the reputations of sponsors, clinical research associates (CRAs), and sites are at risk.

A false accusation or the promulgation of a rumor can have significant consequences on organizations and individuals. There are often moral, legal, and financial implications, including delays in or rejections of regulatory marketing approvals when data from a single site are excluded.

For example, if a study site's data are suspect, a company may elect to present two analyses of the study results—one with the suspect data included and one without. Preparation of two analyses requires a significant amount of additional resources. There is also the possibility that the smaller database will have an insufficient number of study subjects to meet *a priori* statistical objectives. In this case, the sponsor may be forced to re-open enrollment to recruit additional subjects for meeting the needs of statistical analyses.

PROBLEMS DIFFICULT TO DETECT

Seasoned monitors often identify significant issues that can never be detected in databases. Three problems are particularly difficult to detect from a distance:

- First, there can be problems encountered by subjects or site personnel when attempting to use investigational products. Ease of use, malfunctions, or other investigational product–related difficulties encountered by end-users are often important factors not sufficiently captured in electronic or paper questionnaires. Crafting the perfect CRF or patient-reported outcome questionnaire is often very difficult until the investigational product has been used by hundreds of subjects. In the case of rare events (e.g., 0.01% incidence), an observation might not occur during the entire clinical development program. Basically, you don't know what you don't know. If a drug is too hard to mix or apply, or if a device is too difficult to operate, compliance can be significantly impacted. Perhaps the greater risk is that poor product design will be tolerated in the clinical study setting, but will be rejected once the product is approved, released, and marketed.

TABLE 1: Relative Effectiveness of Monitoring Technique

Type of Issue	Relative Effectiveness (★ = minimum; ★★★★★ = maximum)	
	Electronic Data Capture/ Central Monitoring/ Risk-Based Monitoring	Traditional Onsite Monitoring
Inconsistencies within the database	★★★★★	★★★
Inconsistences between source documents, study site trial master file, and database	★★★★	★★★
Noncompliance by end-user conduct	★★	★★★
Noncompliance by site personnel	★★	★★★★
Detecting problems with the protocol or investigational product	★★★	★★★★
Clinical supply accountability	★★★★★	★★★

- Ironically, the second type of problem that is not easily detected remotely involves site personnel and study participants dutifully executing the procedures as described in the protocol. The number of procedures mandated in each protocol has increased, and study visits have become longer and more complicated.[1,18] This has several potential effects, including how, for study subjects and site personnel, excessively long study visits can lead to fatigue and inaccuracies in both objective and subject test results. The duration of office visits can make recruitment more difficult and inadvertently impact the type of subjects who elect to enroll. For the study monitors, more errors lead to excessive time devoted to reconciling databases with source documentation, which poses an unnecessary distraction. An increase in data variability, especially if concentrated in one of the treatment groups, makes it more difficult for sponsors to detect important safety and efficacy signals. Onsite monitoring is a very effective method for recognizing that study visits are too long or procedures too complex.
- The third type of issue that is difficult to identify from a distance covers insufficient investigator oversight, fraud, and noncompliance. This includes confirmation that the principal investigator (PI) understands and is properly carrying out his/her responsibilities. The same applies to sub-investigators, study coordinators, and other site personnel. Too many monitoring visits (and FDA inspections) reveal that PIs have inappropriately delegated key activities to site personnel or not maintained active control. These important noncompliance incidents can be detected by the good detective work provided by experienced monitors.

AN INSPECTOR CALLS…

The FDA's website[20] has many examples of issues discovered at study sites by their inspectors; however, these reports have been heavily edited and do not emphasize the impact on study sponsors. Here are some real-life examples from our personal experiences that may help communicate these concerns:

- Several years ago, we learned about a study that seemed to be progressing quite nicely based on the receipt of CRFs and periodic remote contact. The PI was conducting the study at two urban offices. Enrollment had progressed reasonably well and the number of database errors was proportionately appropriate. While the source documentation matched the CRFs, a routine monitoring visit uncovered some serious concerns. An examination of the front desk calendar revealed that the PI, the only individual authorized to perform several key medical procedures, was at the wrong office on several study visit days. The CRF visit days did not match the front desk calendars. This was a significant deviation that invalidated a significant number of datapoints and raised concerns about all study data. Ultimately, the site's participation in the study was prematurely terminated.
- In another case, a six-month study had progressed well with a good start-up visit followed by good enrollment. Overall, the responsiveness of the site to phone calls and other contacts with the sponsor was outstanding. CRFs were unremarkable. At the Month-3 milestone, a routine monitoring visit uncovered a significant problem. The study coordinator pulled the monitor aside and demonstrated that the investigational medical device malfunctioned when the instructions for use were followed. Specifically, the combination of two investigational products led to excessive foaming that spilled the investigational solution out of the designated vial and left it puddled on the table. This had not been previously reported to the sponsor because there was no place on the CRF to report this type of event, and the site had not reported it in any communication to the sponsor. The study was terminated early and the project abandoned.
- In another occurrence, a large study was close to meeting its enrollment goal when sponsor audits revealed that many adverse events and serious adverse events found in source documentation had no follow-up documentation and/or had not been reported. This caused a significant delay in the study timelines and raised many quality issues that had to be ironed out.

Our view is that clinical monitoring operations have been significantly disrupted by the acceptance of these new and partially automated processes by regulatory bodies and their growing adoption by sponsors, CROs, and sites.

We are in the midst of a "formative" period—one in which sponsor/CRO processes can be influenced; therefore, before the new monitoring practices become standardized across the industry, it is important to raise concerns, some of which are hardly ever discussed or published.

- Elsewhere, six weeks after institutional review board (IRB) approval and receipt of investigational products, an onsite visit revealed that no one had enrolled in a study despite frequent dialog with the site personnel claiming that 12 subjects had been enrolled and randomized (Note: The new processes cannot totally eliminate this problem, since the availability of an EDC system does not guarantee timely data entry by site personnel).
- Then there was the case in which an onsite visit revealed that the duration and complexity of the office exams was excessive—twice as long as planned—and may have led to excess fatigue and data variability.
- An onsite visit regarding another study revealed that site personnel had prepared their own set of in-office written instructions for site personnel and subjects that had not been vetted by the IRB or the sponsor.
- During an onsite visit elsewhere, it was noted that a site staff member with many years of clinical research experience used pencil to document all study data. Per the study coordinator, this would allow her to erase "mistakes" and write over the correct data with a pen.

