

HOME  
STUDY

HS

# Daily Challenges to the Future of Clinical Trial Conduct

## HOME STUDY TEST

Earn 3.0 Continuing Education Credits

This test expires on April 30, 2017

(original release date: 4/1/2016)

### ACRP EDITORIAL ADVISORY BOARD

Michael R. Hamrell, PhD, RAC, FRAPS,  
RQAP-GCP, CCRA (Chair)

Erika J. Stevens, MA (ABOT Liaison)

Suheila Abdul-Karrim, CCRA, CCRT

Victor Chen

Gregory Hale, MD, CPI

Julie M. Haney, RN, BS, MSL, CCRC

Stuart Horowitz, PhD, MBA

Stefanie La Manna, PhD, ARNP, FNP-C

Jamie Meseke, MSM, CCRA

Michelle MocarSKI, MPH, BA, CCRC

Grannum Sant, MD, BCh, BAO (Hons.),  
MA, FRCS, FACS

Paula Smailes, RN, MSN, CCRC, CCRP

Naveen Tirkey, PhD, CCRA:

*Nothing to Disclose*

Jerry Stein, PhD (Vice Chair):

*Consultant to Encore Vision, Contractor  
for various companies*

### ACRP STAFF/ VOLUNTEERS

James Michael Causey

Gary W. Cramer

Jan Kiszko, MD

Jo Northcutt

Deepti Patki, MS, CCRC

Barbara van der Schalie

Christine Streaker

David M. Vulcano, LCSW, MBA, CIP, RAC:

*Nothing to Disclose*

Karen Bachman:

*Alcon speaker's bureau*

In this issue of *Clinical Researcher*, the three articles that follow this page have been selected as the basis for a Home Study test that contains 30 questions. For your convenience, the articles and questions are provided in print as well as online (members only) in the form of a PDF. This activity is anticipated to take three hours.

**Answers must be submitted using the electronic answer form online (members only, \$60).** Those who answer 80% of the questions correctly will receive an electronic statement of credit by e-mail within 24 hours. Those who do not pass can retake the test for no additional fee.

### ACRP DISCLOSURE STATEMENT

As an organization accredited by the Accreditation Council for Continuing Medical Education (ACCME®), the Association of Clinical Research Professionals (ACRP) requires everyone who is in a position to control the planning of content of an education activity to disclose all relevant financial relationships with any commercial interest. Financial relationships in any amount, occurring within the past 12 months of the activity, including financial relationships of a spouse or life partner, that could create a conflict of interest are requested for disclosure.

The intent of this policy is not to prevent individuals with relevant financial relationships from participating; it is intended that such relationships be identified openly so that the audience may form their own judgments about the presentation and the presence of commercial bias with full disclosure of the facts. It remains for the audience to determine whether an individual's outside interests may reflect a possible bias in either the exposition or the conclusions presented.

### CONTINUING EDUCATION INFORMATION

The Association of Clinical Research Professionals (ACRP) is an approved provider of medical, nursing, and clinical research continuing education credits.



#### Contact Hours

The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2016-HMS-004)



#### Continuing Nursing Education

The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2016-HMS-004)



#### Continuing Medical Education

The Association of Clinical Research Professionals (ACRP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Association of Clinical Research Professionals designates this enduring material for a maximum of 3.0 AMA PRA Category 1 Credits™. Each physician should claim only the credit commensurate with the extent of their participation in the activity.

**80%** The pass rate for the Home Study Test is now 80% to be in alignment with ACRP professional development standards.

# Drug Products for Investigator-Initiated Research

PEER REVIEWED | Philip K. Burns

[DOI: 10.14524/CR-15-0040]

**W**hat happens when a clinical investigator is also the person with an idea for a new drug? He or she envisions how and why it works, and possibly has experimented with it to help understand it better, and to confirm the idea is on the right track. Then the researcher begins to think about his or her role as initiator and as the principal investigator (PI), and the roles of study coordinators, project managers, and patient recruiters who will be needed to manage the clinical study phases of the Investigational New Drug (IND)<sup>1</sup> process for approval through the U.S. Food and Drug Administration (FDA).

What about the physical drug itself? This article includes background information about the physical drug path that may be useful to investigator-initiated research teams. Unlike company-sponsored efforts, the source of the physical drug may not be clear. It could be a current drug or combinations of current drugs, with a new use, dosage type, or dosing structure. It may be a chemical that is not currently used as a drug, like a vitamin or food derivative. Or perhaps it's a new chemical entity, reflecting a revision to a precursor chemical, or an entirely new structure.

There are two major aspects for the drug's path forward. One is the clinical research path to provide evidence that the drug works and is not harmful to patients. The other path relates to the physical/chemical drug itself, as without it, nothing can be done. When the drug investigator is also the sponsor, he or she assumes 100% of the sponsor responsibilities that typically are managed by a sponsoring pharmaceutical company. The physical drug path, and the chemistry, manufacturing, and controls (CMCs) needed to produce a drug product for clinical trials and subsequent commercial distribution are discussed.

## The Drug

The active pharmaceutical ingredient (API) must be obtained and converted into a finished drug

for use in clinical testing. APIs may be obtained through manufacturers and suppliers if currently available, or through the chemical manufacturing process on a small scale. There are many forms the finished drug can take, such as tablets or capsules, liquids, creams or ointments, sterile injectable, skin or buccal patch, or an inhaled product.

The physical drug may seem to be the easiest issue to deal with in the overall investigational process, especially when compared to the clinical research involved. In reality, producing a drug with the right physical properties to meet metabolic conditions requires specialized chemistry knowledge, equipment, and supplies. Without a proper development plan, product quality and variation can pose risk to patients and the project.

Small-scale manufacturing in a lab or pharmacy produces limited quantities of drug. The limited scale or imprecise equipment can result in product and batch-to-batch variation. This can affect drug quality, leading to negative impacts on patients, clinical responses, and consistency of outcomes. In addition to drug quality concerns, the veracity of the drug quality can be questioned if the testing is not properly qualified and documented.<sup>2</sup> This can result in patients being put at risk, and delays of the project and FDA reviews and approvals. Corrective action often requires repeating production and clinical efforts.

## LEARNING OBJECTIVE

After reading this article, participants should be able to describe the responsibilities of sponsor-investigators regarding drug product quality in clinical trials they are conducting.

## DISCLOSURES

Philip K. Burns:  
*Nothing to disclose*

When it comes to the drug product development and the clinical efforts, the legal responsibilities for all aspects of the requirements belong to the sponsor. These requirements are established first and foremost to protect the public and patients' rights. Some necessary and useful drugs have never made it to the market, or did not stay on the market, because these requirements were not properly met.

## Getting the Drug Made

There are four major aspects of getting a drug made:

1. Manufacturing of the API
2. Manufacturing of the drug product(s)
3. Packaging of the final drug product
4. Testing of the API and drug product ingredients, processes, final form, and the stability of the API and finished drug product

(Packaging of the API is an aspect of manufacturing the API, but does not have the criticality of packaging the drug product for clinical trials. The manufacturing of the drug product will include the manufacturing of placebo products needed for the clinical trials.)

Pursuance of the physical drug isn't just linked to the clinical plans. Many activities must precede having the dosage ready for first usage in patients. Depending on the history of the drug (new chemical entity, current drug, etc.) some pre-IND stage activities require the API and drug be put through pharmacology and toxicity studies in animal models. Other activities are required to develop a final form for use, and to provide the assurance that all of the drugs used for the clinical trials are equivalent and meet defined specifications. These assurances must be met before the drug product is administered to humans.

## Facilities, Equipment, Personnel

The facilities used to manufacture the API and drug product should be registered for those purposes with the FDA. (The FDA has specific registration requirements for APIs, drug products, testing labs, and other supporting facilities in the drug development and commercial stages.) Some early-stage activities may be allowed in nonregistered facilities, but that action can lead to delays, significant efforts to justify activities, or rejection of the activities.

Depending on the phase of clinical trials, the facility should be qualified and validated. Qualification provides documented and testing evidence regarding the environment (heating, ventilation,

air conditioning, cleaning, microbial levels) and the utility supports (electricity, steam, hot water, process water and water quality). Additional current Good Manufacturing Practice (cGMP) quality systems<sup>3</sup> are required, such as procedures, calibration, documentation, etc. cGMP requirements are extensive, and not typically practiced in a pharmacy or lab setting.

In addition to the FDA, other regulatory agencies may have oversight within the facility, dependent on the activities performed. These can include the Drug Enforcement Administration<sup>4</sup> for scheduled drugs, class materials, and specific equipment reports; the Environmental Protection Agency<sup>5</sup> for environmental exposures of the chemicals; and the Occupational Safety and Health Administration<sup>6</sup> as relates to occupational exposure of workers to activities, chemicals, and solvents. Most companies have their own internal structures to ensure compliance with regulations and laws, but liability can still extend to use of their services without assuring their controls.

