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The mother-daughter team of Donna and Ashley Appell discussed their patient advocacy activities at the ACRP 2014 Global Conference & Exhibition. See page 38.

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October 2014 • Volume 28, Issue 5 • ISSN 2334-1882

EARN 3.0 CREDITS IN THIS ISSUE OF *CLINICAL RESEARCHER*

Clinical Researcher ISSN 2334-1882 (Print) and ISSN 2334-1890 (Online) is published bimonthly. It is provided to ACRP members by the Association of Clinical Research Professionals (ACRP). The views, research methods, and conclusions expressed in material published in *Clinical Researcher* are those of the individual author(s) and not necessarily those of ACRP.

Postmaster: Send address changes to Clinical Researcher
99 Canal Center Plaza, Suite 200,
Alexandria, VA 22314

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A. Veronica Precup

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It's been eight years since I became the editor-in-chief for the Association of Clinical Research Professionals (ACRP). Accomplishments over that time include:

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Now it's your turn. It's time for you to write an article for us, or coauthor one with a colleague. It's time for you to tell your fellow clinical researchers about the latest project—what worked and what didn't, what lessons were learned, and what solutions were implemented. It's time to tell them about the latest regulatory guidance from the competent authorities where you live and work, the most recent ethical dilemma, recruitment and retention issues, newest trends, budget and billing concerns, human subject protection worries, and the list goes on.

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Last but not least, keep sending us your feedback. Whether you like or don't like what you read in our pages, we want to hear from you. You can always reach me at editor@acrpnet.org. I'm looking forward to seeing your articles!

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2015 Editorial Calendar

Issue	Submission Deadline	Main Topic/Theme
February 2015	September 15, 2014	Integrating Research into Healthcare
April 2015	November 15, 2014	Patient Centricity
June 2015	January 15, 2015	Lean Approach, Risk Mitigation/Management
August 2015	March 15, 2015	Phase IV, Postmarketing, and Rare Disease Research
October 2015	May 15, 2015	Research Billing Compliance
December 2015	July 15, 2015	Clinical Research Careers

On an ongoing basis, we plan to publish timely articles on a range of topics of concern to clinical research professionals, including, but not limited to, current trends in clinical research, covering not just the various types and methodologies of trials, but more focused to include hot topics like patient-centered research, personalized medicine, and risk-based monitoring.

We encourage all of our readers to write for us at any time and on any topic pertaining to clinical research studies and the work of those who conduct them.

Sarah Cohen Photography

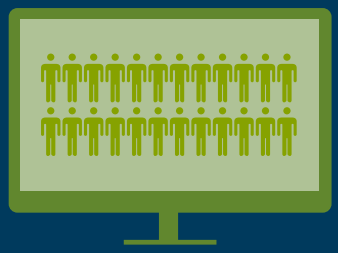
A. Veronica Precup is editor-in-chief of *Clinical Researcher* for the Association of Clinical Research Professionals.

BY THE NUMBERS

Summing up some of the statistics behind efforts to protect human subjects in research projects around the world.

The U.S. Office for Human Research Protections **(OHRP) DATABASE** includes:

9,588



records on the status of registered institutional review boards (IRBs) and

8,178 such records on "IRB organizations" with which OHRP has interacted as it provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services.

Source: http://ohrp.cit.nih.gov/search/irbsearch.aspx and http://ohrp.cit.nih.gov/search/search.aspx

The nonprofit Association for the Accreditation of Human Research Protection Programs (AAHRPP) has granted full or qualified accreditation to

198

organizations in **46** states, Canada, China, India, Mexico, Saudi Arabia, Singapore, South Korea, and Taiwan.

Source: www.aahrpp.org/learn/news-releases

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CRA CENTRAL
Jamie Meseke, MSM, CCRA

Techno-Monitoring: Adjusting to the Speed of Research

Patient-centered research involves identifying the best interventions for an individual patient, not the average patient, and research has shown that technology can have a major impact on closing the gap between clinical research and clinical practice.[1] However, the push to shorten the amount of time needed to move a product to market and the trend toward patient-centricity has resulted in myriad new issues and considerations.

To ensure the protection of the rights, welfare, and safety of subjects, and the maintenance of protocol compliance and data integrity, clinical research associates have to adapt monitoring practices to fit a rapidly changing landscape.

Change and Challenge

Technological enhancements such as video-assistance, electronic consent, web-based interactivity, and online social networks offer the promise of reducing costs and increasing patient awareness; however, these advances also pose potential hazards to subject safety, privacy, and protocol compliance. New technology also affects research monitoring activities. To ensure the protection of the rights, welfare, and safety of subjects, and the maintenance of protocol compliance and data integrity, clinical research associates (CRAs) have to adapt monitoring practices to fit a rapidly changing landscape.

Sponsors are adopting new technology with hopes of expediting patient accrual and making the clinical trial process more efficient and patient-centric:

- Facebook is used by study sponsors (through purchases of advertisements) to target certain audiences by age and geographic location, among other factors.
- Several sponsors, including Janssen, have developed iPad applications (apps) to supplement the delivery of study information during the informed consent process. These apps introduce patients to potential trials through animated video and interactive features, such as glossaries for unfamiliar terminology.[2]
- eResearch Technology, Inc. partners with pharmaceutical sponsors, device manufacturers, contract research organizations, and healthcare organizations worldwide to collect and analyze patient data through a number of devices like the SITEpro® tablet, which captures clinical outcome assessment data directly from the patient. This and other similar devices are being used to capture patient quality-of-life responses and other assessments that historically have been collected via paper questionnaires.
- Electronic consent is also becoming increasingly common, especially for certain low-risk online, noninterventional survey studies and screening evaluations to do preliminary assessments for subject eligibility.

Patients Get into the Game

Technological advances are not limited to sponsor-initiated enhancements used to boost study accrual. Patients are becoming savvier with navigating the web and its social media outlets to learn about clinical trial opportunities and share their experiences.

Although not intended as a method for study recruitment, in 2000, the National Institutes of Health launched ClinicalTrials.gov, a website now offering information on more than 170,000 clinical studies.

An example of a more direct outreach to possible study participants, as noted in the cover story from the April 2014 issue of *Clinical Researcher*, is the Michael J. Fox Foundation's Fox Trial Finder, a web-based tool intended to boost patient participation in clinical trials for Parkinson's disease by matching volunteers to study teams.[3] Similarly, the Leukemia and Lymphoma Society (LLS) developed a web-based tool it calls TrialCheck, which connects patients with actively accruing blood cancer clinical trial opportunities.

Several disease support networks, including LLS, have created virtual discussion boards for fostering peer-to-peer interactions so patients and caregivers may exchange information and receive support. These discussion boards are not limited to patient experiences and exchange of information about the disease, and for many patients, may be the primary resource for learning about available trials.