Remote communication processes between the site and the sponsor/CRO that would detect these types of incidents are often not in place, or are inadequate. The same can be said with cross-checks within electronic databases. In addition, once these deviations are detected, the processes used within sponsor or CRO organizations to manage these events are of potential concern.

Sponsor/CRO organizations typically have well-developed SOPs that specify that noncompliance or suspected fraud must be immediately reported to management and quality assurance departments. Such SOPs mandate many well-defined steps to protect all parties: the monitor, the sponsor, the site, and the subject/public good. However, critics can easily identify conflict of interest factors.

These study site incidents are often complex and rarely receive external visibility due to confidentiality and liability concerns. Feedback to sites suspected of significant noncompliance is often kept intentionally vague. Perhaps more importantly, bad apples often remain in the barrel. The original sponsor may not use the site again, but a competitor may. Confidentiality concerns and the competitive environment are often barriers to the free exchange of this information.

Best Practices

What is the ideal? What are best practices? The potential for improving our processing using EDC, central monitoring, and RBM is extraordinary. It is a significant modernization that needs to move forward. The clinical research enterprise needs to leverage the use of automation to improve efficiency and reduce costs.

However, practical experience accrued from years of traditional monitoring indicates that these new technologies and processes only make sense when used in conjunction with monitoring and data management plans that allow for customization. The customization needs to address:

1. the challenges presented by each specific protocol (e.g., complexity; development stage; project criticality; safety risk);
2. the experience and skill of the site personnel (e.g., certified personnel or novice);
3. the experience of the sponsor or the sponsor/CRO's organization with this type of study;
4. the experience of the specific personnel assigned by the sponsor/CRO to the project; and
5. any new evidence of major noncompliance found during the course of the study.

Frequent onsite monitoring with 100% source data verification should be required at all sites unless evidence is presented to support another approach. Essentially, clinical study managers should build their plans by assuming that noncompliance will occur if the site were allowed to operate without intense intervention (guilty unless proven innocent). Less intensive onsite monitoring should occur only when it is justified, and all monitoring plans periodically reviewed based on available evidence.

Finally, the quality and frequency of site visits needs to be addressed. Quality is highly dependent on the detective work provided by CRAs who have a strong foundation of extensive training and experience. ACRP's Certified Clinical Research Associate (CCRA®) program has recognized the requisite skill sets, and most organizations impose a field-training element.

These study site incidents are often complex and rarely receive external visibility due to confidentiality and liability concerns. Feedback to sites suspected of significant noncompliance is often kept intentionally vague. Perhaps more importantly, bad apples often remain in the barrel.

The full utilization of a CRA's skills requires a good relationship between the monitor and the site personnel; however, the concern amongst many clinical research professionals is that the new monitoring models will reduce the number of site visits and contact time with key site personnel.[13,21] Success building professional relationships may be adversely impacted if visits are inappropriately reduced.

Many of the noncompliance incidents described above were uncovered when CRAs asked questions that were not specified in monitoring plans. The discoveries relied on personal relationships developed over time. Sponsors and CROs should be concerned that the pressure to reduce onsite monitoring time combined with high turnover rate amongst monitors will spur unwelcome consequences in product development.

Summary and Conclusions

The potential for efficiency improvements using the new data monitoring tools and processes is significant. There is an opportunity to significantly reduce development costs and improve data quality. However, the clinical research literature has rarely focused on the problems that cannot be detected without the onsite presence of a skilled monitor.

While the safety risk to individual subjects or the risk to the project may appear to be small, the hidden, underestimated value provided by onsite monitoring is significant. Companies should seek the appropriate balance between remote and onsite monitoring that will take advantages of new technologies while maintaining the benefits provided by site visits.

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[DOI: 10.14524/CR-17-0022]

The Real Reason Sites Need *eSource*

PEER REVIEWED

Raymond Nomizu, JD

Most discussion about electronic source (eSource) documentation in the clinical research enterprise starts from a sponsor standpoint, with eSource being viewed as an extension—almost a mobile version—of electronic data capture (EDC). In this view, sponsors provide sites with eSource systems that the sites use to collect data, which are then transmitted to the EDC system. This is a sensible view, but it misses a bigger opportunity. Independent of a sponsor mandate, sites need eSource technology for one fundamental reason: to manage complex operations in an efficient and high-quality manner.

Clinical research is a complicated business. Research protocols are nuanced, with numerous requirements for patient compliance, investigational product administration, clinical procedures, and data capture. To execute protocols properly requires extensive and rigorous project planning, task management, and data collection processes.

However, to date, few good technology options have existed that enable sites to manage these processes efficiently. Electronic health record (EHR) systems, for instance, are not optimized for clinical research and lack critical features sites need, such as the ability to easily build research-specific templates, pre-program visit windows, or provide isolated, study-specific views to clinical research associates (CRAs). As a result, 96% of site staff recently surveyed report using paper, and not EHR, as their primary data collection tool.1

Without good technology, sites end up spending too much time on inefficient and error-prone pen-and-paper processes. This misallocation of time limits the attention site staff can devote to patient recruitment and retention, and serves as a drag on the financial health of the industry.

Without good technology, sites end up spending too much time on inefficient and error-prone pen-and-paper processes. This misallocation of time limits the attention site staff can devote to patient recruitment and retention, and serves as a drag on the financial health of the industry.

TABLE 1: Average Metrics for Phase III Protocols

	2001–05	2011–15
Endpoints	7	13
Eligibility criteria	31	50
Procedures	110	187
Visits	12	15
Number of sites	124	196

Source: Tufts Center for the Study of Drug Development[2]

The Growing Complexity of Research Protocols

The complexity of clinical research seems to be an ever-growing trend. As Table 1 indicates, Phase III studies have more visits, procedures, endpoints, and eligibility criteria than they did 10 years ago.[2] All of this complexity leads to greater data collection requirements, which in turn lead to more complex research procedures.