Like the facility, any equipment used in the manufacturing, packaging, and testing of the drug product needs to be qualified and validated. Qualification assures that it has been installed properly and is operating as intended. Validation is testing of the equipment for specific purposes, and is different from operational qualification checks. In addition, there are specific validation requirements based on processes and test methods (discussed below). The quality system controls must extend to the equipment.

The personnel performing manufacturing, packaging, and testing; support personnel (like maintenance, quality); and supervision/management must all be qualified and trained for their assigned tasks. This includes training on the quality systems used to control the facility and equipment, and in the cGMP regulations.

## Manufacturing

The chemical synthesis of APIs can be simple to complex and influences the manufacturing process and costs. It can also influence its use in the drug product and the stability of the API and drug product. The primary factors are the ingredients, the process and controls, and the specifications.

### INGREDIENTS

Availability and quality influence the selection of ingredients. Some may be readily available but their quality questionable. The long-term

There are two major aspects for the drug's path forward. One is the clinical research path to provide evidence that the drug works and is not harmful to patients. The other path relates to the physical/chemical drug itself, as without it, nothing can be done.

## → HOME STUDY

*Daily Challenges to the Future  
of Clinical Trial Conduct*

The legal responsibility and liability for assurance that drug requirements are met is equivalent to that taken for the clinical trial efforts. Attempts to save time or money on the physical product or its requirements are shortsighted and can put at risk all the good work completed or planned.

implications of availability and quality need to be thought through. Lower quality ingredients can result in unacceptable levels of impurities or influence the ability to purify the final drug substance. Some ingredients impact the intended final product's reaction rates or conditions, and can result in expensive processes. Early-stage use may be low and seem to be inconsequential, but scaling up to clinical or commercial levels could be problematic and expensive.

#### PROCESS AND CONTROLS

If the chemical process can be varied, then the effects of any variations on the long-term research need to be assessed. Variations could cause issues with costs of ingredients or impact the physical structure of the final form. This structure can have a major impact on drug product formulation and processes. Once the primary process is established, then the specific process controls and purification need to be finalized. These efforts support the development reports, which then impact the process validation. (Process validation refers to validating the specific ingredients, equipment, processes, and controls to produce a known compound of specific and defined attributes.)

The final API will need to be physically and chemically characterized. This information is used to develop the API specification. That specification includes the product attributes that are critical to its use (as a drug product), and includes limits of manufacturing and degradation impurities. Part of this characterization includes stability testing of the API. That testing assesses the impacts of temperature, moisture, and time on the API, and includes assessing for protective aspects of packaging. Accelerated stability testing and forced degradation are also performed using acids, bases, and light exposures.

#### DRUG PRODUCT

Each of the drug products (dosage forms, strengths) undergo efforts similar to the API—ingredients (formula), processes, and controls. Unlike chemical synthesis, most drug product processes change the physical characteristics of the API and the ingredients added. These physical characteristics can have a direct impact on the properties, stability, and pharmacokinetics of the finished product.

Validation ensures the equivalence of drug products from batch to batch, or before and after any process changes. Control of product variation is critical

to ensure the equivalence of clinical trial materials and their potential effect on clinical outcomes. Making multiple small batches in a pharmacy or lab can result in significant unit variability that directly impacts clinical outcome statistics. To set the proper batch size, consider the long-term demand for the drug, through multiple clinical efforts, laboratory testing, and stability assessments (plus sufficient retained samples as required for all studies).

The drug product specification is developed to ensure the proper level of API is present and the physical state (dosage form, color, condition, etc.) of the drug product is appropriate for use. It also ensures that active ingredient is stable, based on levels of degradation impurities. The API can degrade due to the environmental conditions it is exposed to and its interaction with other ingredients. The physical state of the drug can change due to these exposures. Stability is influenced by environmental exposure and the protective nature of packaging.

#### Packaging

Packaging is critical to providing protective conditions for the contents of a package. In addition to the packaging container and its closure, there are other critical aspects of packaging at the clinical (and then commercial) stages.

- **Labeling** identifies the contents of the package and includes specific directions for the dispenser or user of the product contained. The controls for creating and printing this labeling, and attaching it to the packaged product, assure the medications given match the clinical protocol design criteria.
- **Blinding** is a specific type of labeling of product or placebo to ensure there are no biases in the clinical trial effort (by the staff or the patient).
- **Traceability** of packaging and supporting records and documentation (including distribution) provides assurance of the identity of any given drug product and package as being of a specific API, manufacturing, packaging and labeling batch, and handling of that batch post production (including use by the laboratory).

#### Testing

Testing provides the evidence of outcomes from the physical drug and clinical trials. The veracity of the drug, the clinical protocol, and the tests all must be assured. Evidence is achieved through testing.



Lack of evidence, no matter how minor, can result in patient risk and questioning of the drug quality, clinical efforts, and the statistical outcome. Typically the only way to overcome such a condition is to repeat the efforts. Repeating any of the manufacturing, testing, and/or associated clinical trials will have a significant impact on the project's cost and result in a delay of product approvals.

The facility and equipment qualification and validation, and the personnel requirements that apply to manufacturing and packaging, also apply to laboratories. A minor exercise like calibration checks of a laboratory balance can have major implications on test results. (Example: If calibration failure results in the incorrect amount of standard being weighed, and that standard is used for critical stability or clinical trial testing, the resulting data may not appropriately reflect (+ or -) what actually occurred.)

Drug standards must be established and characterized. These standards (typically from a batch of the API that has been further purified) are used to qualify subsequent standards or directly for testing. Some standard lots can be used for years, so their initial and ongoing quality and storage, and re-verification, can impact laboratory outcomes for those years.

Just as manufacturing processes are validated for outcomes, analytical test methods must be validated. Analytical methods taken from the *United States Pharmacopeia-National Formulary* are to be qualified for their use in the lab. The requirements for method validation are extensive and specific. They include linearity, accuracy, precision, system suitability, detection and quantitation limits, and robustness. They serve not only to assess the methodology, but also the equipment, the laboratory, and the personnel involved.

Analytical methods are needed for testing the specification properties and attributes of the API and drug product. Examples of these chemical and physical tests include:

- Assays looking for trouble spots, including impurities (via manufacturing processes, residual solvents, and degradation)
- Methods for identification of the API and drug product against a recognized or qualified standard
- Explorations of the API's and drug product's physical properties such as structural elucidation and dissolution

- Examinations of biological properties (at the microscopic level, etc.)

These methods may apply to the final forms of the API and drug product, or may be used to test intermediate forms for validation or process controls, or after packaging as applied to stability and shipping integrity. (Similar method validation efforts apply to the specific analysis of patient biological fluid samples from clinical trials.)

## Conclusions

The thought and background research efforts that lead to major projects resulting in new drugs or drug forms represent exciting and impactful steps on the road to improvements in healthcare. The clinical trial efforts of the various research team members are seen as a continuation of the earliest stages of the research. The development of the physical drug is critical to the clinical research efforts in pursuit of drug approvals. The physical drug efforts are part of the stepwise reporting of CMC activity to the FDA, through the IND and various clinical phases of drug research and development.

How the physical drug is produced can impact the patients, costs, timing of supply, and acceptance of the drug product. The quality of the activity can influence the potency, precision, and accuracy of the drug and its use in the clinical environment. The compliance of the activities to registration, reporting, statutory, and guidance requirements will influence their acceptance by the regulatory authorities and serve for long-term evidence of performance of the drug product to meet those requirements.

The legal responsibility and liability for assurance that drug requirements are met is equivalent to that taken for the clinical trial efforts. Attempts to save time or money on the physical product or its requirements are shortsighted and can put at risk all the good work completed or planned. Proper support and direction can help ensure all outcomes move toward supporting the product's approval by the regulatory agencies. These efforts support the overall value and intellectual property of the drug. Knowledge of the physical drug product activities helps the sponsor-investigator, and all of the various supporting managers and coordinators, to ensure that drug variability is not the source of clinical variation. This ensures clinical research reflects clinical outcomes and not product issues.

## References

1. FDA website for New Drug Development and approval process: [www.fda.gov/Drugs/BIODEvelopment/ApprovalProcess/default.htm](http://www.fda.gov/Drugs/BIODEvelopment/ApprovalProcess/default.htm)
2. Guidance for Industry Q9 Quality Risk Management: [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf)
3. Guidance for Industry Q10 Pharmaceutical Quality System: [www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm073517.pdf](http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm073517.pdf)
4. [www.dea.gov/index.shtml](http://www.dea.gov/index.shtml)
5. <http://www3.epa.gov>
6. <https://www.osha.gov>

---

**Philip K. Burns** (phil@cro-consulting.net) provides compliance, regulatory, and operations consulting to pharmaceutical and medical device clients, and is a founder and partner of CRO-Consulting.