Benefits and Drawbacks at a Glance

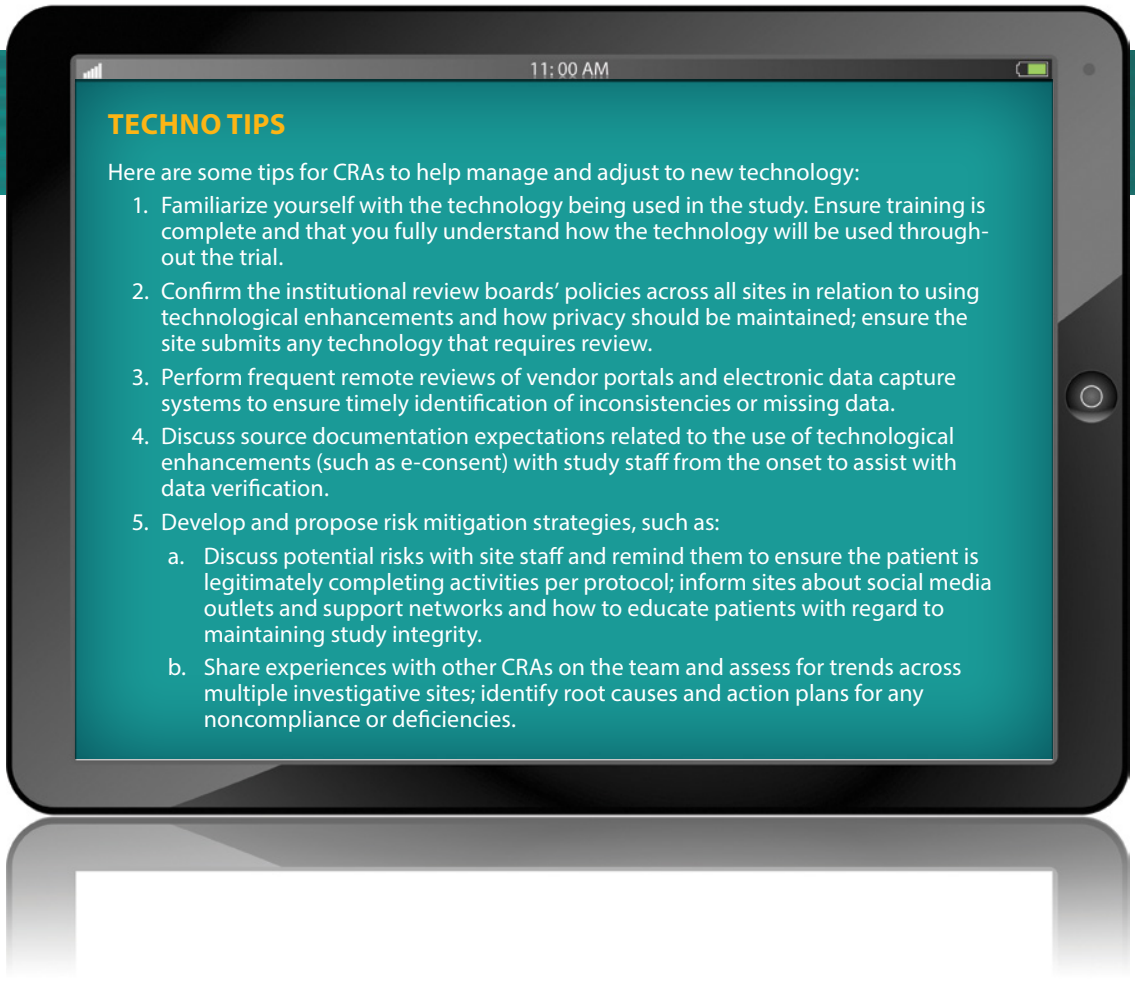
At first blush, the benefits of these new technological enhancements seem to outweigh the risks. By using e-consents and social media outlets, sponsors and clinical trial teams are able to reach a much larger audience of potential patients, and information may be rapidly transmitted. Similarly, patients are better able to find trial opportunities and share their personal experiences with other patients who may be participating on the same, or in a similar, study.

Current research is mixed with regard to whether compliance is greater with paper or e-diaries. However, there seems to be a consensus that overall data quality may be improved when e-diaries are used.

Some people suggest that these types of technological enhancements may increase patient understanding of the research study, and as a result, patients may be more engaged and experience less anxiety related to participation.[4] E-consenting and the incorporation of video snippets and interactive modules also provide a means for ensuring consistency in the delivery of study information, and may even accelerate the screening and consenting process.

In theory, expanding access to more patients and streamlining the consent process should lead to reduced accrual timelines, which would also translate to reduced overall trial costs. However, a few inherent risks and challenges should be considered with these technology enhancements:

- Foremost, when the patient and research staff member are not physically located at the same place, it can be difficult, if not impossible, to verify the person completing the e-consent or tablet-based study assessment is legitimately the potential study participant.
- Likewise, patients may not be fully informed about who will have access to the information they provide electronically, and there may be justifiable concerns related to confidentiality of the healthcare data.
- Social media and online support networks allow for the possibility that study blinds could be broken, data could be skewed, or patients could become noncompliant, based on experiences or comments from others.
- For study sponsors, the cost of developing, incorporating, and maintaining the technology must be weighed in relation to the expected benefit over traditional recruitment methods.
- The U.S. Food and Drug Administration and other regulatory agencies around the world have not yet implemented robust guidelines for the use of electronic technologies in clinical research.
- Finally, research results are mixed regarding whether technology enhancements actually increase overall attainment of informed consent.[5]



What Does it All Mean for CRAs?

New technology creates challenges and opportunities for CRAs, and changes in monitoring practices (such as reduced source verification) require CRAs to adopt a much broader mindset toward overall quality and risk assessment.

CRAs now have to think critically about the significance of trends identified across multiple investigative sites, and the process of verifying source data is not always straightforward. For example, the informed consent process may not be well documented when e-consent is used, so it can be challenging for the CRA to confirm whether a participant was fully and properly consented.

Likewise, monitoring electronic patient diaries may seem like a daunting task when the CRA cannot verify whether the diaries were legitimately completed by the patient. In fact, current research is mixed with regard to whether compliance is greater with paper or e-diaries. However, there seems to be a consensus that overall data quality may be improved when e-diaries are used.

With paper diaries, participants can backfill multiple entries at one time and potentially introduce bias into the data since recall of times, doses, and events may be unreliable.[6] New e-diaries feature enhancements such as time and date stamps, which serve as audit trails to confirm participant compliance. The CRA, therefore, must assess both the risks involved with participant use of new technology as well as the overall quality of the data collected.

Summary

Technology offers tremendous potential for reducing product time to market and increasing patient engagement. As sponsors and patients adapt to the changing processes, CRAs must also become accustomed to thinking about quality and risks in a new and much broader way.

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Tips for Successful Study Implementation in England:

The Sponsor Perspective on Using Sites of the National Health Service

PEER REVIEWED | Heiko Ballies, MA, CCRA | Georgia Mitchell, MA

[DOI: 10.14524/CR-14-0022]

The publicly funded healthcare system in the United Kingdom, known as the National Health Service (NHS), provides public healthcare to each of the four countries in the U.K. (i.e., England, Scotland, Wales, and Northern Ireland). In 2006, England set up the National Institute for Health Research (NIHR) to provide quality and focus to NHS research.[1] As part of the NIHR, the Clinical Research Network (CRN) was developed as a service to provide an infrastructure to support clinical research in the NHS in England through a variety of free services and support.[2] Part of the CRN's job is to manage the "portfolio," which is a database of clinical trials that NIHR has determined to be of high quality and therefore eligible for CRN support.[3]

LEARNING OBJECTIVE
After reading this article, participants should be able to describe key steps sponsors need to know for successful clinical trial implementation in the United Kingdom.

DISCLOSURES
Heiko Ballies, MA, CCRA: *Employee of Stryker Trauma GmbH*
Georgia Mitchell, MA: *Employee of Stryker Howmedica Osteonics*

Consider Portfolio Adoption

The CRN has a pathway for industry sponsors to submit their clinical trials for "portfolio adoption."[3] The portfolio adoption submission is made using the NHS's Integrated Research Application System (IRAS),[4] a web-based system that automatically generates the NIHR CRN Portfolio Application Form once question 5b of the IRAS Project Filter is answered in the affirmative.

Portfolio adoption has a number of advantages. For one, the CRN will provide assistance in identifying potentially suitable sites by disseminating blinded information on the clinical study (i.e., study phase, device and/or condition under investigation, inclusion/exclusion criteria, target population, study objectives) to NHS sites in England that have expressed interest in conducting research.[5]

Additionally, sites participating in a portfolio-adopted study may ask the CRN for staffing resources (e.g., research coordinators, study nurses).[3] Portfolio-adopted studies are eligible for staffing support by the CRN at no cost to the site or sponsor. In the authors' experience, these resources provided by the CRN have facilitated the negotiation of sponsor/site contracts because the personnel expenditures at the site were decreased.

As the main point of contact to the sponsor, the CRN:

- works to identify the staff support needed at the sites,
- keeps the sponsor-identified chief investigator (more about this individual below) informed on the progress at the individual research networks, and
- helps to resolve any problems that may arise.[5]

In return, the CRN expects sponsors to provide monthly updates on the performance of the U.K. sites, either by e-mail or teleconference.