It is hard to execute many clinical trial procedures accurately using pen and paper. Take, for instance, a "simple" procedure such as contraception. The purpose of this procedure is to ensure that subjects do not become pregnant or cause pregnancy during the course of a study. Nearly every interventional drug study will have a requirement that women of childbearing potential agree to use contraception during the life of the study.

Table 2 depicts actual variations across study protocols in how the contraception requirement is to be fulfilled. As the table shows, protocols differ in their definition of "post-menopausal," what procedures are considered surgical sterilization, how much and what kind of contraception is required, and what is required of male subjects.

This complexity is difficult to manage using paper templates. Figure 1 shows an actual example of a paper source template written by a research site against one of the "female contraception requirement" protocols above. Note how easy it is to miss checkboxes or branching logic. For example, a harried coordinator could check off "N/A [Male]" at the top, but then miss the requirement that the male subject be educated about refraining from sperm donation.

Coordinators routinely miss required data fields because paper is not interactive and does not provide the real-time alerts to ensure accurate data at point of capture. CRAs may come to visit a site weeks after the fact and catch a mistake, which means the coordinator then has to update the missing data field (often requiring a call to a patient for follow-up). Because the paper source was not adequately completed in the first place, a coordinator has to spend precious time on data correction down the road.

This "simple" procedure isn't so simple then! The average study could easily have more than 20 procedures. Picture a small research site with five coordinators who manage 15 studies at any given time and have to collect data against 300 complex and unique requirement sets.

Collecting Data Outside Visits is Also Challenging

The above example is about data collected during a visit; however, research trials require extensive management of tasks before and after visits. For instance, coordinators have to schedule visits within precise visit windows (e.g., the Week 8 visit must be eight weeks from Baseline Visit, plus/minus three days). Coordinators must keep track of new informed consent form (ICF) versions and re-consent patients before conducting procedures at their next visit, and keep track of central lab results, ECG interpretations, third-party medical records, and other documents that come in between visits, and which are critical to determining eligibility.

TABLE 2: Sample Protocol Language on Childbearing Potential/Contraception

	Protocol 1	**Protocol 2**	**Protocol 3**
Female contraception requirement	1 from pre-defined list	2 from pre-defined list	2, including 1 from "highly effective" sub-list
Surgical sterilization	Includes tubal ligation	Excludes tubal ligation	Includes tubal ligation
"Post-menopausal" defined as	12 months	24 months	12 months
Male contraception requirement	1 from pre-defined list and cannot donate sperm	None	2, including 1 from "highly effective" sub-list

Research staff have to manage patient compliance; they often have to schedule offsite procedures, train patients how to use diaries, and check online patient portals to track compliance. They must remind patients prior to certain visits of visit-specific requirements, such as medication wash-out, fasting, or exceptions from their normal study routine (e.g., skip the morning dose of study medication).

Here's an example of a *single protocol* that had differing visit requirements within the same study:

- Visit A: Fasting visit
- Visit B: Fasting visit and skip morning dose
- Visit C: Take morning dose but time visit so pharmacokinetic sample can be done within two to four hours of dose
- All other visits: No fasting; take morning dose on the day of the visit

With all this complexity, before, during, and after a visit, is it any wonder that sites struggle to keep up with the demands of modern protocols?

The Research Industry Needs Operational Technology

Every modern industry utilizes technology to streamline and automate operations. Can you imagine a bank balancing its ledgers with paper books? Or a major retailer managing inventory from paper logs?

Just like banks or retailers, research sites are running complex *operations,* but unlike other industries, too many sites are running these operations using pen-and-paper processes. Inventory is kept on paper logs (the "investigational product [IP] logs"); design specifications (the source templates) are done in Word and then printed out and delivered by hand to the production staff (the research teams); production (data capture) is done manually, with no technological guardrails.

In such an environment, quality of output rises and falls with the individual skill and commitment of the person doing it. This is why site-centric eSource technology can significantly improve operations. Well-designed eSource technology allows sites to construct and put in place technological guardrails against protocol deviations, and to automate processes that are routine, such as ICF version tracking, visit window calculation, or body mass index and other calculations. It standardizes workflow and makes output less dependent on the individual coordinator's skills.

Site-centric eSource technology features should, at minimum, allow sites to:

- design and manage all of their own studies in a single platform;
- house research-specific templates and create their own for future use;
- collect data and receive real-time alerts to ensure accurate data collection;
- provide CRAs with study-specific, anonymized access to view and quality control subjects and visits;
- enables routing, digital annotation, and e-signature of lab reports, ECG tracings, and other documents; and
- take advantage of research-specific workflows such as visit scheduling, ICF version tracking, internal quality control, patient reminders, and task management.

What would be the impact of a technology like this on site operations? Technology like this should:

- Save significant time by reducing the need to print and manage paper binders, populate data fields that can be automated, reduce re-work, and eliminate the need to transport binders. A site that recently adopted eSource, in fact, reported productivity gains of 20% compared to its previous paper-based process.[3]
- Enhance principal investigator (PI) oversight by allowing them to access and modify source data at any time. For instance, if a patient has a high-risk adverse event (AE) while the PI is offsite, the PI could log into the eSource record to review the AE and related information, thus facilitating timely assessment and action.

FIGURE 1: Sample Paper Source Template

CONTRACEPTION [BIRTH CONTROL] ❒ Not Done

Is the subject of Childbearing Status? ❒ Yes ❒ No ❒ N/A [Male]

If no, which of the following applies to the subject:

❒ ***Post Menopausal***

❒ ***Surgically Sterile*** ➡ **Select One:** ❒ **Hysterectomy** ❒ **Bilateral Oophorectomy** ❒ **Tubal Ligation**

What method of birth control does the subject *[MALE OR FEMALE]* use and agree to continue to use throughout the study?