# Key Considerations for Social Media Recruitment Platforms

PEER REVIEWED | Deborah D. Rupert, MS, CCRC, MA

[DOI: 10.14524/CR-15-0019]

**T**hrough a variety of social media platforms, the Internet offers access to a relatively large and untapped pool of potential clinical trial participants. The Pew Research Center's January 2013 survey on Internet & American Life concluded that 72% of adults have searched for health-related information at least once during the past year.<sup>1</sup>

In the context of low overall participation rates, the question becomes: How can clinical trial professionals better employ social media for study recruitment? Despite rising demand and ample interest from such professionals, and even institutions on a more global level, there is a notable lack of progress on this front.

Popular social media sites have grown exponentially over time, changing the way users interact socially (Facebook), network professionally (LinkedIn), and find medical care (ZocDoc). The challenge is to harness what have become familiar platforms to achieve improved recruitment into clinical trials.

A detailed discussion of tactics is beyond the scope of this article; however, several potential approaches seem promising for expanding upon tried-and-true recruitment methods (e.g., promoting recruitment-focused social media website use through physician-patient interactions) as well as more alternative approaches (e.g., advertisements or links on support group or pharmaceutical websites).

No matter what approach is used for channeling patients toward social media-based platforms, success depends on adequately addressing the needs of these potential participants.

## What Patients Want: Accessibility

A recent survey in *Medical News Today* reported that almost 85% of patients were not aware that clinical trials were a possible treatment option.<sup>2</sup>

To this point, no singular site has acted as an all-encompassing educational and recruitment tool for the public for clinical trials. None of the most widely known clinical trial recruitment-related sites to which patients have the most direct access (in terms of ease of discovery), such as ResearchMatch<sup>3</sup> or PatientsLikeMe,<sup>4</sup> nor ClinicalTrials.gov,<sup>5</sup> which provides a great deal of data on active trials, but does not serve as a recruitment tool, quite provide a “start-from-the-beginning” approach. Instead, patients must fend for themselves as they sift through various sites with disparate focus: disease/ailment education, support groups and networking, physician searches, news updates, scientific research, company marketing, etc.

Patients, whether they become self-informed or are informed by family, friends, or physicians that clinical trials may be the right fit, find an overwhelming amount of data when they turn to the Internet. For example, in the last 15 years, the ClinicalTrials.gov database of U.S.-based trials has registered more than 180,000 studies—an increase of approximately 4,000%.<sup>5</sup> While this site is an excellent and increasingly comprehensive tool for researchers, and for a very select group of patients “in the know” (e.g., who themselves work in healthcare or healthcare-related fields), this growth undeniably makes the site difficult to navigate.

What patients need is an easy-to-understand, hierarchical-based platform to help guide them through the labyrinth of information with the

## HS

### LEARNING OBJECTIVE

After reading this article, participants should be able to describe the pros and cons of integrating a social media platform into the patient recruitment processes, and identify the foundation elements a successful platform would require.

### DISCLOSURES

Deborah D. Rupert, MS, CCRC, MA:  
*Nothing to disclose*

---

**72%** of adults have searched for health-related information at least once during the past year.

---

**85%** of patients were not aware that clinical trials were a possible treatment option.

---

primary end goal of presenting a “match” to clinical trial options, and with the secondary goal of enhancing patient understanding of the field of clinical trials.

### Patient Networking

Participant-to-participant interactions—the core of social media—have largely been excluded from the arena of clinical trials due to the concern for potential bias on a trial’s outcome or future recruitment. Patient-to-patient communication has generally been reserved for support group sites.

At the same time, researchers are beginning to reach out to support group websites, bridging clinical trials to these more socially oriented platforms. In one such recruitment effort, a team of Mayo Clinic cardiologists coordinated with a patient-run support group known as WomenHeart: The National Coalition for Women with Heart Disease. In doing so, the website became a bridge between a large pool of potential patients seeking to join a clinical trial and Mayo’s researchers, resulting in a virtual registry and DNA biomarker bank. Most remarkable was that the impetus for approaching WomenHeart, as a social media recruitment platform, was proposed by a survivor of heart disease.<sup>6</sup>

Given today’s ever-connected world, the era of subject-subject isolation is coming to an end. Patients show an increased interest in sharing their experiences; turning to platforms like Facebook to create illness-focused online communities. Clinical trial participants also seek a greater perspective, a trend reflected both in the growth of online communities (e.g., PatientsLikeMe<sup>7</sup>) and in the longstanding history of typical questions directed toward clinical research coordinators (CRCs) (e.g., the number of participants enrolled at institutions and common adverse events) during the consent process or follow-up.

Despite the potential risks, such as those to privacy, the field of clinical trials must meet this change prepared to use it to good advantage. By offering a platform for patients to discuss clinical trial options within specific disease categories, a social media-based recruitment site could draw more attention and more interest from the general public.

It is not the place of research personnel to encourage or facilitate conversation between study

No matter what approach is used for channeling patients toward social media-based platforms, success depends on adequately addressing the needs of these potential participants.

participants. Rather, a social media-based recruitment site itself is a means by which patients with shared interests (not shared study participation) could seek each other out. The decision whether, and how much, to share with others remains in the hands of the patient.

### Understanding the Patient Experience

Patient-centric research is becoming the focus and driving force of the future. Steps must be taken to: 1) better understand the patient’s clinical trial experience, 2) strengthen the connection between patients and researchers, and 3) cultivate an environment in which participants recognize their role in the progress of clinical research.

Patient testimonials regarding clinical trials may become an important part of a patient’s decision to participate in one trial over another. Learning about other patients’ experiences with similar treatments (as part of clinical trials or otherwise) is a powerful motivation for study participation, retention, and treatment compliance.

Patient feedback through social media is also an avenue to improve the design of and implementation of trial work, while addressing quality assurance issues. Researchers can fine-tune further studies based on patient data and align their studies with patients’ concerns and health issues (e.g., helping select clinically meaningful endpoints).

Another key aspect of successful patient-focused recruitment websites is the ability for patients to control the privacy level of their data. The Institute of Medicine survey reported that the number one fear of patients was that their health information would not be kept confidential.<sup>2</sup>

Regardless of the platform or type of information, individuals are constantly called upon to make personal decisions for sharing information on social media-based websites. Patient-controlled access means providing various data-sharing options or levels, which are selected by the patient (e.g., choosing whether to link their medical records directly to the site, providing their own medical history or only certain components, or opting out entirely).

Platforms built on collecting data from patients and allowing data access to researchers represent a

## → HOME STUDY

*Daily Challenges to the Future  
of Clinical Trial Conduct*

Given today's ever-connected world, the era of subject-subject isolation is coming to an end. Patients show an increased interest in sharing their experiences; turning to platforms like Facebook to create illness-focused online communities.

modernized version of Health Insurance Portability and Accountability Act (HIPAA) contracts. One such platform is PrivateAccess, which provides patient control of medical records and personal information based on the patient's selected privacy settings. On the opposite side of the equation, PrivateAccess provides access of patients' data to researchers and partners with ClinicalTrials.gov. A potential additional layer of security could be provided by assigning users a code making anonymous any information they present.

### Addressing the Researcher Perspective: Efficiency in Screening and Recruitment

In a recent survey conducted by Pfizer, Inc., it was reported by physicians that 31% "did not refer patients to trials due to, among other things, lack of information."<sup>2</sup> A physician's time is a limited resource, and while many physicians show great dedication to clinical trial work, their focus is providing the best patient care possible. They are further faced with the impossible task of knowing the details of every clinical trial for which a patient may be eligible, and the screening and enrollment requirements of those protocols.

Tools to support physicians and their research staff in the increasingly involved recruitment process are needed. In one example, to better equip physicians, Case Western Reserve University developed a software program known as Trial Prospector. This system provided oncologists at Seidman Cancer Center in Cleveland, Ohio a report that matched patients to their cancer trials against the eligibility criteria for any of the University Hospitals Case Medical Center's 300 trials.<sup>8</sup>

Social media is increasingly being used to support the physician-patient relationship, although more commonly in the context of standard medical care (e.g., ZocDoc or use of text messages for communication), rather than to support clinical trials. The same approach can be taken for clinical trial recruitment; however, the success of the social media-based clinical trial platform, as for other platforms, will depend upon physician involvement. The key would be not just to refer patients to the platform, but to also allow physicians to access the site.

A simple algorithm based on a patient's lab reports and demographic data, which are

automatically uploaded from electronic medical records, is one means of providing the physician a list of appropriate clinical trials. However, physician-patient communication will be further enhanced by expanding on existing algorithm-based sites by allowing physicians and CRCs to announce messages to groups of patients (e.g., those participating in a particular trial).

Further, the involvement of hospitals and individual physicians (principal investigators and sub-investigators) is key for successfully recruiting for site-specific trials while also allowing patients to gather information on trials outside that research site. In the long term, a social media-based recruitment effort will only be as successful as the intrinsic relationships involved (between physician and patient, between patient and CRC, and between hospital and physician).