Appoint a Chief Investigator

Before applying for portfolio adoption, the sponsor must identify a "chief investigator" (CI) who, during the initiation phase of a clinical study, acts as the main point of contact for the sponsor's submission to the applicable research ethics committee (REC). Normally, a local principal investigator assumes the CI role, since RECs prefer the appointment of researchers who are professionally based in the U.K.

In exceptional cases, a person from outside the U.K. may be appointed as a CI, but the final decision is at the discretion of the REC.[6] The International Conference on Harmonization's Guideline for Good Clinical Practice (ICH GCP) E6[7] and REC guidelines are similar in that the CI must have ample experience in the design and conduct of clinical research. This individual will assume responsibility for:

- ethical and legal study conduct,
- study design,
- study management, and
- reporting, including the review and reporting of adverse events to the REC.[8]

Since the CI's role is not explicitly defined in the model Clinical Trials Agreement (mCTA) provided by the NIHR, negotiation of a separate agreement defining the CI's duties and the reimbursement associated with those duties is advisable. Further information regarding the mCTA is provided below.

Special Requirements for Sponsors

As per the European Commission's directives 2001/83/EC ("Medicinal Products for Human Use") and 93/42/EEC ("Medical Devices"), manufacturers that are based in a third-party country outside of the European Union (EU) need to appoint a "representative of the marketing authorization holder" (2001/83/EC) or an "authorized representative" (93/42/EEC), respectively, established in the EU. This person acts and may be addressed by the respective authorities and regulatory bodies when applying for market authorization.[9,10]

For clinical trials, there are currently no binding directives in place that uniformly require the nomination of such representatives for study sponsors of third-party countries for the entire EU. However, the European Commission has drafted a proposal for a decree aimed at replacing the existing GCP directive 2001/20/EC ("Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use"). Part of this proposal is to demand that clinical trial sponsors appoint an "EU contact person" if the sponsor is established in a third-party country.[11] At the time of this writing, this proposal is not yet in force, but will come into effect in mid-2016 for all EU member states. Therefore, the need for appointing contact persons for study sponsors currently varies from country to country.

Part of the Clinical Research Network's job in the U.K. is to manage the "portfolio," which is a database of clinical trials that the National Institute for Health Research has determined to be of high quality and therefore eligible for network support.

There is a strong culture of clinical research in the U.K., and in general, U.K. clinicians are highly motivated to participate in research.

Meanwhile, the U.K. Department of Health issued the "Research Governance Framework for Health and Social Care" in 2005. This guidance states that sponsors of clinical trials interested either in adding U.K. sites that fall under the NHS trust, or in conducting research that includes social care services, must either be based in the U.K. themselves or have a legal representative based in the U.K.[8]

The Medicines and Healthcare Products Regulatory Agency (MHRA), however, has issued a separate guidance specific to medicinal products. According to the MHRA, which is responsible for regulating all medicines and medical devices in the U.K., a clinical trial involving medicinal products merely requires sponsors not legally based in the European Economic Area (EEA) to appoint a legal representative that is based in the EEA.[12]

As of this writing, the EEA includes the EU Member States plus Liechtenstein, Iceland, and Norway.[13] The legal representative may be an individual or an entity, but must have an established address either in the U.K. (according to the Department of Health's "Research Governance Framework") or in a country within the EEA (according to the MHRA).

In general, the legal representative does not assume the legal liabilities of the sponsor, but serves as the sponsor's agent regarding any legal proceedings that may take place. The NHS advises that a contract be in place between the sponsor and legal representative to ensure the responsibilities, risks, and liabilities are clearly defined.[14] Due to the uncertainties surrounding this delicate matter, the authors recommend that sponsors liaise directly with the Department of Health and/or MHRA and ask for guidance. We have provided helpful links in a sidebar with this article.

Register Your Study

In some cases, submissions through IRAS have become compulsory (e.g., the "NIHR Coordinated System for gaining NHS permission" [NIHR CSP] in England, and the NHS Research Scotland [NRS] multicenter review system). As soon as the sponsor has appointed a CI and the lead NHS research and development (R&D) contact (usually located with the CI site's NHS R&D team) has been identified, the sponsor should submit to IRAS. This submission will allow for the next steps of identifying the responsible review bodies, registering the study with the CRN, and submitting documents to the REC.[15]

Even though the IRAS is intended to reduce complexity by providing a clear framework, there are some challenges for sponsors. Cooperation with a local contact who is experienced in using IRAS is advisable. Individuals who are required to provide their approval and signature on certain forms (e.g., medical physics experts, clinical radiation experts) should be identified early in the project.

Also, IRAS is continually updated without prior notice to the research applicant, which can make it difficult to adhere to the standardized procedure. The authors advise that the IRAS standardized procedure be followed, as deviations from the procedure will likely lead to delays in receiving registration or portfolio adoption.

Useful Links

Clinical Research Network (CRN): www.crn.nihr.ac.uk

CRN portfolio adopted study searchable database: http://public.ukcrn.org.uk/search

Department of Health: https://www.gov.uk/government/organisations/department-of-health

Integrated Research Application System (IRAS): https://www.myresearchproject.org.uk

National Institute for Health Research (NIHR): www.nihr.ac.uk

NIHR Clinical Trials Toolkit: www.ct-toolkit.ac.uk/routemap/sponsorship

Medicines and Healthcare Products Regulatory Agency (MHRA): www.mhra.gov.uk

Contracting with Sites

Once the study has been registered with the CRN and the REC's final approval has been obtained, the sponsor may contact sites to begin the contract negotiation process. The authors have found it helpful in reducing time and complexity to use the NIHR's mCTA with NHS sites rather than a sponsor's contract template, as these sites are familiar with the format and legalese of the mCTA. The NIHR has made the mCTA available for all types of clinical research supported by the NHS.[16]

In addition to the mCTA, most NHS sites will urge sponsors to make use of the NIHR's Industry Costing Template, which makes the process of negotiating costs transparent by clearly depicting the time and materials the site calculates for every step of the research project. However, use of the template can be a lengthy and complicated process, especially for first-time users. Also, this template is updated by the NIHR on a regular basis without prior notice, so keeping track of the latest version can be challenging. We advise sponsors work with someone who is experienced in its use.

Further, all NHS sites must calculate budgets and accept payments in pounds sterling (GBP) only. This item can become tricky, especially when applied to international multicenter clinical studies, since most sponsors calculate their budgets and site payments in U.S. dollars.

Conclusion

Including NHS sites can provide enrichment to your clinical research project. There is a strong culture of clinical research in the U.K., and in general, U.K. clinicians are highly motivated to participate in research. However, sponsors are expected to adhere to the process established by the NHS, which can prove to be challenging, especially if the sponsor is bound to its own standard operating procedures and/or there are study-specific restrictions that limit the sponsor's leeway.

Sponsors should always keep in mind that deviating from the NHS's proscribed process will likely result in delay. We recommend working with individuals who are knowledgeable about the process; however, sponsors should become familiar with the process as well as with the terminology used in the U.K., develop a plan early, and continually check the IRAS for updates.

CHECKLIST

- ✔ Appoint a chief investigator
- ✔ Nominate a legal representative (for non-U.K. sponsors only)
- ✔ Prepare and submit documents via IRAS
- ✔ Check for updates to IRAS regularly
- ✔ Identify potential sites by contacting CRN
- ✔ Use the mCTA for contracting with sites
- ✔ Use GBP to negotiate study costs

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Education and Training Needs Among Clinical Investigators and Medicines Development Professionals from Two Latin American Countries

LEARNING OBJECTIVE
After reading this article, participants should be able to (a) explain the value of a needs assessment prior to planning an educational initiative for clinical investigators and drug development professionals and (b) recognize the different requirements for planning an educational initiative in Brazil and Peru.