- ❒ **Hormonal contraceptives (ie, oral, patch, injection, implant)**
- ❒ **Male condom with intravaginal spermicide**
- ❒ **Diaphragm or cervical cap with spermicide**
- ❒ **Vaginal contraceptive ring**
- ❒ **Intrauterine device**
- ❒ **Vasectomized partner**
- ❒ **Sexual abstinence**
- ❒ **MALE SUBJECTS ONLY: Male participants should refrain from donating sperm during study**

Coordinator Signature: _____ _____ / _____ / _____

Well-designed eSource technology allows sites to construct and put in place technological guardrails against protocol deviations, and to automate processes that are routine.

The biggest challenge comes from the learning curve faced in the adoption of any new technology and workflow. Every member of the site must adopt the technology and accompanying process changes.

- Improve quality through the use of real-time alerts to guide investigators and coordinators as they complete data entry. A third-party auditor, for instance, found that well-designed eSource provides safeguards against 50% of the most commonly cited deviations.[4]
- Enable more rapid onboarding of new employees by standardizing their workflow, and enable more coverage among site staff. For instance, back-up coordinators are much more likely to be successful if they can work with interactive eSource, and not to have to rely on soft knowledge of a protocol that the prime coordinator has through extensive training.

What are the Challenges and Caveats to Implementation?

The biggest challenge comes from the learning curve faced in the adoption of any new technology and workflow. Every member of the site must adopt the technology and accompanying process changes.

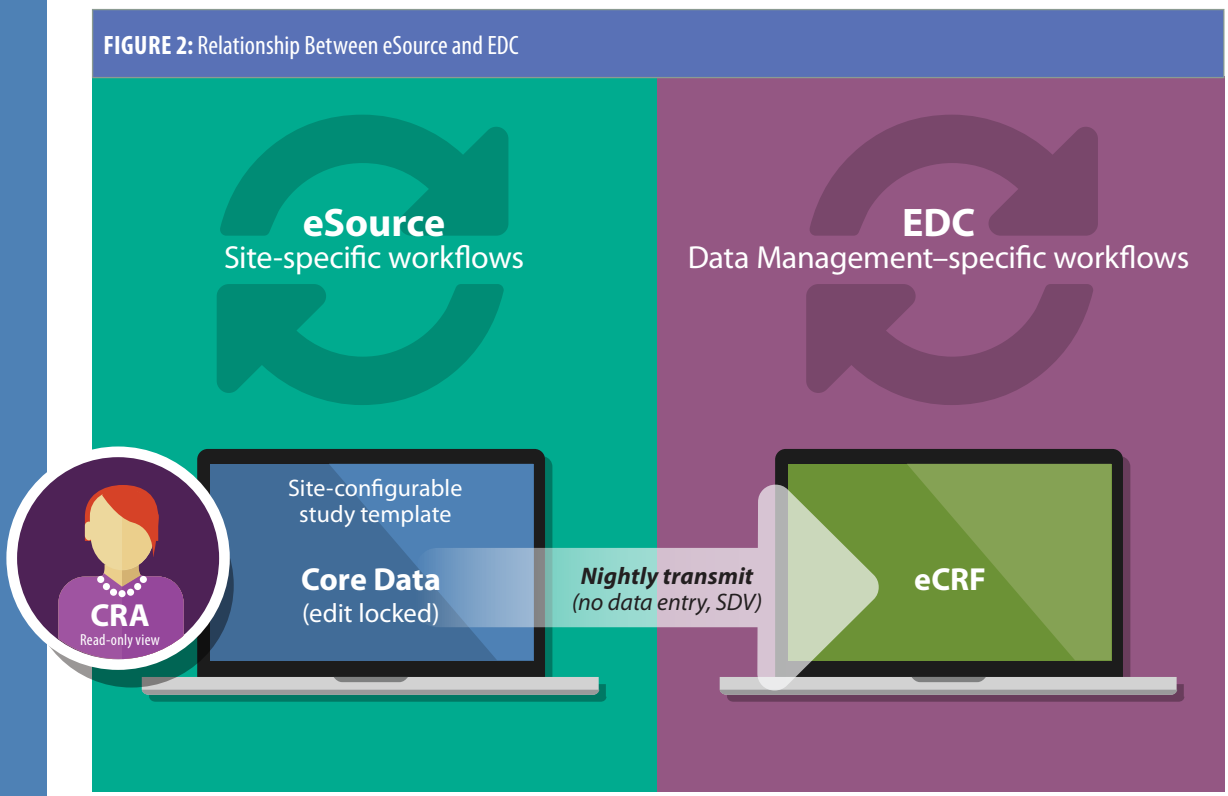
For many, real-time EDC will be a new experience. It may not feel as "real" or as substantive as handwritten paper templates. The templates will likely present themselves differently than on paper; there will be new features and workflows to master.

To overcome these challenges, site management needs to implement a staged roll-out accompanied by extensive staff training and communication.

Sites must also develop, or outsource, a strong eSource design capability. As with paper source templates, eSource templates need to be thoughtfully designed and tailored to protocol requirements. In addition, they should incorporate appropriate use of technological features such as alerts and branching logic. Only when the templates are well designed will the site realize significant efficiency and data quality gains, so site management should identify, at the outset, who will be designing their eSource templates and how they will be trained. They should also develop robust processes for eSource template design and quality control.

In addition, site leaders must ensure that any eSource system used complies with local regulations. The PI is ultimately responsible for compliance (not the vendor), and this means that sites should have in place an eSource standard operating procedure governing the use of the technology as well as documentation concerning the system's compliance with regulatory requirements. For the U.S., this means compliance with expectations regarding electronic records and electronic signatures found in 21 CFR Part 11 of the *Code of Federal*

FIGURE 2: Relationship Between eSource and EDC



Regulations. For the European Union, this means compliance with Annex 11 to Volume 4 of the Rules Governing Medicinal Products in the European Community, Computerized Systems.

Sites also may need to manage other stakeholders. For large healthcare networks, that may mean the engagement and approval of groups tasked with procurement, compliance, technology, or governance. If site leaders anticipate that only staff members and not patients will use the system, they will likely not need local institutional review board (IRB) approval, although they should check their IRB's requirements first.