### Support of Big Pharma

To better understand the perspective of sponsoring companies ("big pharma") and their incorporation of social media into clinical trial work, the Tufts Center for the Study of Drug Development convened a focus group of 20 such companies, including contract research organizations. The goal of this focus group was to examine the current and future use of social media in clinical trials from a corporate perspective. The resulting report was not limited to recruitment initiatives, but given the topic of this article, recruitment conclusions are discussed here.<sup>9</sup>

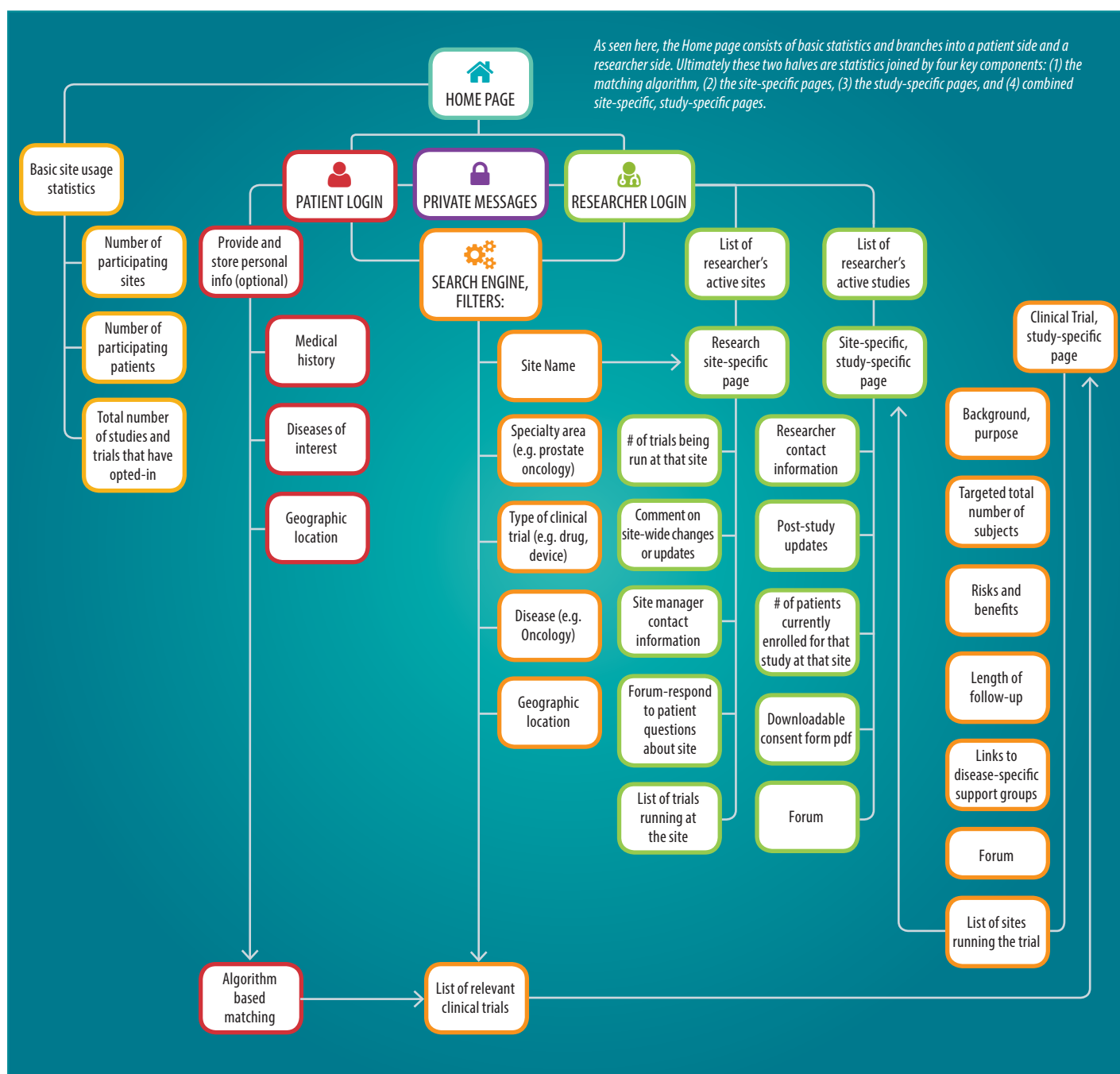
Companies surveyed agreed that social media use is widely distributed and poorly tracked, calling for a more centralized system and improving its management. It was further determined that the current use of social media is limited to gathering results on using marketed products. Of the small amount of social media used for recruitment, less than one-third of companies interacted directly with patients.

Companies that reported using pre-established social media communities used Facebook. It was also reported that growth in using social media for recruitment is expected with 75% and 42% of U.S. and Western European companies, respectively, planning to increase initiatives.

Participation in clinical trials, especially drug studies, is complex; therefore, patient involvement



**FIGURE 1:** Hierarchical map of proposed ideal social media–based clinical trial recruitment and retention tool.



must be encouraged starting at the recruitment stage. Some big pharma companies are currently allocating resources toward social media. In partnership with PrivateAccess, Pfizer is attempting to accelerate its drug clinical studies and shorten the timeline for bringing drugs to market.<sup>2</sup> Working together, Pfizer and PrivateAccess also want to recruit other companies into the online community, such as research sites and patient advocacy groups.

### Proposed Design for a More Ideal Social Media–Based Recruitment and Retention Tool

The ideal social media tool sifts through the dispersed, and sometimes obscure, sources of information to educate, match, and create a multi-connected communication for patients searching to participate in clinical trials (see Figure 1 for a visualization of a proposed design for this tool).

## → HOME STUDY

*Daily Challenges to the Future  
of Clinical Trial Conduct*

To begin with, the website is expected to integrate an algorithm-based matching system. However, patients must also be able to search for areas of interest, including those not necessarily pertinent to their own medical concerns, but those of a loved one, or to gain a greater understanding of clinical trials prior to taking action. This calls for a website designed to match patients to trials in manners beyond providing multiple filters by which to narrow searches based on location, disease (e.g., oncology, cardiology, gastroenterology), subcategory of disease (e.g., ophthalmology oncology, hypercholesterolemia, irritable bowel syndrome), and trial type.

Social media-based clinical trial recruitment efforts should also collect and distribute information on what most who work in the field consider “commonly understood” aspects of clinical trial participation. Such aspects include a historical background relevant to aspects of clinical trials (e.g., the foundations of HIPAA), key term definitions, the purposes of principles such as intent to treat, types of clinical trials, what to expect when participating in those various types, and other frequently asked questions.

Providing these tools will increase patient education and reduce CRC and physician burden. Well-informed patients admitted into a clinical trial are more likely to become interested, active, and well-retained participants for the duration of a study.

The extent to which trial or study information is presented on a site will depend upon the opting-in and privacy settings of different parties into the system allowing patients, physicians, and researchers (and research sites, institutions, and companies) to determine their levels of data sharing and involvement. The most basic option, under the circumstances where none of the interested parties chose to opt-in, would result in publicly accessible information.

Public information includes materials drawn from the company’s website, certain past publications, press releases, ClinicalTrials.gov, and other clinical trial listings. Thus, the functionality of the proposed site remains its ability to educate and ease the search burden that currently exists for interested participants.

On the other end of the spectrum, under conditions of institutional review board approval and where all parties choose to opt-in, details such

What patients need is an easy-to-understand, hierarchical-based platform to help guide them through the labyrinth of information with the primary end goal of presenting a “match” to clinical trial options, and with the secondary goal of enhancing patient understanding of the field of clinical trials.

as specific study personnel contact information, number of subjects enrolled in a given trial and at a given site, the follow-up timeline, and other pertinent information would be included and expanded upon. One could even imagine including patient testimonials and reports on their experiences for each clinical trial included on the site.

Each individual study site would also have its own page to present site-specific information, including research personal contact details, pertinent news and updates, and the trials into which the site is currently enrolling. Site-specific pages would link to site-specific, study-specific pages.

Whereas study-specific pages would present information about the study’s performance at sites across the nation and about the sponsoring company, site-specific, study-specific pages would include details such as a downloadable PDF of the study consent form, a study synopsis from the principal investigator, and comparative statistics. Facilities conducting similar trials could have access to each other’s results (depending on the privacy settings of the study sites) to allow for an exchange of information and to produce tangible data for “what works.”

Patients’ involvement would be encouraged through personalized (and potentially anonymous) individual accounts. Through these accounts patients, could provide varying levels of background, change their privacy settings, and customize the features of the website to their needs. Patients can also provide medical records release from institutions at which they receive care, allowing lab data to be more efficiently transferred. Thus, patients and research sites would have ownership over the website content, similar to Facebook or LinkedIn.

The website would act as a semi-open forum for patient-research-physician communications. These communications may be public “posts” or private “messages” depending on the format in which they are submitted. For example, both site-specific and study-specific pages would allow for communication between research staff and interested potential participants in open forum discussions.

Thus, patients could ask more general questions about a study site, or more specific questions about a study at a particular site within the respective forums. Indirectly, this helps patients educate

each other and reduces the time research sites spend answering similar questions. However, individual patients can also send particular sites, CRCs, or physicians private messages, or use the contact information provided on the site-specific pages to send e-mails or text messages outside the application.