DISCLOSURES
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PEER REVIEWED | Honorio Silva, MD | Gustavo F. Kesselring, MD | Juan Luis Yrivarren, MD | João Massud Filho, MD | Thomas M. Thomson, PhD | Alejandro Silva, MS | Stephen Sonstein, PhD | Marcelo V. de Lima, MD | Pablo A. Pulido, MD, DMSc

[DOI: 10.14524/CR-14-0026]

There is increasing demand within the medicines development industry for sponsors and sites to improve clinical trial performance. Suggested methods include cost reduction, simplifying trial complexity, limiting patient risk, and improving trial efficiency, while at the same time increasing patient safety and ensuring the quality of the trial data.

Proper education and training for all members of the clinical research team have been regarded as of utmost importance to ensure the validity and quality of the data collected in the trial, and the primary training content has been based on the International Conference on Harmonization's (ICH's) Guideline for Good Clinical Practice (GCP).[1]Meanwhile, the U.S. Food and Drug Administration (FDA) requires that investigators and staff participating in clinical trials be qualified by training and experience to investigate drugs, biologics, and medical devices.

Due to such expectations, before a clinical trial begins, the trial sponsors generally require investigators to complete training related to GCP that is applicable to any trial, as well as specific training on the plan and techniques for the particular trial at hand. As a result, investigators who participate in clinical trials with more than one sponsor often complete GCP training multiple times, as required by sponsors' practices to comply with regulations.

Let's Talk Training

The Declaration of Helsinki has recently been modified to state that clinical research must be conducted by individuals with appropriate ethics and scientific education, training, and qualifications.[2] A risk-based recommendation for the oversight of clinical trials was also released by the FDA.[3] Therefore, the scope of education and training should expand beyond GCP; however, there is no harmonized standard for investigator or staff qualification. On a positive note, initiatives based on competency-based education, including the identification and harmonization of professional competencies and standards for accreditation of educational programs to be used for certification of the clinical research team, are under way.[4–9]

Even though there have been numerous recommendations to increase the content related to clinical research in the medical school curriculum, there is still very little or none included in the educational programs at the undergraduate (as reported in some Latin American countries) and postgraduate levels offered by medical schools all over the world.[10–13]

In the United States, around 60 Clinical and Translational Science Award programs in academic health centers have received grants from the National Institutes of Health and award a master's degree in clinical research.[14] The authors have also found approximately 50 programs at colleges and universities that offer academic degrees from associate- to doctoral-level programs.

In spite of the growing, though still insufficient, number of programs, there is no postgraduate education requirement for individuals performing and taking responsibility for clinical trials. Thus, education and training through continuing professional development (CPD) is emerging as the contingency approach to address such needs.[15] A number of accredited and non-accredited CPD activities are organized by professional associations tied to the clinical research enterprise; however, most of these training activities are related to the logistical and operational aspects of clinical trials.

The Need for Needs Assessment

The training needs assessment is a critical activity fundamental for the planning of any educational initiative. A needs assessment is a systematic process for determining and addressing needs (or "gaps") between current conditions and desired conditions.[16] The discrepancy between the current condition and the desired condition must be measured to appropriately identify the need. By clearly identifying the problem, finite resources can be directed toward developing and implementing feasible and applicable solutions.[17,18]

There are three types of needs assessment for any institution: organizational, occupational, and individual. A well-designed needs assessment would align the individual training needs with the organizational needs, and ensure that the training design will respond to the specific needs and establish the foundation for post-training evaluation.

A diverse array of tools is available to conduct a needs assessment, such as observation, interviews, questionnaires, job descriptions, appraisal reviews, analysis of organizational policy, and more. The use of questionnaires allows for a general description of the environment by asking respondents identical questions, usually includes more respondents than individual interviews, and takes less time than other tools. Furthermore, the data collected can be analyzed in a more quantitative way than in individual interviews.

Interestingly, very limited information is available regarding the use of a needs assessment in planning systematic education and training in clinical research and medicines development. In 2011, the former Academy of Pharmaceutical Physicians and Investigators (now renamed to Academy of Physicians in Clinical Research [APCR]) conducted an online survey to identify the training needs, educational background, and extent of actual training in pharmaceutical medicine achieved by pharmaceutical physicians in the U.S.[19] A similar exercise was conducted in the United Kingdom in 1992, prior to the introduction of specific training in pharmaceutical medicine and medicines development.[20]

The Inter American Foundation for Clinical Research and the Pan-American Federation of Associations of Medical Schools entered into a strategic collaboration with the Brazilian Society of Pharmaceutical Medicine (SBMF), the Peruvian Association for the Promotion of Clinical Research (APIC), and the Peruvian Association of Pharmaceutical Medicine (APMF), and agreed to conduct an educational needs assessment of the professionals involved in medicines development and clinical research in Brazil and Peru. The ultimate objective was to develop a leveraged curricular design of CPD or postgraduate educational activities in their respective countries.

Methods

Biomedical professionals listed in the membership of SBMF, APIC, APMF, and the Peruvian Registry for Clinical Trials were invited by the respective organizations to complete an online survey during the period November 2012 to March 2013. The survey, adapted from one conducted by Stonier and his colleagues[19], was focused on the following domains:

- Demographic data (age, type of organization worked for, main area of activity)
- Perceived value for the daily work and training needs in 26 basic knowledge areas in clinical research operations and medicines development
- Perceived value for the daily work and training needs in 17 interpersonal and business management skills
- Perceived value of investigational site accreditation and certification of the clinical research team to leverage clinical trial quality to formal requirements by the regulatory authorities
- Perceived value of the effectiveness of and preferences toward individual CPD activities

Feedback on the questionnaire's items was rated in a numerical scale from 1 (very little) to 5 (very large extent, very high).

All individuals identified in this convenience sample received weekly or biweekly reminders sent via e-mail, along with telephone calls aimed at ensuring the questionnaire acquired responses during the above-mentioned period and at achieving the desired error margin (5%) and confidence level (95%). With a confidence level of 95%, the percentage of people who marked 4 or 5 in the scale would be more than the margin of error away from the true answer. The true answer is the percentage that would occur if the data had been collected from the whole list.

The 43 items included in the questionnaire were arbitrarily assessed as "confirmed" educational and training needs if more than 60% of the respondents indicated that the relevance and knowledge needed for each of the individual subjects was high or very high (4 or 5 on the scale).

The online survey was created using software provided by SurveyMonkey.com. A data analysis plan including conventional descriptive, parametric, and nonparametric statistical tools was prepared. The raw data from SurveyMonkey were exported via Microsoft Excel to SAS (version 9.3.1) for analysis.

Results

The sample included 222 respondents in Peru and 490 in Brazil. The expectations for an error margin less than 5% and a 95% confidence level were met.

In Peru, approximately 60% of the respondents participated in research conducted in hospitals or academic institutions, whereas in Brazil, a similar percentage worked in the pharmaceutical or medical device industry or with contract research organizations. Thus, the Peruvian cohort was mostly composed of investigators and co-investigators (65%), whereas the Brazilian group was mostly composed of clinical research

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TABLE 1. Job Affiliation in Brazil and Peru (as percentage of total)

INSTITUTIONS	PERU	BRAZIL
Pharmaceutical Company	13	39
Biotech	1	3
Medical Device	1	1
Government/Regulatory	2	1
Hospital	54	17
Contract Research Organization	18	19
Academic Institution	2	9
Independent Consulting	1	3
Others	8	8
Total	100	100

TABLE 2. Clinical Research Responsibilities in the Surveyed Countries (as percentage of total)

FUNCTION	PERU (n = 222)	BRAZIL (n = 467)
Clinical Research Associate	11	18
Co-investigator	10	3
Pharmaceutical Physician	3	9
Study Coordinator/Project Manager	4	38
Clinical Research Nurse	1	1
Principal Investigator	56	4
Safety	1	5
Regulatory Affairs	3	11
Data Management	1	2
Quality Assurance	1	1
Training	1	7
Others	8	1
Total	100	100

coordinators (CRCs) and clinical research associates (CRAs) (see Tables 1 and 2). The two groups were comparable in work experience, since 60–70% of the combined group had been involved in clinical research for up to a decade.