For industry-funded trials, sites need to develop a policy on how and when to notify sponsors and provide access to, and train, the CRAs. While the PI has the absolute right to use electronic instead of paper source, site management must factor in the sponsor's right to ascertain compliance and the CRAs' need for access.

Finally, site personnel should understand that while there are basic regulatory requirements that govern the use of eSource, the technology is new and no standards have emerged. Since eSource is an internal workflow tool, sites do not need interoperability with other systems to reap the benefits. However, site leaders may want to consider how eSource can or will integrate with other systems, such as sponsor EDC systems. If using an outside vendor, they may ask about interoperability with EDC systems and the vendor's adherence to Clinical Data Interchange Standards Consortium (CDISC) standards, which are a set of protocols that govern the transference and presentation of data within the clinical research industry.

How Would This Work with EDC Systems?

Many eSource systems start with the needs of the EDC system; however, as discussed above, a good eSource system should start with the needs of the site. Ideally, the two systems "talk" to each other to enable seamless flow of data from eSource to EDC.

Figure 2 depicts the ideal relationship between eSource and EDC. The left-hand side depicts eSource as a workflow tool optimized for research sites. The right-hand side depicts EDC as a workflow tool optimized for the sponsor's data management group.

The eSource template contains all the data required to populate the electronic case report form (eCRF) *plus all the compliance data* required to document protocol compliance. For example, while eCRF might require that only the systolic and diastolic blood pressure be entered, the equivalent eSource might include documentation on the patient's position (e.g., sitting), the time of position, the time of vitals, and the arm used. All of these data elements are important to document that the vitals were obtained in a manner consistent with the protocol.

In this model, a subset of the eSource data fields are mapped to their eCRF-equivalent data fields. These data fields should be edit locked, so that the user does not "break" the integration by modifying them. The rest of the eSource data fields relate to protocol compliance and site workflows, and have no analogous eCRF fields. These fields can be configured by the site.

This arrangement has numerous advantages:

- It preserves site independence since the site's data are housed in a separate database.
- It allows sites to configure source templates to match site workflow requirements, while standardizing the fields that are required to preserve the integrity of the eCRF mapping for sponsor analysis.
- It enables an "opt in" strategy, in which sponsors can standardize their data collection on a single, global platform across the trial, while individual sites can opt to use an eSource system or traditional manual data capture with subsequent data entry.

A data model like this ensures that site staff can use a workflow tool that meets their needs, while realizing the efficiency of EDC integration. When free to choose their own system, site leaders are incentivized to select one that maximizes their own staff productivity.

Conclusion

Increasingly, sites are recognizing the advantages of technology and incorporating it into workflows. Many have adopted the recent spate of purpose-built eRegulatory or eSource solutions provided by vendors, without waiting for data integrations that will take longer to mature. In going paperless, these sites are furthering the evolution of the industry to a more technology-centric approach, which will be critical to manage the ever-growing complexity of clinical trials.

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[DOI: 10.14524/CR-17-0023]

STANDARD OPERATING PROCEDURES

Critical Components of Quality at Clinical Research Sites

PEER REVIEWED | Soumya J. Niranjan, BPharm, MS, CCRP

The U.S. Food and Drug Administration (FDA) expects clinical researchers to abide by standards of Good Clinical Practice (GCP), and when they are not in compliance, investigators are subject to receiving a Warning Letter from the FDA. Between January 2005 and December 2010, 129 Warning Letters were issued to investigators, with the most common deviations at study sites being noncompliance with the investigational plan, failure to maintain accurate and adequate case histories, and informed consent issues.[1] The frequency of these deviations and, consequently, the receipt of Warning Letters can be greatly minimized if standard operating procedures (SOPs) are in place for all study-related activities at research sites.

In clinical research, SOPs are detailed instructions that help define and standardize how and by whom a unit's procedures are conducted to assure execution of research tasks in accordance with institutional, state, and federal guidances. According to the International Council for Harmonization (ICH) Guideline for GCP E6 2.13, "Systems with procedures that assure the quality of every aspect of the trial should be implemented." This is generally accomplished through the implementation of an SOP program.[2] The ICH GCP guideline is upheld by regulatory authorities in the U.S., Canada, European Union, Japan, and Switzerland.

Quality in clinical research starts with a systems approach.[3] In this context, "systems" include training programs, role definition, organizational structure, responsibilities and accountability, SOPs, and metrics. All clinical research sites should have quality systems to ensure that the clinical trials conducted are of the highest quality and in compliance with the tenets of GCP, study protocols, and local and federal requirements. In essence, SOPs answer the who, what, when, where, and how questions of all clinical trial activities and its management.

Thus, SOPs serve the following objectives:

- Improve and maintain quality of operations
- Standardize working practices
- Ensure high-quality, consistent, and reproducible results
- Define best practices
- Define roles and responsibilities of the individuals involved
- Ensure compliance with GCP guidance and regulatory guidelines
- Save time

FDA Recommendations

A key part of quality is consistent performance of procedures producing a consistent result. A critical part of these quality actions is developing SOPs, so that anyone performing the procedure will complete it in the same way and produce the same result. In addition to providing a standard for procedures, SOPs provide training information for new hires on what kinds of clinical trial activities are ongoing at their new workplace.

Further, SOPs set the measure for quality results so staff performance can be measured to the standard required.[4] Establishing and improving quality of clinical trials requires the use of the systems approach, tools, and models. In this regard, FDA recommends a four-step systems approach[5]: (a) Say what you do (b) Do what you say (c) Prove it (d) Improve it.

SAY WHAT YOU DO

The site should have a qualified and responsible management team to provide governance of the clinical trial process in its entirety. SOPs should define procedures and responsibilities for all key clinical trial processes, from site qualification to site close out.

DO WHAT YOU SAY

This step largely describes uniform education and training of all site staff regarding the trial protocol, study requirements, policies, and procedures. All site staff need in-depth training in regulatory requirements, ethics, consent process, and protocol compliance.[6] Needless to say, it is imperative that site staff are aware of their responsibilities.