The need for a one-stop centralized clearinghouse that helps patients and physicians sift quickly through overwhelming data is unarguable. For social media-based recruitment to become a reality, several entities must unite within the same platform:

- a database containing patient demographics and history to compare against clinical trial inclusion/exclusion criteria;
- a matching algorithm to accomplish that comparison;
- geographic mapping of studies based on the sites currently enrolling; and
- modules for communication between different parties.

## Conclusions and Further Considerations

Social media tool development for clinical trials is a field in its infancy. However, it is clear from the current trends that social media will develop into a reliable recruitment and retention platform in the next five to 10 years. Importantly, social media should not be considered a panacea, but rather as an additional tool (with its own set of limitations) for implementation with traditional recruitment approaches.

It is hoped that this article acts as a “jumping-off point” for further discussion into the roles social media will play in the field of clinical trials. Intellectual discussion on the practical and logistical aspects of regulatory concerns tied to social media in this context warrants further contributions.

## References

1. Fox S, Duggan M. and Maeve Duggan, “Information Triage,” PewResearchCenter, Internet, *Science & Tech, Health Online* 2013. January 15, 2013. Accessed February 12, 2015. [www.pewinternet.org/2013/01/15/information-triage/](http://www.pewinternet.org/2013/01/15/information-triage/)
2. *Medical News Today*. “Pfizer and Private Access Announce Plans to Develop Online Community to Accelerate Clinical Research.” Last updated August 28, 2009. Accessed March 21, 2015. [www.medicalnewstoday.com/releases/162134.php](http://www.medicalnewstoday.com/releases/162134.php)
3. ResearchMatch. “About Us.” Accessed February 23, 2015. <https://www.researchmatch.org/about/>
4. PatientsLikeMe. Accessed February 1, 2015. <http://patientslikeme.com>
5. ClinicalTrials.gov. A Service of the U.S. National Institutes of Health. “Trends, Charts and Maps.” January 2015. Accessed February 11, 2015. <https://clinicaltrials.gov/ct2/resources/trends#TypesOfRegisteredStudies>
6. *CenterWatch News Online*. “Mayo Clinic Sees Potential of Social Media in Patient Recruitment,” September 1, 2011. Accessed January 10, 2015. [www.centerwatch.com/news-online/article/2158/mayo-clinic-sees-potential-of-social-media-in-patient-recruitment#sthash.bYEyUH6R.dpbs](http://www.centerwatch.com/news-online/article/2158/mayo-clinic-sees-potential-of-social-media-in-patient-recruitment#sthash.bYEyUH6R.dpbs)
7. Open Research Exchange by PatientsLikeMe. Supported by Robert Wood Johnson Foundation. Accessed March 18, 2015. <https://www.openresearchexchange.com>
8. Townsend A. “University Hospitals Creates Effective Tools to Overcome Barriers to Cancer Clinical Trials.” June 3, 2013. Accessed February 2, 2015. [www.cleveland.com/healthfit/index.ssf/2013/06/university\\_hospitals\\_creates\\_e.html](http://www.cleveland.com/healthfit/index.ssf/2013/06/university_hospitals_creates_e.html)
9. Lamberti MJ, Stergiopoulos S, et al. Tufts University. Tufts Center for the Study of Drug Development. “Industry Usage of Social and Digital Media Communities in Clinical Research.” Between March and December 2013. Accessed February 2, 2015. [http://csdd.tufts.edu/files/uploads/TCSDD\\_Social\\_Media\\_Final.pdf](http://csdd.tufts.edu/files/uploads/TCSDD_Social_Media_Final.pdf)

---

**Deborah D. Rupert, MS, CCRC, MA**, ([rupert.deedee@gmail.com](mailto:rupert.deedee@gmail.com)) is a Certified Clinical Research Coordinator and worked at the Center for Interventional Vascular Therapy at Columbia University Medical Center.

# Challenges and Training Needs for Clinical Research Associates—A Survey

PEER REVIEWED | Niranjan Kulkarni | Arun Bhatt, MD, FICP, FICR | Jeroze Dalal, PhD

[DOI: 10.14524/CR-15-0039]

Clinical research associates (CRAs) perform a vital role in monitoring clinical trials. Monitoring undertaken without adequate CRA training, including competency assessment and following a monitoring methodology, can spell disaster.<sup>1</sup> Frequent changes in regulations across global regions, variances in participation across multinational and multicenter trials, development issues faced by newer sites, and challenges associated with complex protocols have increasingly emphasized the demanding role played by CRAs.<sup>2</sup>

As there is hardly any published information aimed at understanding CRAs' perceptions of the challenges they face in performing their roles and their expectations of training requirements, the survey described in this article seeks to address these topics.

## Materials and Methods

The survey was conducted amongst clinical research professionals who were working or who had worked as CRAs, and only those who consented were requested to respond to the questionnaire, which was designed using Google forms.

The survey questionnaire addressed:

1. Time spent on each activity during monitoring visit and time and effort required for achieving expertise on a scale of 1 to 5 (1=Minimum, 5=Maximum) for the following monitoring activities:

- Informed consent form (ICF) review
- Investigational product (IP) accountability
- Source document verification (SDV)
- Training provided to the site staff
- Interaction with principal investigator (PI)
- Resolution of data queries
- Site file review
- Reporting adverse events (AEs) and serious adverse events (SAEs)

2. Importance of the above monitoring activities in protecting the rights, safety, and well-being of subjects and ensuring data integrity graded as not important, somewhat important, or very important
3. Reasons why issues go undetected during monitoring, including:

### • Study-related factors

- » too many documents to refer to for confirming compliance
- » complexity of protocol
- » no clear guidance on minimum requirement for source documentation

### • Training-related factors

- » lack of therapeutic area training
- » inadequate training of monitors
- » inadequate training to site staff
- » lack of adequate monitoring experience
- » lack of monitoring tools

### • Time management-related factors

- » time constraints
- » interruptions during monitoring visits

These were graded on a five-point scale indicating strongly disagree, disagree, neither disagree nor agree, agree, or strongly agree. The grades for agree and strongly agree were combined for analysis.

## HS

## LEARNING OBJECTIVE

After reading this article, participants should be able to evaluate training strategy for CRAs, adopt the best training approaches for different monitoring activities, avoid factors leading to issues being undetected, and prioritize development of soft skills.

## DISCLOSURES

Niranjan Kulkarni;  
Arun Bhatt, MD, FICP, FICR;  
Jeroze Dalal, PhD:  
*Nothing to disclose*



4. Preferred approaches to learning monitoring activities; the five preset options were co-monitoring visit, interactive workshop, self learning, classroom training, and web-based training (only one option could be selected)
5. Adequacy of training provided to a CRA: less than adequate, adequate, more than adequate
6. Need for standardization of site training for the informed consent process, source documents, data entry, site file, and reporting AEs and SAEs (the three preset options were standardization is required, standardization is not required, and no idea)
7. Importance of the soft skills (communication, computing, leadership, presentation, team work, negotiation, conflict management, and interpersonal) graded as not important, somewhat important, or very important

Descriptive statistics were applied for analysis of the responses to the above items.

## Results

The survey was open from August 12, 2014 to March 2, 2015. We received 192 responses, of which the majority (165, 86%) were from Asia. Two responses (or 1% each) came from the United States, the Pacifica region, and from Europe, while 21 (11%) came from other regions. The response rate is unknown because respondents were asked to forward the survey to their networks of CRAs. The distribution of monitoring experience was 40% of respondents with more than five years, 45% with two to five years, and 15% with less than two years.

## TIME SPENT ON DIFFERENT ACTIVITIES DURING MONITORING VISITS

SDV was rated as the most time-consuming activity by 70.3% of respondents (see Table 1), followed by ICF review (26.6%). The least amount of time was spent on interacting with PIs.

**TABLE 1:** Time Spent on Different Activities During Monitoring Visit

	Individuals (n=192) responding on a scale of 5 (maximum) to 1 (minimum) (% of total response)				
Monitoring Activity	5	4	3	2	1
SDV	135 (70.3%)	46 (24%)	8 (4.2%)	3 (1.5%)	0 (0%)
ICF Review	51 (26.6%)	41 (21.4%)	45 (23.4%)	38 (19.7%)	17 (8.9%)
IP Accountability	33 (17.2%)	57 (29.7%)	56 (29.2%)	36 (18.7%)	10 (5.2%)
Reporting AEs and SAEs	29 (15.1%)	42 (21.9%)	64 (33.3%)	46 (24%)	11 (5.7%)
Resolving Data Queries	26 (13.5%)	44 (22.9%)	71 (37.1%)	44 (22.9%)	7 (3.6%)
Site File Review	21 (10.9%)	45 (23.4%)	64 (33.3%)	49 (25.6%)	13 (6.8%)
Training Site Staff	13 (6.8%)	34 (17.7%)	73 (38%)	63 (32.8%)	9 (4.7%)
Interaction with PI	12 (6.3%)	21 (10.9%)	59 (30.7%)	64 (33.3%)	36 (18.8%)

## TIME AND EFFORT REQUIRED FOR ACHIEVING EXPERTISE IN DIFFERENT MONITORING ACTIVITIES

More than 50% of the respondents considered SDV as an activity requiring maximum time and effort to achieve expertise (see Table 2).