The 26 items considered as "basic knowledge areas" were rated very highly in both countries. However, the individual relevance of emerging areas—as related to translational research, health economics, medical devices, data management, and biostatistics—was rated lower in Brazil as compared to Peru. Other subjects were regarded as less relevant, and thus significant differences were found between the two countries, particularly as related to GCP and clinical operations (see Table 3).

The cohorts from both countries agreed on the need for additional training in most of the proposed areas (see Table 4). Interestingly, the groups uniformly agreed on the need for additional training as related to GCPs and clinical operations; however, significant differences were noticed in the perception of training needs for other knowledge areas, such as translational medicine, biotechnology, and medical devices.

The relevance of the 17 "interpersonal and business management skills" to an individual's responsibility was very highly rated in both countries; most were in the 80–90% range (see Table 5). Also, both cohorts agreed on the need for additional education and training. However, each individual skill was rated differently, again generating statistical differences between countries, particularly as related to medical writing and media skills (see Table 6).

Both countries accepted the relevance of site accreditation as a tool to enhance the quality of clinical research (60% and 66% in agreement). Likewise, the individual certification of principal investigators and associated personnel (e.g., CRAs and CRCs) was highly rated. Both agreed that accreditation and certification initiatives should be led by national or international nonprofit organizations (see Table 7). No statistical differences were found between the groups.

Both cohorts agreed CPD activities would help in meeting their knowledge needs, particularly didactic sessions (conferences, courses) and interactive workshops, as well as mentoring and tutoring. Again, differences between countries were observed, particularly relating to the value of e-learning, which surprisingly received lower rates in Brazil (see Table 8).

TABLE 3. Percentage of Respondents Rating Basic Knowledge Area as "Important" or "Very important" for Daily Clinical Research Practice

BASIC KNOWLEDGE AREA	PERU (n = 220)	BRAZIL (n = 490)
Drug Discovery Process	86.3	74.7 *
Clinical Pharmacology Basics	77.9	59.5 *
Understanding Regulations	95.1	92.4
The Clinical Trials Process: Why? What? How?	96.1	83.3 *
GCP and Clinical Trial Operations	98.0	92.2 **
Ethical and Legal Aspects	97.1	95.4
Ethics Committees and Informed Consent	95.1	86.1 *
Norms for Clinical Trials and Standard Operating Procedures	95.1	89.3
Project Management and Project Management Tools	85.8	85.2
Quality Assurance and Audits	91.7	85.7 **
Contracts and Legal Matters	82.4	74.7 *
Site Selection and Monitoring	89.2	80.7 *
Drug Safety and Pharmacovigilance	93.1	68.2 *
Basic Biostatistics	78.9	55.0 *
Data Management and Statistical Analysis Plan	77.0	55.9 *
Basic Epidemiology and Clinical Trial Design	84.3	61. 3*
Trends in Clinical Research	84.3	75.9 *
Information Technology	82.4	59.4 *
Healthcare Economics	68.6	51.6 *
Translational Medicine	58.8	50.9
Biotechnology	71.6	56.3 **
Medical Devices	72.5	44.0 *
Drug/Device Combinations	77.0	48.1 *
Business Management and Supervision	75.5	74.5
Knowledge Management and Dissemination	78.9	79.2
Patient Recruitment Techniques	92.2	NA

** $p < 0.001$. ** $p < 0.05$*

TABLE 4. Percentage of Respondents Who Thought Additional Training was Needed in a Basic Knowledge Area

KNOWLEDGE AREA	PERU	BRAZIL
Clinical Pharmacology Basics	76.3	53.9 *
Understanding Regulations	76.8	60.9 *
The Clinical Trials Process: Why? What? How?	81.3	58.5 *
GCP and Clinical Trial Operations	82.8	87.4
Ethical and Legal Aspects	81.8	83.4
Ethics Committees and Informed Consent	85.4	89.3
Norms for Clinical Trials and Standard Operating Procedures	82.8	76.5
Project Management and Project Management Tools	84.3	79.8
Quality Assurance and Audits	79.3	80.7
Contracts and Legal Matters	86.9	83.5
Site Selection and Monitoring	81.8	73.2 *
Drug Safety and Pharmacovigilance	76.8	73.6
Basic Biostatistics	83.8	59.4 *
Data Management and Statistical Analysis Plan	76.3	49.5 *
Basic Epidemiology and Clinical Trial Design	74.2	54.8 *
Trends in Clinical Research	77.3	55.3 **
Information Technology	79.8	72.1 *
Healthcare Economics	75.8	52.8 *
Translational Medicine	72.7	48.4 **
Biotechnology	63.6	50.8 *
Medical Devices	71.2	56.7 *
Drug/Device Combinations	67.7	39.5 *
Business Management and Supervision	70.2	44.1 ***
Knowledge Management and Dissemination	78.3	70.7
Patient Recruitment Techniques	76.3	73.6

** $p < 0.001$. ** $p < 0.05 > 0.001$. *** $p < 0.05$*

Both cohorts agreed CPD activities would help in meeting their knowledge needs, particularly didactic sessions (conferences, courses) and interactive workshops, as well as mentoring and tutoring.

TABLE 5. Comparison of Percentage of Respondents Who Rated Interpersonal and Business Management Skills as Highly Relevant for their Daily Work

SKILL	PERU	BRAZIL
Communication and Presentation Skills	96.5	97.3
Leadership	96.5	94.3
Teamwork	98.5	97.5
Tutoring and Mentoring Others	96.0	94.3
Negotiation	90.4	89.1
Medical Writing	84.3	64.0 *
Network Development	89.4	90.1
Conflict Management and Resolution	94.4	94.0
Media Skills	84.3	53.4*
Communication with Study Participants	90.4	71.1 *
Interpersonal Communication with the Team	94.9	93.3
Decision Making	98.0	96.8
Project Planning	96.4	91.0 *
Crisis Management	91.3	90.0
Human Resources Management	91.3	84.0 **
Financial Management	90.8	71.9 *
Time and Stress Management	93.4	91.7

*$p < 0.001$. **$p < 0.05 > 0.001$.

TABLE 6. Percentage of Respondents Who Needed Additional Training in Interpersonal and Business Management Skills

SKILL	PERU	BRAZIL
Communication and Presentation Skills	86.3	87.8
Leadership	84.8	87.8
Teamwork	85.3	87.5
Tutoring and Mentoring Others	83.8	83.8
Negotiation	82.2	87.2
Medical Writing	80.7	62.1 *
Network Development	80.2	77.9
Conflict Management and Resolution	88.3	90.3
Media Skills	77.2	56.3 *
Communication with Study Participants	77.2	71.5
Interpersonal Communication with the Team	88.8	85.9
Decision Making	86.7	90.0
Project Planning	87.8	88.9
Crisis Management	84.2	88.5
Human Resources Management	85.2	86.5
Financial Management	88.3	77.5 **
Time and Stress Management	87.8	88.7

*$p < 0.001$. **$p < 0.002$.

TABLE 7. Perception of Value (Agreement/High Agreement) of Accreditation and Certification Initiatives to Leverage Clinical Research Quality (as percentage of total)

INITIATIVE	PERU	BRAZIL
Certification of Principal Investigators	60.1	66.6
Certification of Research Staff	79.0	84.2
Investigational Site Accreditation	76.9	84.8
Accreditation/Certification by National Regulatory Agency	60.3	79.5
Accreditation/Certification by International Nonprofit Organization	73.0	80.7
Accreditation/Certification by International For-Profit Organization	27.0	58.8

TABLE 8. Comparative Perception of Value (High/Very High) of CPD Activities (as percentage of total)

CPD ACTIVITY	PERU	BRAZIL
Conferences, Courses	85.1	66.5*
Interactive Workshops	87.0	66.8*
e-Learning Programs	72.1	38.7*
Teaching, Training, Tutoring	77.9	66.2**
Team Learning	85.6	69.8*

*$p < 0.001$. **$p = 0.02$.

The scope of education and training should expand beyond GCP; however, there is no harmonized standard for investigator or staff qualification.