PROVE IT

This step utilizes risk-based monitoring and trend analysis, which would be functions of an institution's internal quality assurance unit.[7] Risk-based monitoring focuses on process management and verification of critical activities, including quality control, to ensure that they are carried out as planned.[4] Trend analysis looks at data as compliance intelligence, and employs such approaches as statistical monitoring to assess data trends across the sites and trials with an objective of proactively identifying and evaluating compliance signals and unanticipated risks.[4]

IMPROVE IT

Improving quality will require actions—namely, effective corrective and preventive actions (CAPAs). For a CAPA plan to be effective, there should be an in-depth analysis of the root cause of any issue that is degrading quality at a site, and a search for an action plan that can provide long-term and sustainable solutions.[5] The system and processes should be reassessed to ascertain how the problem occurred in the first place.[6,8]

Get Your Studies Off to the Right Start

Take control of your processes and ensure compliance with your organization's SOPs and study regulatory requirements. The central feature of mapping out the required SOPs is a list of the steps or activities that constitute the required task. One way to do this is to begin by creating a flowchart of the clinical research process (cradle to grave); identify the individual steps (what to do) and place them in logical order.[9]

Based on the author's perspective, here are the three most important SOPs that any site should develop and apply to the conduct of clinical research:

1. **SOP for Preparing and Maintaining SOPs**—This is the primary SOP, as it helps in preparing, maintaining, numbering, and formatting SOPs. It helps the research team to prepare SOPs that comply with the guidelines set by ICH GCP and regulatory authorities.
2. **SOP for Responsibilities of the Research Team**—This SOP defines the responsibilities of the research team, such that all conditions defined by the relevant regulatory authority on the use of investigational articles are followed. The principal investigator acts as the head of the team and is responsible for implementing the guidelines. This in turn will help in preparing SOPs detailing each of the tasks under site staff responsibility. For example, it is the responsibility of the investigator to assess adverse events. This will help in preparing an SOP detailing toxicity evaluations, as just one example.
3. **SOP for Training and Education**—This SOP defines the standard training procedures that must be adopted to ensure that clinical research is carried out in a responsible manner. The purpose of the SOP is to define guidelines for GCP at the site in compliance with regulatory expectations.

In essence, SOPs answer the who, what, when, where, and how questions of all clinical trial activities and its management.

Accordingly, the most common SOPs present at research sites in the author's experience are:

- GCP Training
- Authority and Delegations of Responsibilities of Research Staff
- Subject Screening and Recruitment
- Informed Consent Process and Documentation
- Eligibility Confirmation
- Source Documentation
- Data Management
- Protocol Deviations
- Adverse Events and Serious Adverse Events Reporting
- Drug/Device Storage, Accountability, and Management
- Regulatory Document Submission Process (Initial Submissions, Amendments, and Continuing Reviews)
- Sample Processing and Shipping Procedure and its Training
- Monitoring Visits
- Sponsor, Contract Research Organization, and Internal Audits
- FDA Audits
- Writing SOPs
- Record Organization and Retention
- Sub-Site/Ancillary Site Management

Indeed, FDA's 2009 guidance on investigator responsibilities[10] recommends that sites have procedures for many study activities, including ones to ensure high-quality source data, protocol compliance, and proper adverse event reporting.

Who Writes SOPs and How Should They be Written?

The process of developing an effective SOP is critical to its successful implementation, and the process should be inclusive.[11] Highly successful managers actively engage their teams, and it is human nature that people support what they help create. Thus, managers who write SOPs without input from workers run the risk of upsetting them, while those who enlist the talents of their workers increase buy-in.

Apparently, the most convincing reason to involve others is that individuals who participate in the process are positive about generating ideas, accept the SOPs, and feel a sense of ownership in them, which is not the case when workers feel that management is imposing an SOP without regard to their input.[12]

As suggested above, start with an overall view. Once the process is mapped, improvisations, revisions, and edits must be expected. Then, turn the flowchart into a narrative that assigns process steps to roles (who will do it) and includes details as necessary (how to do it).[9]

Highly successful managers actively engage their teams, and it is human nature that people support what they help create. Thus, managers who write SOPs without input from workers run the risk of upsetting them, while those who enlist the talents of their workers increase buy-in.

Zimmerman[13] discusses an eight-step process for writing SOPs that involves the following:

- Process Mapping
- Authoring
- Formatting (includes language considerations)
- Editing
- Authorizing
- Training
- Implementing
- Revising and Archiving

During SOP development, start with an understanding of such sections of the *Code of Federal Regulations* as 45 CFR 46 (pertaining to research overseen by the Office for Human Research Protections [OHRP]) and 21 CFR 50, 56, and 312 (pertaining to research overseen by FDA); the ICH GCP guidelines and other pertinent guidance from OHRP and FDA; and applicable institutional policies. As written previously, include representatives from every impacted institutional area in the process.

SOPs should not merely duplicate regulations or guidelines; rather, they should be instructive as to how the regulations and guidelines will be followed in a consistent manner. Each procedure should be clearly and concisely written with little room for interpretation, while ensuring that the procedure is compliant with applicable laws and regulations. A good SOP should clearly identify the scope, be separated into easily identifiable sections, and include responsibilities for specific tasks, detailed procedures to perform tasks, and any associated documents/forms/tools to support the work governed by the SOP, such as checklists and templates.[14]

The benefits of SOPs are obvious, in that they provide a level of formal accountability for team members and prevent noncompliance on a systemic level. They help to ensure that all research conducted as part of the clinical trial follows federal regulations, ICH GCP, and institutional policies. They ensure processes have been examined, optimized, and standardized.

If used right, SOPs can provide valuable sustenance to new employees in need of details on how activities are required to be performed. Most importantly, SOPs allow for continued operations if a key staff member is unavailable. By referring to the SOP, someone can handle an urgent task and do it correctly the first time. This becomes necessary especially if research sites are experiencing high turnover rate.