**TABLE 2:** Time and Effort Required for Achieving Expertise in Different Monitoring Activities

	Individuals (n=192) responding on a scale of 5 (maximum) to 1 (minimum) (% of total response)				
Monitoring Activity	5	4	3	2	1
SDV	103 (53.6%)	55 (28.6%)	26 (13.6%)	7 (3.7%)	1 (0.5%)
ICF Review	55 (28.6%)	54 (28.1%)	44 (23%)	26 (13.5%)	13 (6.8%)
IP Accountability	35 (18.2%)	49 (25.5%)	58 (30.3%)	43 (22.4%)	7 (3.6%)
Reporting AEs and SAEs	43 (22.4%)	60 (31.2%)	61 (31.8%)	24 (12.5%)	4 (2.1%)
Resolving Data Queries	27 (14.1%)	49 (25.5%)	68 (35.4%)	38 (19.8%)	10 (5.2%)
Site File Review	28 (14.6%)	48 (25%)	74 (38.5%)	33 (17.2%)	9 (4.7%)
Training Site Staff	30 (15.6%)	63 (32.8%)	68 (35.4%)	28 (14.6%)	3 (1.6%)
Interaction with PI	26 (13.5%)	53 (27.6%)	65 (33.9%)	39 (20.3%)	9 (4.7%)

## HOME STUDY

### Daily Challenges to the Future of Clinical Trial Conduct

#### ACTIVITIES PERCEIVED TO PROTECT RIGHTS, SAFETY, AND WELL-BEING OF SUBJECTS AND ENSURING DATA INTEGRITY

More than 50% of the respondents considered reporting AEs/SAEs, ICF review, training of the site staff, SDV, IP accountability, and meeting PIs to be very important activities to ensure protection of the rights, safety, and well-being of subjects (see Table 3).

**TABLE 3:** Perceived Importance of Activities in Protecting Rights, Safety, and Well-Being of Patients

Monitoring Activity	Individuals (n=192) rating each activity (% of total response) as...		
	Very Important	Somewhat Important	Not Important
SDV	146 (76%)	44 (23%)	2 (1%)
ICF Review	178 (92.7%)	12 (6.3%)	2 (1%)
IP Accountability	133 (69.3%)	55 (28.6%)	4 (2.1%)
Reporting AEs and SAEs	182 (94.8%)	10 (5.2%)	0 (0%)
Resolving Data Queries	61 (31.8%)	105 (54.7%)	26 (13.5%)
Site File Review	52 (27.1%)	116 (60.4%)	24 (12.5%)
Training Site Staff	149 (77.6%)	42 (21.9%)	1 (0.5%)
Interaction with PI	114 (59.4%)	77 (40.1%)	1 (0.5%)

#### ACTIVITIES PERCEIVED TO ENSURE DATA INTEGRITY

More than 60% of the respondents considered that reporting AEs/SAEs, SDV, site training, resolving data queries, IP accountability, and ICF review were very important to ensure data integrity in a clinical trial (see Table 4).

**TABLE 4:** Perceived Importance of Activities in Ensuring Integrity of Data

Monitoring Activity	Individuals (n=192) rating each activity (% of total response) as...		
	Very Important	Somewhat Important	Not Important
SDV	166 (86.5%)	25 (13%)	1 (0.5%)
ICF Review	132 (68.8%)	53 (27.6%)	7 (3.6%)
IP Accountability	134 (69.8%)	55 (28.6%)	3 (1.6%)
Reporting AEs and SAEs	167 (87%)	24 (12.5%)	1 (0.5%)
Resolving Data Queries	139 (72.4%)	48 (25%)	5 (2.6%)
Site File Review	71 (37%)	105 (54.7%)	16 (8.3%)
Training Site Staff	143 (74.5%)	49 (25.5%)	0 (0%)
Interaction with PI	83 (43.2%)	100 (52.1%)	9 (4.7%)

#### PREFERRED APPROACHES TO LEARN MONITORING SKILLS

Taking part in a co-monitoring visit was considered the preferred approach for learning ICF review, IP accountability, SDV, site file review, and meeting with PIs (see Table 5). For site training and reporting AEs and SAEs, interactive workshops were preferred by more than 30% of the respondents; web-based training was identified as the preferred approach by 29.7% to learn data query resolution.

**TABLE 5:** Preferred Approaches to Learn Different Monitoring Activities

Monitoring Activity	Individuals (n=192) rating a particular approach as the best for learning the listed monitoring activities (% of total response)				
	Co-Monitoring Visit	Interactive Workshops	Self-Learning	Classroom Training	Web-Based Training
ICF Review	97 (50.5%)	65 (33.9%)	10 (5.2%)	14 (7.3%)	6 (3.1%)
IP Accountability	114 (59.4%)	35 (18.2%)	24 (12.5%)	12 (6.3%)	7 (3.6%)
SDV	121 (63%)	43 (22.5%)	16 (8.3%)	6 (3.1%)	6 (3.1%)
Site File Review	74 (38.5%)	38 (19.8%)	37 (19.3%)	35 (18.2%)	8 (4.2%)
Training Site Staff	53 (27.6%)	63 (32.8%)	14 (7.3%)	35 (18.2%)	27 (14.1%)
Meeting PI	98 (51%)	47 (24.5%)	27 (14.1%)	12 (6.3%)	8 (4.2%)
Resolving Data Queries	41 (21.4%)	35 (18.2%)	34 (17.7%)	25 (13%)	57 (29.7%)
Reporting AEs and SAEs	50 (26%)	66 (34.4%)	9 (4.7%)	38 (19.8%)	29 (15.1%)

#### ADEQUACY OF TRAINING PROVIDED BY THE SPONSORS

For all monitoring activities except PI interaction, the training provided by sponsors to the CRAs was considered adequate or more than adequate by more than 50% respondents (see Table 6). However, 50.5% of respondents considered training provided for conducting meetings with PIs less than adequate.

**TABLE 6:** Adequacy of Training Provided on Monitoring Activity

Monitoring Activity	Individuals (n=192) rating the training provided (% of total response) as...		
	More than Adequate	Adequate	Less than Adequate
ICF Review	37 (19.3%)	140 (72.9%)	15 (7.8%)
IP Accountability	9 (4.7%)	119 (62%)	64 (33.3%)
SDV	23 (12%)	110 (57.3%)	59 (30.7%)
Site File Review	12 (6.2%)	110 (57.3%)	70 (36.5%)
Training Site Staff	11 (5.7%)	110 (57.3%)	71 (37%)
Meeting PI	8 (4.2%)	87 (45.3%)	97 (50.5%)
Resolving Data Queries	16 (8.3%)	132 (68.8%)	44 (22.9%)
Reporting AEs and SAEs	22 (11.5%)	139 (72.4%)	31 (16.1%)

## REQUIREMENT TO STANDARDIZE TRAINING FOR SITE STAFF

More than 50% of the respondents stated that standardization was required for training site staff on the informed consent process (87.5%), reporting AEs/SAEs (84.4%), the required level of details in source documentation (75%), site file maintenance (68.8%), and data entry (59.9%).

## REASONS FOR ISSUES GOING UNDETECTED DURING MONITORING

According to 74% or more of the respondents, common reasons for issues going undetected during monitoring were too many documents to refer to in order to confirm compliance, complex protocols, no clear guidance on minimum requirements for source documentation, and time constraints during monitoring (see Figure 1).

## IMPORTANCE OF SKILLS REQUIRED BY CRAs

More than 50% of the responding CRAs considered communication, interpersonal, conflict management, negotiation, teamwork, and presentation skills very important (see Table 7).