Discussion

The authors conducted a needs assessment on education and training through CPD via an online survey of a convenience sample of professionals involved in clinical research and medicines development affiliated with professional associations in Peru and Brazil. While the sample is not representative of the entire universe of clinical research professionals, its error margin and confidence level are acceptable for formulating further specific educational research in the area.

Despite the fact that Peru and Brazil are two distinct countries in terms of size, population, language, cultural traditions, and the like, their medical practices are similar. Brazil is well established as the leader in clinical research activity in Latin America, whereas Peru is rapidly emerging among sponsors as an alternative location for conducting clinical trials.[21,22]

Our needs assessment was conducted among two distinct populations: clinical investigators (and associated staff) from hospitals and academic institutions, and biomedical professionals serving in the pharmaceutical or biotech industry and contract research organizations. The first group had a higher representation in Peru and the second in Brazil. Nonetheless, both populations rated the basic knowledge areas and interpersonal and business management skills as highly relevant to their daily activities; thus, these components should be considered appropriate for the planning and preparation of basic curricula for postgraduate and CPD education. Particular attention should be paid to the business management skills, since such topics are included as part of CPD activities organized by professional associations in many countries.

As expected, there were differences in the rating of each basic knowledge area and business management skill among the cohorts from each country. These could be attributed to the above-mentioned differences in professional background and affiliation or previous experience in clinical research. Since this study was one of the first explorations of educational needs, further assessment on functional bases should be conducted at the time of planning any specific educational activity. On the other hand, the harmonized core competencies for clinical research professionals are already available,[8] and thus a competency-based needs assessment should be the preferred approach.

The overall results from Brazil and Peru are comparable to similar findings in the U.S. among pharmaceutical physicians,[19] and therefore corroborate proposed initiatives toward creating a core curriculum for education either at the postgraduate or CPD levels based on core professional competencies.[8] These initiatives might be the best approach for clinical research professionals in general, regardless of differences in their geographic settings, professional backgrounds, or functional roles in drug development and clinical trials. At the present time, most of the education and training of clinical research professionals is based upon GCP knowledge and application, so a harmonized assessment of core competencies (knowledge, skills, and abilities) could be the next step. Thus, further education and training initiatives would be based upon the competency domains as recommended.

Both countries had very favorable opinion of the value of investigational site accreditation and the certification of the clinical research team. Interestingly, it was felt that such initiatives should be run by the national regulatory agency or nonprofit international organizations. This observation provides some support to professional associations or multiprofessional organizations that share similar objectives and aim for such a role (such as ACRP, APCR, the Alliance for Clinical Research Excellence and Safety, or PharmaTrain).

The cohorts in both countries prefer collaborative learning methods and attending formal group events. This is in line with published literature.[23,24] The relatively low ratings received for e-learning programs in Brazil deserve further evaluation.

Important limitations hamper further generalization of the results of our survey. Additional needs assessment tools for confirming such preliminary findings would be needed, and a more granular exploration of specific basic knowledge areas or functions might be appropriate. In any event, the results confirm the need to conduct a specific needs assessment before any planned educational activity, regardless of geography or functional groups.

At the same time, there is little evidence that a needs assessment alone enhances educational effectiveness and outcomes; so it must be placed within the wider process of planned learning, relevance to practice, and reinforcement in the appropriate context.[16]

Both countries had very favorable opinion of the value of investigational site accreditation and the certification of the clinical research team.

At the present time, most of the education and training of clinical research professionals is based on GCP knowledge and application. A harmonized assessment of core competencies should be the next step, so that further education and training initiatives would be based upon competency domains.

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The Benefits of Sponsor–Site Management Organization Partnerships: *An Indian Perspective*

PEER REVIEWED | Zarina S. Irani, LLB | Feruzan Irani Williams, PhD | Jeroze Dalal, PhD

[DOI: 10.14524/CR-14-0024]

The path leading from the proposal of a new medical therapy to its use becoming accepted practice is long and undulating, and it is one that is traversed via clinical trials. Along the way, the various major stakeholders involved in clinical research, including patients, industry, physicians, ethics committees, and medical institutions, play their roles. Most clinical trials typically call for patients to tread the path for a few weeks or months. For scientists, however, the overall drug development journey may take years before the final breakthrough to the desired destination is achieved—an effective treatment that is readily available to those who need it most.[1]

An upsurge in the number of new drugs being developed by sponsor companies as rapidly as modern processes and regulations allow has led to an increase in the number of clinical trials, for which recruiters attempt to enroll a target number of patients within a defined timeframe. Physician investigators play a very important role, as they are responsible for either personally conducting, or supervising the conduct, of a trial and for protecting the rights, safety, and welfare of patients enrolled into the study.

However, trial-related duties such as patient recruitment, obtaining informed consent, and other follow-up procedures—over and above their routine clinical practice and other administrative duties—may discourage physicians from actively participating in clinical research. Poor physician participation is also blamed on factors of insufficient research experience and training and lack of support staff.[2]

Moreover, clinical trials must follow strict legal guidelines. In addition to national laws, these trials are governed by well-established international guidelines and directives, including European Union regulations, the International Conference on Harmonization Guideline for Good Clinical Practice (ICH GCP), and the World Medical Association's Declaration of Helsinki. All stakeholders on research teams, including those from pharmaceutical companies and contract research organizations (CROs) carrying out clinical trials, are expected to understand and follow these guidelines and directives, which aim to ensure the safety of patients while participating in a clinical trial.

Behind each legal document or guidance is the goal of ensuring that patients have voluntarily consented to participate in the trial and that the data obtained are scientifically valid. All such requirements can create significant barriers to participation in, and success of, clinical trials, and generate fertile ground for assistance provided by an outside organization specializing in management of clinical trials, such as a site management organization (SMO).

As the name suggests, an SMO is an organization that may be employed to work in partnership with a sponsor (a pharmaceutical or biotechnology company), CRO, or medical institution to manage clinical research sites. SMOs appoint clinical research coordinators (CRCs) to help investigators perform various tasks throughout the clinical trial process, such as selecting patients, managing the schedule for protocol-specified laboratory examinations, administering study drugs, collecting and recording trial data, resolving data queries, and preparing for audits or inspections.

CRCs also help to ensure that clinical trials are performed with minimal glitches, so that investigators can remain focused on patient care. In fact, as many as 128 different tasks have been identified as CRC responsibilities.[3]

The Indian Perspective

A growing market for clinical research trials in India is driven by many favorable factors, including a huge population whose members are diverse and accessible and effective resources available at low costs.[4] Indeed, the average costs of conducting clinical trials in India are 50% to 60% of those for typical U.S. trials, due to the lower cost of technical services.[5]

In India, the Central Drugs Standard Control Organization (CDSCO), headed by the Drugs Controller General of India (DCGI) within the Ministry of Health and Family Welfare, is the national regulatory body for pharmaceuticals and medical devices. Additionally, Schedule Y of the Drugs and Cosmetics Rules, 1945, formulated by CDSCO, provides the regulations for conducting clinical trials of new drugs in India.

LEARNING OBJECTIVE

After reading this article, participants should be able to (a) discuss the clinical research regulatory environments within the Indian and international contexts and (b) describe the requirements to create a successful partnership between sponsors and site management organizations.

DISCLOSURES

Zarina S. Irani, LLB; Feruzan Irani Williams, PhD; Jeroze Dalal, PhD: *Nothing to Disclose*

In 2013,[6] the Indian government took several measures to strengthen the regulatory mechanism of clinical trials in the country. These new requirements are, in fact, more stringent than the ICH GCP guidelines. Some of the reforms that have affected investigational sites are:

- Independent reporting of all serious adverse events (SAEs), including deaths, by sponsors and investigators to the DCGI and ethics committees within 24 hours of occurrence. This is a change from the earlier regulatory requirement, which required investigators to notify only the sponsor of any SAEs within 24 hours of awareness of an event; the sponsor was then responsible for reporting the SAEs to the regulatory body.
- In case of death during a clinical trial or an injury occurring to a trial patient, the patient's nominee (in case of death) or the patient is entitled to financial compensation as per the order of the DCGI, who then determines the amount of compensation to be paid by the sponsor. It has now become mandatory for investigators to analyze the reports of all SAEs, including deaths, occurring during clinical trials, and report these SAEs within 24 hours of their occurrence to multiple entities, including the regulatory authority, sponsor, institution head, and ethics committee. In case the investigator fails to report any SAE within the stipulated period, he/she must provide a reason for the delay to the satisfaction of the DCGI, along with the report of the SAE.
- Mandatory audiovisual recording of the informed consent process for new patients recruited into a trial.