Further, SOPs may in some cases support institutional practices that sponsors may dispute.[15]

Last, but not the least, SOPs help reduce errors or variations and improve the quality of the data collected.[9] Thus, an effective SOP should:

- Be written in a simple, easy-to-understand language
- Be a comprehensive document
- Differentiate between instructions and general information
- Describe procedures thoroughly
- Contain a descriptive title
- Contain an indication of the SOP's position among other SOPs

Writing SOPs Isn't Enough: Challenges Ahead

Although SOPs are invaluable, they can be burdensome—especially when one considers the elaborate steps involved in such tasks as document control, revision, review, and training, and the high levels of scrutiny for strict adherence that come with established SOPs. It would be wise to consider the following before writing an SOP:

- Can the SOP be consistently followed?
- How will all staff be trained on the SOP initially, as new staff are added, and as the SOP is revised?
- How will compliance to SOPs be assessed?
- What are the added regulatory burdens and costs of compliance?

Thus, writing SOPs is simply the beginning in achieving quality results. As written previously, everyone must be trained on the SOPs, and performance must be measured against the standard to ensure the correct results. Metrics must be collected on a regular basis to ensure staff are following the SOPs; if metrics and performance measurements are not undertaken, SOP compliance, standardization, and quality will inevitably decrease and the efforts taken in designing and writing the SOPs will prove to be futile.

In short, for standard processes leading to quality to be effective, there must be written SOPs, training on the SOPs, and metrics and measurement on the compliance to the SOPs—this, in effect, is the trifecta for quality in clinical research.

The Future of SOPs

Traditionally, SOPs are documented in unwieldy manuals; however, this need not be the case if resources permit the use of documentation applications to build a database of information. Most software systems will not only be able to support creation and maintenance of SOPs, but can manage organizational charts, instructions, and checklists in a centralized domain.

Conclusion

SOPs make it simpler for the research team to carry out trials in compliance with the standards set by regulatory authorities, sponsors, and institutions. The twin objectives of quality—data integrity and subject projection—can be met by a systematic approach to the conduct of clinical trial process.

Research relies on repeatable, reliable, accurate data; a breach or compromise in any of these facets can be disastrous to the research study. Compliance to quality requirements is the foundation of a scientifically valid and ethically sound clinical trial. The recent regulatory approaches of risk-based inspections and real-time oversight, combined with a specific focus on quality systems, demand continuous vigilance and continuous process improvement, from scientific and operational design to the conduct and monitoring of clinical trials.

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AUGUST 2017 CLINICAL RESEARCHER

HOME STUDY

SITES: THE FRONT LINES OF CLINICAL RESEARCH

The Hidden Value of Onsite Monitoring

LEARNING OBJECTIVE

After reading this article, participants should be able to differentiate between the types of study site issues that can be more easily detected remotely using new technologies and those that are more easily detected using traditional onsite monitoring.

DISCLOSURE

Jerry Stein, PhD; Elham Einolhayat, RN: *Nothing to disclose*

1. Which of the following is noted in the article as an observation made by the Clinical Trials Transformation Initiative (CTTI)?

A. An occasional random error should not make a significant difference in data analysis.

B. Electronic data capture (EDC) can significantly decrease site turnover rates.

C. Improved monitoring can impact on site error rates and study costs.

D. More free-market principles would dramatically impact study costs.

2. The U.S. Food and Drug Administration's (FDA's) risk-based monitoring (RBM) guidelines do which of the following?

A. Require onsite monitoring at three clinical milestones.

B. Mandate specific monitoring techniques and site visit schedules.

C. Can include a variety of acceptable approaches.

D. Recognize the efficiency of 100% source data verification.

3. EDC, central monitoring, and RBM techniques are particularly adept at identifying which of the following?

A. Inconsistencies within the database

B. Sources for site personnel bias

C. Ambiguous case report form (CRF) questions

D. Study site personnel changes

4. Which of the following is a valuable capability made possible by using semi-automated, remote data management systems?

A. Identifying difficulties using an investigational medical device.

B. Detecting insufficient oversight by the principal investigator.

C. Detecting patient discomfort not assessed on the CRF.

D. Detecting trends across multicenter studies.

5. Which of the following categories of study site problems are particularly difficult to detect remotely?

1. Issues experienced when attempting to use investigational products.
2. Data entry errors out of range or missing values.
3. Study subject fatigue related to an excess number of study procedures.
4. Insufficient investigator oversight, fraud, and noncompliance.

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. This article indicates that, traditionally, a significant proportion of onsite monitoring has been devoted to which of the following?

1. Reviewing to see if site study files and source documentation are in place.
2. Verification of whether all study information is accurate and properly documented.
3. Checking every datapoint in the sponsor's database against patient charts.
4. Remote review of data recorded in eCRF.

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. According to the article, which of the following is true about frequent onsite monitoring with 100% source data verification?

A. It is required for all clinical drug trials, regardless of their length and indication.

B. It is required at all sites unless evidence is presented to support another approach.

C. It is restricted exclusively to medical devices clinical trials.

D. It has been completely abandoned as industry moves to RBM approaches.

8. Factors that inhibit the sharing of information between sponsors concerning problematic sites include which of the following?

A. Liability and confidentiality concerns

B. FDA guidance and international regulations

C. Institutional review board/ethics committee regulations

D. Informed consent forms

9. According to the authors, which statement describing monitoring and data management plans is correct?

A. They have a standard format and fixed content no matter where the sponsor is based or what kind of product is under study.

B. Their reporting deadlines should be standardized across all protocols to meet guidance from FDA and other regulatory authorities.

C. They should reflect study-related factors such as criticality, safety risk, and research team members' experience.

D. They are required for all new studies effective November 1, 2018, according to the World Medical Association.

10. Which of the following is true about building a personal relationship between the monitor and the study site personnel?

A. It is becoming of little value with the adoption of new technologies.

B. It is often an important factor allowing monitors to detect study site issues.

C. It is a time-consuming and expensive activity that should be severely reduced.

D. It is a good business practice since sites are frequently sponsor customers.

The Real Reason Sites Need eSource

LEARNING OBJECTIVE

After reading this article, participants should be able to articulate the reason sites benefit from eSource, identify the challenges involved in implementing eSource, and define a potential relationship between eSource and electronic data capture systems.