**TABLE 7: Clinical Research Skill Areas for CRAs**

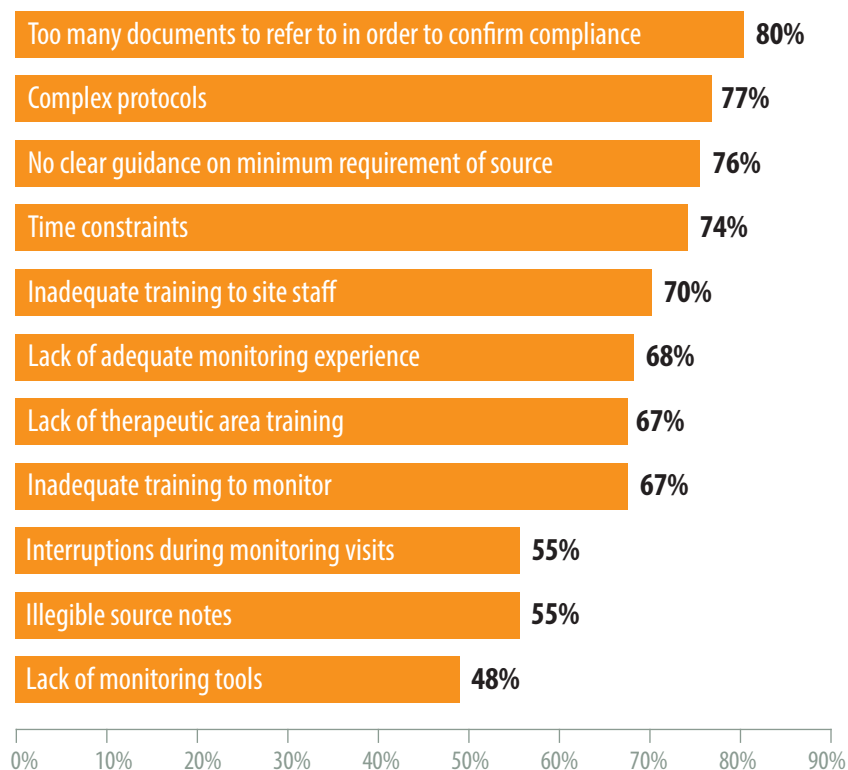
Skills	Individuals (n=192) rating each skill (% of total response) as...		
	Very Important	Somewhat Important	Not Important
Computing	71 (37%)	114 (59.4%)	7 (3.6%)
Leadership	84 (43.8%)	100 (52.1%)	8 (4.2%)
Presentation	111 (57.8%)	77 (40.1%)	4 (2.1%)
Team Work	137 (71.4%)	51 (26.6%)	4 (2.1%)
Negotiation	157 (81.8%)	32 (16.7%)	3 (1.6%)
Conflict Management	157 (81.8%)	34 (17.7%)	1 (0.5%)
Interpersonal	161 (83.9%)	31 (16.1%)	0 (0%)
Communication	184 (95.8%)	8 (4.2%)	0 (0%)

## Discussion

### MONITORING ACTIVITIES: PERCEPTIONS VERSUS PERFORMANCE

Our survey showed that more than 50% of respondents considered reporting AEs and SAEs, ICF review, training of site staff, SDV, IP accountability, and meetings with PIs as important activities for human subjects protection. For ensuring data integrity, all of these activities except interacting

**FIGURE 1: Reasons for issues going undetected**



with PIs were considered important by more than 60% of respondents. However, the most time was spent on SDV onsite by 70.3% of respondents, on ICF review by 26.6%, and on interaction with PI or training the site staff by nearly 6%. This is also reflected in the responses for time and effort required to achieve expertise, where more than 50% consider SDV as the most difficult activity in which to achieve expertise.

The respondents' major focus on SDV during monitoring at the cost of other activities, especially ICF, AE and SAE review, interaction with PIs, and training site staff is cause for concern. Their predominant focus on SDV could be due to the industry's practice of monitoring 100% of data, increasingly complex protocols, and a lack of medical background among some CRAs.

The U.S. Food and Drug Administration regulations do not mandate that monitors should check every source datapoint at each and every investigator site.<sup>3</sup> According to one study, SDV—a manual review process—is only 85% accurate.<sup>3</sup> However, 100% SDV has become a standard industry practice, as the industry believes this practice to be the best way to ensure the validity and integrity of clinical trial data.<sup>3</sup> Hopefully, risk-based monitoring may lead to changes in industry practices for SDV.

Although CRAs consider reporting AEs/SAEs important, the actual time spent doing so may be

Our survey showed that more than 50% of respondents considered reporting AEs and SAEs, ICF review, training of site staff, SDV, IP accountability, and meetings with PIs as important activities for human subjects protection.

## → HOME STUDY

### *Daily Challenges to the Future of Clinical Trial Conduct*

In the future, computing skills are expected to become vital as sponsors adopt risk-based monitoring approaches, which involve working with sophisticated systems and software.

less than it seems at first, since it may be thought of as part of SDV. Meanwhile, ICF reviews may be limited to checking signatures and dates on the ICF and the adequacy of the consent narrative.

Interaction with the monitor is crucial for the PI to receive independent feedback on the performance of his/her site, noncompliance to protocol or regulations, overall data quality, areas of risk/improvement, and any actions he/she needs to take to ensure that the highest quality standards are met at the site. Hence, the importance of interaction with the PI cannot be undermined. Further, training of site staff has a direct impact on the way the clinical trial is conducted, and the availability of well-trained site staff helps CRAs to perform their work efficiently.

The results showed less focus on site file review and resolution of data queries than on other tasks. Site file review is indispensable to ensure that the essential documents are accurately filed in a timely manner, and are available to demonstrate compliance with good clinical practice and regulatory requirements.<sup>4</sup> Resolution of data queries is also necessary to obtain high-quality data.

Less time spent on activities other than SDV could be due to perceived time constraints and inadequate training of monitors. Other reasons that were reported for issues going undetected included the complexity of protocols and multiple documents for review, which may be interlinked.

Clinical trial protocols have become more complex, demanding, and burdensome for monitors and sites. According to Getz et al., between 1999 and 2005, the average number of inclusion criteria increased threefold, and the average number of procedures grew annually by 6.5%, reaching a median number of 35 procedures in 2005. In 2012, a typical Phase III protocol included 50 eligibility criteria, 167 procedures, and 13 endpoints.<sup>5,6</sup> This is compounded by the fact that more than 66% of CRAs come from a nonmedical background.<sup>1</sup> Hence, they could face difficulties while reviewing physicians' notes (illegible handwriting, use of unfamiliar terms or shorthand, difficult-to-understand endpoints). This also implies a possible gap in training on familiarity with clinical documentation practices.<sup>1</sup>

It is difficult to ascertain the amount of experience that would make a CRA capable of monitoring a study independently. Hence, competency assessments held prior to and periodically after CRA undertake independent monitoring are strongly recommended.

### TRAINING: ADEQUACY AND PREFERRED APPROACHES

More than half of the respondents reported inadequate training for conducting meetings with PIs. Also, 30% to 37% felt that training for conduct of SDV, IP accountability, site file review, and site staff training was inadequate. This could have a significant influence on a CRA's functioning and performance, in terms of managing all activities required to ensure subject protection and data integrity during a monitoring visit.

A majority of the respondents preferred face-to-face training approaches. Co-monitoring was rated as the most preferred approach by 50% to 63% for critical activities like SDV, IP accountability, meeting PIs, and ICF review. In addition, interactive workshops were favored by the respondents.

The hands-on experience of monitoring activities and interactions with experienced colleagues or study managers help trainee CRAs learn the intricacies of the job and retain more than in a classroom environment or a web-based module. An effective co-monitoring program advances the knowledge and skills of CRAs.<sup>7</sup>

There is an increasing trend in the amount of web-based training. This may be because of time and cost constraints, technology advancement, training standardization requirements, and work being performed remotely by CRAs. Our survey suggests that web-based training is perceived to be the least preferred way to learn most monitoring activities. Sponsors may want to make an effort to replace or to combine web-based training with hands-on training and/or with interactive workshops.

### IMPORTANCE OF SKILLS

More than 95% of the respondents rated communication skills as very important. However, these skills are often overlooked in CRA training.<sup>8</sup> Communication skills should be imparted early in the monitor's career, along with technical training before starting independent monitoring.

Other skills rated very important by more than 50% of the respondents were interpersonal, conflict management, negotiations/teamwork, and presentation. In addition, the overall responses emphasize that CRAs have to learn time management skills, assertiveness in terms of minimizing interruptions during monitoring, and the art of providing objective feedback on site performance.



Usually, CRAs are exposed to these skills in workshop settings; however, their use can only be sharpened in on-the-job situations during actual monitoring. Inadequate knowledge and lack of some skills (e.g., assertive communication, negotiation, time management) could explain why CRAs devote less time to some important activities (e.g., interaction with PIs).

In the future, computing skills are expected to become vital as sponsors adopt risk-based monitoring approaches, which involve working with sophisticated systems and software. Thus, CRAs have to be savvy about information technology.<sup>9</sup> In addition, they should be able to use their analytical skills to derive appropriate action plans based on available data metrics.

Some of the limitations of this survey include that there was no information on respondents' electronic data capture system usage, therapeutic areas of specialty, and routine level of study complexity. A detailed analysis of this information may open new facets to the discussion.

## Conclusion

In conclusion, our CRA respondents are aware of the vital role they play in ensuring protection of clinical trial participants' rights, safety, and well-being, as well as protecting data integrity, but they often are unable to balance the requirements of SDV and other critical activities. In this regard, the industry's focus on risk-based monitoring looks promising; however, this practice will almost certainly still require all essential training requirements for CRAs and sites being fulfilled to provide its intended benefits.

The generalizability of the survey findings are limited by the relatively small sample size, and by the fact that a majority of respondents were from Asia. However, the results garnered from this survey can be good indicators to the leadership of sponsor organizations that they need to prioritize the development of CRA skills. This includes allocating adequate amounts of training time for each monitoring activity, adopting the best approaches to train CRAs on different monitoring activities, and working toward avoidance of factors leading to issues going undetected in studies.