In addition, the regulatory authority can make visits, with or without prior notice, to sponsors' or investigators' premises to ensure compliance with regulations. If noncompliance is detected, the regulators may issue warning letters, reject or discontinue the clinical trial, suspend or cancel the clinical trial permission, and debar investigators or sponsors from conducting future clinical trials in India.[6]

SMOs tend to be most effective in those situations where recruitment is adversely affected by site-level resource limitation, rather than due to unavailability of patients.

Purpose

Given these growing responsibilities and requirements, many investigators and sponsors in India are considering employing the services of SMOs. One of the major purposes of this paper is to investigate whether SMOs add value to the clinical trial process. The paper also explores the requirements for creating a successful partnership between sponsors and SMOs in order to accrue maximum benefits.

Based on past experience and anecdotal evidence, the research questions of interest are:

1. Would the number of days taken for query resolution be fewer when partnering with an SMO as opposed to not partnering with an SMO, irrespective of differing study protocols? A query is defined as a discrepancy that is detected when a validation check is run on the data. The fewer the number of "days to query resolution," the better the turnover time of data management.
2. Would recruitment of subjects be more successful when partnering with an SMO as opposed to not partnering with an SMO, irrespective of differing study protocols? Recruitment to target is a clear indicator of the success of the clinical trial, and is defined as the number of patients recruited within a defined timeframe. The higher the "number of patients recruited," the more representative the data.

As many as **128** different tasks have been identified as **CRC responsibilities.**

Method

Data were collected from clinical trials conducted in India by a large sponsor company, with and without the services of an SMO, in order to assess the number of days to query resolution (DQR) and the number of patients recruited (NPR). Each trial was conducted at multiple sites; some were supported by SMOs and the remaining sites had their own resources. Hence, the data reflect true comparisons and evaluations.

The sample consisted of 44 investigators (trial sites) working on eight clinical trials in India. Twenty-seven of these investigators (61.4%) were assigned the services of an SMO, while the remaining 17 (38.6%) worked independently with their own resources. The total number of patients enrolled in the trials was 645 (369 at trial sites assigned to an SMO and 276 at trial sites without SMO support).

All trial sites in the sample had CRCs, whether appointed by the SMO or by an investigator. However, although an SMO CRC is dedicated to a particular study and site, the CRC appointed by an investigator is an institute resource, and may have other duties over and above those relating to clinical research.

Results

Site-levels were analyzed using Statistical Package for Social Sciences (SPSS) version 21. Independent sample t-tests were conducted to determine whether there was a statistically significant difference in DQR and/or NPR when using the services of an SMO versus not using the services of an SMO. The results from these tests are presented in Tables 1 and 2.

As can be observed in Table 2, the assumption of equal variance in the groups is satisfied for both NPR and DQR ($F = 0.926$, $p = 0.342$ and $F = 1.919$, $p = 0.173$, respectively). The mean difference between using an SMO and not using one was statistically significant in the case of DQR ($t = -2.38$, $df = 42$, $p = 0.022$). Thus, we conclude that using the services of an SMO versus working independently results in a statistically significant difference in the number of days required to resolve a query.

More specifically, examining the group means and the mean difference in DQR demonstrates that using the services of an SMO statistically significantly reduces the time required for query resolution by more than six days. However, in the case of NPR, there does not appear to be a statistically significant difference between sites using the services of an SMO versus sites not supported by an SMO ($t = -0.39$, $df = 42$, $p = 0.696$).

Discussion

This study sought to examine the value added from partnering with SMOs, as demonstrated by potential reductions in the number of days taken for query resolution and enhancements in patient recruitment. Per our study, using the services of an SMO can help reduce DQR by more than six days, irrespective of differing study protocols. In other words, non-SMO sites took 50% more time to resolve data queries than those managed by SMOs.

From a business perspective, this has a potentially big effect on cost efficiency, because any days saved in the completion of a trial will result in substantial cost savings. In fact, according to one estimate, the sponsor may lose up to $8 million a day for each day's delay in bringing the drug to the market.[7] Additionally, as per our own observations, quicker query resolution time generally goes hand-in-hand with quicker data entry, leading to fewer outstanding queries. All of this ensures that databases are locked and data analyzed in a timely manner.

However, no statistically significant enhancement in NPR was detected at the sites supported by dedicated SMO CRCs. One reason could be that seven of the eight clinical trials in the sample chosen were oncology trials, for which it is often difficult to recruit subjects. The oncology trials followed very stringent

TABLE 1. Descriptive Statistics of Days to Query Resolution and Number of Patients Recruited per Investigational Site With or Without Services of a Site Management Organization (SMO)

	SMO	Number of Sites	Mean	Standard Deviation	Standard Error Mean
Days to query resolution	SMO Used	27	11.9963	7.74420	1.49037
	No SMO Used	17	18.1647	9.28769	2.25260
Number of patients recruited	SMO Used	27	13.6667	15.87208	3.05458
	No SMO Used	17	16.2353	27.49893	6.66947

TABLE 2. Independent Sample t-test to Determine the Difference in Days to Query Resolution and Number of Patients Recruited per Investigational Site With or Without Using the Services of an SMO

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Standard Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Days to query resolution	Equal variances assumed	1.919	.173	-2.381	42	.022	-6.16841	2.59018	-11.39560	-.94122
	Equal variances not assumed			-2.284	29.585	.030	-6.16841	2.70100	-11.68783	-.64899
Number of patients recruited	Equal variances assumed	.926	.342	-.394	42	.696	-2.56863	6.52415	-15.73489	10.59764
	Equal variances not assumed			-.350	22.799	.729	-2.56863	7.33569	-17.75106	12.61381

inclusion criteria, leading to a very small pool of eligible patients. This, perhaps, may have overcome potential advantages that SMOs have to offer.

Additionally, in our own experience, SMOs tend to be most effective in those situations where recruitment is adversely affected by site-level resource limitation, rather than due to unavailability of patients. Hence, future research should look at the effect of SMOs in such studies.

Another probable factor could be that the recruitment time available was very short, since recruitment was globally competitive and the trial startup was delayed due to long regulatory approval timelines. Moreover, patient recruitment is known to depend significantly on study protocol. Thus, further research is required to arrive at a more definitive conclusion about whether, and in what circumstances, using the services of SMOs would lead to enhanced patient recruitment.

When SMO coordinators are vigilant in escalating potential critical issues to the sponsor, they ensure protocol compliance, patient safety, and up-to-date document management.

Perhaps a more important question concerns whether using the services of SMOs actually enhances data quality; this should be explored further. Although DQR turnaround time is one important indicator of data quality, future research should focus on whether SMO services also enhance other parameters of data quality, such as the number of protocol deviations and the number of transcription errors. These can be verified by audit-finding comparisons between sites with and without SMO support.

In addition, these data were all collected within the context of one country, India. Although it was beyond the scope of this paper, it would be valuable for future research to gather and analyze similar data in other countries—especially those with growing SMO use, such as South Africa, the United Kingdom, France, Russia, Latin America, and a few Asian countries. This would provide a more complete picture of the benefits of partnering with SMOs, irrespective of geography. Additionally, further studies with larger sample sizes are recommended to confirm the current observations.

SMOs can play an important and effective role in alleviating the mounting responsibilities held

A site management organization (SMO), as the name suggests, is an organization that may be employed to work in partnership with a sponsor, CRO, or medical institution to manage clinical research sites.

by investigators. This is so because, as mentioned previously, an SMO CRC is committed to a particular study and site, whereas the CRC appointed by an investigator likely has many other duties beyond those tied to any one study. Some of the common advantages of working with an SMO include cost-effectiveness, access to operational know-how, sharing of best practices, and process enhancement due to focused oversight. The SMO business model is fast evolving, with the presence of only a limited number of service providers in the market.