DISCLOSURE

Raymond Nomizu, JD: *Employee and major stock shareholder of Clinical Research IO, Inc.*

11. Among other factors mentioned in the article, complexity in clinical research is evident in the growing number of which of the following?

1. Drugs from different companies targeting the same conditions

2. Procedures performed during clinical trials

3. Specialized study sites located far from major cities

4. Eligibility criteria set for participants in trials

A. 1 and 2 only

B. 1 and 3 only

C. 2 and 4 only

D. 3 and 4 only

12. What is an example of how eSource helps manage the challenge of capturing complex data requirements accurately?

A. It has written instructions that tell the coordinator in detail which questions to answer and which to skip based on previous answers.

B. It has alerts that appear in real-time to notify the user of a potential defect or inconsistency in the answer.

C. It can be done on a mobile device and is therefore easier to carry around.

D. It is available via the Internet after a patient's visit is complete.

13. What is the author's purpose for comparing clinical research site operations to other industries?

A. To illustrate that clinical research is uniquely complex.

B. To show that other industries had growing pains when adopting new technologies.

C. To argue that there is nothing to learn or benefit from other industry technologies.

D. To show that the rationale for using technology also applies to the clinical research industry.

14. Which of the following are required features of site-centric eSource?

1. Enables patient-reported outcomes and electronic consents
2. Allows sites to house all of their studies in one portal
3. Provides monitors with study-specific, anonymized views of source data
4. Allows sites to create their own study templates for future re-use

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

15. According to the article, a site that adopted eSource reported what type of productivity gains?

A. About 50% better than when using paper

B. About 20% better than when using paper

C. About the same as when using paper

D. Significantly less than when using paper

16. If a site adopts eSource, who is ultimately responsible for compliance with local regulations?

A. The principal investigator (PI)

B. The technology vendor

C. The sponsor

D. The technology decision-maker at the site

17. What is an accurate statement of the rights of the PI and the sponsor in terms of the site adopting eSource on a trial?

A. Only the sponsor can dictate whether eSource is to be used on the trial.

B. The PI has the absolute right to use eSource, and the sponsor has no review rights.

C. The PI has the absolute right to use eSource, and the sponsor has the limited right to review the PI's chosen system for compliance.

D. The PI and the sponsor together determine the best method of source data collection for the site.

18. What is the source of the standards that govern interoperability across electronic systems in the clinical research industry?

A. The Clinical Data Interchange Standards Consortium

B. The Health Insurance Portability and Accountability Act

C. 21 CFR Part 11 of the *Code of Federal Regulations*

D. Annex 11 to Volume 4 of the Rules Governing Medicinal Products in the European Community, Computerized Systems

19. Which statement best describes the relationship between eSource and EDC datapoints?

A. They will likely contain an equal amount of datapoints, including compliance-related data.

B. There are no datapoints in eSource that do not have an analogue in EDC.

C. The eSource will likely contain all data required for EDC plus additional, compliance-related data.

D. eSource and EDC contain wholly unrelated datapoints.

20. Which statement best describes the author's view on eSource and EDC?

A. Both systems are workflow tools equally used by sites and by sponsor data management.

B. eSource is a workflow tool for sites and EDC is a workflow tool for sponsor data management.

C. Both systems are workflow tools for the site.

D. eSource and EDC are not workflow tools at all.

Standard Operating Procedures: Critical Components of Quality at Clinical Research Sites

LEARNING OBJECTIVE

After reading this article, participants should be able to understand the importance of standard operating procedures (SOPs), identify clinical trial activities that warrant an SOP, recognize some of the related challenges that research sites face in implementing and ensuring compliance to SOPs, and use SOPs to achieve clinical trial quality.

DISCLOSURE

Soumya J. Niranjan, BPharm, MS, CCRP: *Nothing to disclose*

21. How many Warning letters were been issued by the FDA between January 2005 and December 2010?

A. 100
B. 105
C. 120
D. 129

22. The ICH GCP guideline is upheld by regulatory authorities in which of the following?

1. The United States
2. French Polynesia
3. European Union
4. Canada

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

23. Which of the following questions related to clinical trial activities and its management are among those addressed in SOPs?

1. Who
2. What
3. When
4. Why

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

24. Which of the following steps are among those recommended by the FDA in utilizing a “systems approach” in order to establish and improve quality of clinical trials?

1. Say what you do
2. Do what you say

3. Disprove it
4. Improve it

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

25. What are the three main objectives of SOPs?

1. Define roles and responsibilities of the individuals involved
2. Standardize working practices
3. Define best practices
4. Improve and maintain quality of operations

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

26. According to this article, which are the three primary SOPs that a site should develop and apply to the conduct of clinical research?

1. SOP for Preparing and Maintaining SOPs
2. SOP for Responsibilities of the Research Team
3. SOP for Training and Education
4. SOP for Clinical Activities

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

27. What is the first step in the eight-step process for writing SOPs?
A. Authoring
B. Formatting
C. Process Mapping
D. Revising

28. Which of the following is a benefit of SOPs at a clinical research site?
A. They provide a level of formal accountability for team members.
B. They prevent all possible errors that can be made by site staff.
C. They guarantee full site compliance with study execution.
D. They guarantee that all research conducted as part of the clinical trial follows federal regulations, ICH GCP, and institutional policies.

29. Which of the following reflects a characteristic of an effective SOP?
A. It should describe procedures generally and in detail.
B. It must differentiate between instructions and general information.
C. It should be reviewed and approved by the study sponsor.
D. It should be written in a simple, easy-to-understand language.

30. According to the author, it would be wise to consider which of the following before writing an SOP?
A. How much time will it take to create the SOP?
B. Can the SOP be consistently followed?
C. How will site monitors be trained on the SOP initially, and as the SOP is revised?
D. Will the SOP meet the sponsor's expectations and requirements?