*Disclaimer: All opinions expressed herewith are those of the authors, and do not reflect the views of their organizations.*

---

Interaction with the monitor is crucial for the PI to receive independent feedback on the performance of his/her site, noncompliance to protocol or regulations, overall data quality, areas of risk/improvement, and any actions he/she needs to take to ensure that the highest quality standards are met at the site.

---

## References

1. Matzat J. 2011. Educating and training CRAs for the field: the pursuit of excellence. *Monitor* 25(1):32–5.
2. Rai K. 2011. Integrated monitoring: setting new standards for the next decade of clinical trial practice. *Perspect Clin Res* 2:28–33.
3. Korieth K. 2011. The high cost and questionable impact of 100% SDV. *CenterWatch Monthly* 18(2).
4. International Conference on Harmonisation Harmonised Tripartite Guideline For Good Clinical Practice E6(R1). Available from [www.ich.org/fileadmin/Public/Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public/Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf) (last accessed on September 3, 2015).
5. Getz K. 2008. Protocol design trends and their effect on clinical trial performance. *Reg Aff J – Pharma* 19:315–6.
6. Getz KA. 2014. Opportunities to optimize study design to drive development performance and efficiency. *Clin Res* 28(2):28–31.
7. Weeks E. 2008. The art of assessment: performance evaluation co-monitoring visits. *Journal Clin Res Best Pract* 4(11):1–2.
8. Donati C. 2001. Communication skills for monitors: a vital training opportunity. *Appl Clin Trials* 10(7):36–9.
9. Getz K. 2007. A CRA: jack of all trades. *Appl Clin Trials* 16(7):36–8.

---

**Niranjana Kulkarni** (ninjukulkarni@gmail.com) is a trial manager with Novartis HealthCare Ltd.

**Arun Bhatt, MD, FICP, FICR** (arun\_dbhatt@hotmail.com) is a consultant in clinical research and development.

**Jeroze Dalal, PhD**, is global clinical operations leader for Novartis HealthCare Ltd.

# Daily Challenges to the Future of Clinical Trial Conduct

## OPEN BOOK TEST

This test expires on April 30, 2017

(original release date: 4/1/2016)

### Drug Products for Investigator-Initiated Research

1. Drug sources for a clinical trial are typically managed by:
    - A. A local pharmacy
    - B. A pharmaceutical company
    - C. An analytical laboratory
    - D. The U.S. Food and Drug Administration
  2. Drugs require the right physical properties to meet:
    - A. Suitable appearance
    - B. Ease of location
    - C. Consumer preferences
    - D. Metabolic conditions
  3. Limited scale or imprecise equipment can result in:
    - A. Operator safety issues
    - B. Incomplete sampling
    - C. Product variation
    - D. Utility disruptions
  4. What is the primary reason to establish legal responsibilities for drug requirements?
    - A. Protection of the public and patients' rights
    - B. Support for collection of product taxes
    - C. Enforcement of patent and trademark rights
    - D. To follow individual state laws
  5. The drug product must be assessed for which of the following prior to its administration in humans?
    - A. Size in relation/proportion to the patient
    - B. Total count of the dispensing container
    - C. Likelihood of confusion with existing products
    - D. Whether it meets defined specifications
  6. Low and questionable quality ingredients can result in:
    - A. Unacceptable levels of impurities
    - B. Excessive dust in the process
    - C. Greater demands for addition of water
    - D. Inadequate storage locations for inventory
  7. Which of the following is a consequence of making multiple small batches of the drug product?
    - A. Depletion of holding containers
    - B. Increased sample disposals
    - C. Product unit variability
    - D. Complex lot numbering
  8. The critical aspects of packaging include:
    1. Labeling
    2. Traceability
    3. Sealing
    4. Blinding
      - 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. Lack of testing evidence can result in:
    - A. Additional investigator requirements
    - B. Production delays
    - C. Patient risk
    - D. Detailed document reviews
  10. A drug standard is typically taken from a batch that is:
    - A. Produced first
    - B. Stored in glass
    - C. Low in moisture
    - D. Further purified
- ### Key Considerations for Social Media Recruitment Platforms
11. Successfully using social media platforms to recruit patients primarily depends on:
    - A. Addressing the needs of the study's principal investigator
    - B. Using an online system to run all aspects of the clinical trial
    - C. Addressing the needs of the targeted patient population
    - D. Honing the aesthetics of the social media recruitment platform
  12. According to a recent study, what percentage of patients were unaware that clinical trials were a treatment option?
    - A. 65%
    - B. 75%
    - C. 85%
    - D. 95%
  13. Approximately how many studies are currently registered with ClinicalTrials.gov?
    - A. 180,000
    - B. 200,000
    - C. 150,000
    - D. 100,000
  14. Which of the following is a drawback of using ClinicalTrials.gov for patient recruitment?
    - A. An insufficient number of studies are registered with this site
    - B. Poorly informed patients may find it difficult to navigate
    - C. It provides insufficient detail about many of the listed trials
    - D. It is not promoted enough to patients by clinical researchers
  15. Although prevalent in patient support groups, patient-to-patient communication has historically been uncommon in clinical trials because:
    - A. Legal restrictions on such activities are placed upon research sites
    - B. Patients involved in support groups may not also be involved in studies
    - C. Good clinical practice discourages site staff from allowing patient interaction
    - D. It may lead to bias on a trial's outcome or future recruitment
  16. One area of concern when using social media platforms for recruitment is:
    - A. An overwhelming number of patients will approach study personnel
    - B. Patients will decline participation in clinical trials due to overload of information
    - C. Patient privacy protection is an ongoing and challenging issue
    - D. Once a platform is up and running it cannot be inactivated

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

- 17.** Which of the following software platforms was created at a major university to support researchers' study recruitment efforts?
- A. Trial Prospector
  - B. ZocDoc
  - C. PrivateAccess
  - D. PatientsLikeMe
- 18.** Which of the following social media platforms is currently used to support physician-patient relationships in the context of standard medical care?
- A. Trial Prospector
  - B. ZocDoc
  - C. PrivateAccess
  - D. PatientsLikeMe
- 19.** According to a study done by the Tufts Center for the Study of Drug Development, what percentage of pharmaceutical and biotechnology companies in the U.S. expect to increase their use of social media for patient recruitment?
- A. 50%
  - B. 65%
  - C. 75%
  - D. 95%
- 20.** Which of the following is the most fundamental aspect for the proposed ideal social media-based recruitment tool?
- A. A coded database containing patient demographics and history
  - B. Geographic mapping of studies based on the sites currently enrolling
  - C. Its ability to integrate an algorithm-based matching system
  - D. Modules for communication between different parties involved in the process

#### Challenges and Training Needs for Clinical Research Associates—A Survey

- 21.** Per the survey, on which monitoring activity did most CRAs (respondents) spend the maximum amount of time during monitoring visits?
- A. Interaction with principal investigator
  - B. Resolving data queries
  - C. Source document verification
  - D. Site file review
- 22.** Per the survey, on which monitoring activity did CRAs (respondents) spend the least time?
- A. Interaction with principal investigator
  - B. Resolving data queries
  - C. Source document verification
  - D. Site file review
- 23.** Maximum time and effort are required to achieve expertise in which of the following monitoring activities?
- A. Interaction with principal investigator
  - B. Resolving data queries
  - C. Source document verification
  - D. Site file review
- 24.** Which of the following activities was perceived as most critical for protecting the rights, safety, and wellbeing of subjects?
- A. Investigational product accountability
  - B. Reporting AEs and SAEs
  - C. Resolving data queries
  - D. Site file review
- 25.** Which of the following activities was perceived as least critical for ensuring the integrity of the data?
- A. Investigational product accountability
  - B. Reporting AEs and SAEs
  - C. Resolving data queries
  - D. Site file review
- 26.** Which training approach was rated as the most preferred for the majority of monitoring activities?
- A. Classroom trainings
  - B. Co-monitoring visits
  - C. Self-learning
  - D. Web-based training
- 27.** Which of the following is a preferred approach for learning to resolve data queries?
- A. Classroom trainings
  - B. Co-monitoring visits
  - C. Self-learning
  - D. Web-based training
- 28.** According to most of the CRAs (respondents), less than adequate training is provided for which of the following monitoring activities?
- A. Informed consent form review
  - B. Investigational product accountability
  - C. Meeting principal investigator
  - D. Resolving data queries
- 29.** What is the most common reason for issues going undetected during monitoring?
- A. Interruptions by patients during monitoring visits
  - B. Inadequate training by monitors to site staff
  - C. Lack of proper monitoring tools due to budget cuts
  - D. Too many documents to confirm compliance
- 30.** Which skill was rated as "very important" to CRAs by the highest number of survey respondents?
- A. Computing
  - B. Communication
  - C. Teamwork
  - D. Presentation