Furthermore, working with SMOs can help with the routine responsibilities of running a clinical trial and ensuring adherence to data management timelines. When SMO coordinators are vigilant in escalating potential critical issues to the sponsor, they ensure protocol compliance, patient safety, and up-to-date document management.

To be at peak effectiveness, SMO CRCs need to be rigorously trained with a focus on good clinical practices, source data review, ethics, and the prevalent local laws. We have observed that, on an average, the SMO CRC spends approximately 10 hours per month on training.

Recommendations for a Successful Partnership

Based on our extensive prior experience with SMOs, the following strategies have been found to work successfully in sponsor-SMO partnerships:

- **Establishing and clarifying the expectations of both parties.** This working relationship is based on mutual trust, and the key to a successful partnership is good communication. Working out and agreeing to communication plans right at the onset of partnership formation are essential, detailing processes for performance expectations and escalation of issues, so that timely action can be taken as and where required. Holding weekly meetings as well as sharing and discussing data performance metrics, like open queries, time to query resolution, and regular visit data, will further help in quickly resolving issues at sites.
- **Training.** Providing regular training to SMOs on the study protocol and the sponsor's standard operating procedures, safety reporting process, and trial documentation helps in better management of the clinical trial. Face-to-face training is preferred, but may not always be possible.
- **Sharing best practices.** This habit should be widely followed, so that both the sponsor and the SMO work on the same platform and are equally benefited. This will engender less ambiguity and lead to better management and oversight of the trial.

Both stakeholders should be willing to learn and grow together, and to improve and improvise, as required. Hence, frequent communication, face-to-face meetings, and training programs will contribute to the success of working together as partners.

On the flip side, because SMOs are typically hired by, and receive financial compensation from, sponsors (usually pharmaceutical companies), they may experience conflict of interest.[8] Consequently, there is some risk of poor data collection as SMOs' financial viability may conflict with the integrity of their research.[8]

Continuous data monitoring and oversight by the sponsor can help in mitigating risks associated with conflict of interest. Indeed, a survey by Henderson[9] found that sponsor respondents indicated that oversight reduced timelines of the study and increased data quality.

Finally, sponsors will need to ensure that the SMOs they work with employ trained and qualified CRCs, by checking their training records and ensuring that the SMOs are imparting continuous refresher training to their CRCs.

Conclusion

In summary, India provides fertile ground for SMOs to expand their networks as doctors, hospitals, and medical institutions increase both in numbers and geographic reach. SMOs help bridge the gap between the sponsor and the clinical trial site by assisting investigators in their various trial responsibilities, including dealing with a rapidly evolving regulatory environment. Therefore, we recommend that sponsors build strong ties and working partnerships with SMOs in order to fully reap the available benefits that can lead to optimized conduct of clinical trials.

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HOME STUDY HS

International Perspectives on Clinical Research

OPEN BOOK TEST

This test expires on October 31, 2015

(original release date: 10/01/2014)

Tips for Successful Study Implementation in England: The Sponsor Perspective on Using Sites of the National Health Service

1. What is the name of the public healthcare system in the United Kingdom?

A. Clinical Research Network (CRN)
B. National Institutes of Health (NIH)
C. National Health Service (NHS)
D. Ministry of Health (MH)

2. What does it mean for a trial to be portfolio adopted?

1. CRN has determined that the trial is of high quality.
2. The trial has been submitted to CRN for review.
3. The trial is eligible for support by the CRN.
4. The trial is included in the CRN's database.

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

3. IRAS is the system sponsors should use to:

1. register the trial with CRN.
2. apply for portfolio adoption.
3. identify the chief investigator.
4. identify the lead research and development contact.

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

4. Adoption of the study to the CRN's portfolio offers which of the following benefits?

1. Assistance in identifying potentially eligible sites
2. Provision of staffing resources to sites at no cost
3. Provision of monthly recruitment updates of sites to sponsor
4. Identification and mitigation of problems in cooperation with sponsor

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

5. In the U.K., sponsors for clinical research must identify which of the following individuals?

A. Sub-investigator
B. Study nurse
C. Research coordinator
D. Chief investigator

6. Which of the following is a prerequisite for the role of chief investigator?

A. Must be professionally based in the European Union
B. Must be a certified physician investigator (CPI)
C. Must be professionally based in the U.K. (except at discretion of research ethics committee [REC])
D. Must have ample experience in the conduct of preclinical research

7. Chief investigators are responsible for which of the following?

1. Study design and study management for multicenter trials
2. Reporting of adverse events to the REC
3. Ethical and legal study conduct for all U.K. sites
4. Monthly updates on study performance to all U.K. sites

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

8. Sponsors who are not legally based in the U.K. or in the European Economic Area must have which of the following?

A. A legal representative
B. A waiver granted from the National Institute for Health Research (NIHR)
C. A legal representative and a waiver granted from the NIHR
D. Approval granted from the U.K. Ministry of Health

9. Which of the following provides contract templates for clinical trials (mCTA)?

A. FDA
B. NIHR
C. MHRA
D. CDRH

10. Why is it recommended that the NIHR's Industry Costing Template be used for negotiating budgets with NHS sites?

A. It is easy to understand for first-time users.
B. It allows sponsors to use their preferred currency for issuing site payments.
C. The NIHR provides prior notification of updates to all users.
D. It is often preferred by NHS sites over a sponsor's budget template.

Education and Training Needs Among Clinical Investigators and Medicines Development Professionals from Two Latin American Countries

11. A training needs assessment is a systematic process for determining:

A. which individuals on the clinical research team are in need of training.
B. gaps between current conditions and desired conditions.
C. how to conduct specific training programs.
D. the resources required to implement an appropriate training program.

12. The use of questionnaires for individual needs assessment:

A. should be limited to personal individual interviews.
B. is limited to a restricted number of respondents.
C. is comparable to appraisal reviews.
D. usually takes less time than other methods.

13. What is the perceived value for the daily clinical research practice of the 26 basic knowledge areas (BKAs)?

A. Uniformly higher in Brazil
B. Particularly high for translational research in both countries
C. Showed significant differences between the two countries in 18 BKAs
D. Particularly low for good clinical practice (GCP) and related operations

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

14. What were the additional training needs in BKA among respondents from both countries?
- **A.** Generally comparable
- **B.** Significantly different in more than half of the BKAs
- **C.** Particularly high for healthcare economics and drug device combinations in Brazil
- **D.** Particularly low for GCP and related operations

15. What were the additional training needs in business management skills (BMS) among respondents from both countries?
- **A.** Uniformly high
- **B.** Significantly different in more than half of BMS
- **C.** Particularly low for conflict management and resolutions
- **D.** Particularly high for medical writing in Brazil

16. What was the perception of value of accreditation and certification initiatives to leverage clinical research quality?
- **A.** Very low for site accreditation in both countries
- **B.** Higher when conducted by international for-profit organizations
- **C.** Significantly different between the two countries
- **D.** Very high for certification of research staff in both countries

17. Clinical research activity in Brazil:
- **A.** is recognized as the leader in Latin America.
- **B.** has very little pharmaceutical/biotechnology industry representation.
- **C.** differs considerably from Peru in how medicine is practiced.
- **D.** offers a large number of postgraduate clinical research education programs.

18. Clinical research activity in Peru:
- **A.** has a large national pharmaceutical/biotechnology industry sponsoring local clinical research.
- **B.** is rapidly emerging among sponsors as an alternative location for conducting clinical trials.
- **C.** has developed extensive networks of academic research sites.
- **D.** offers a large number of postgraduate clinical research education programs.

19. The differences in the rating of each BKA and BMS among the cohorts from both countries:
- **A.** can be explained because of the high error margin and low confidence level of the sample.
- **B.** can be attributed to different languages spoken in Brazil and Peru.
- **C.** can be explained by the demographic differences in professional affiliation and background among the two cohorts.
- **D.** are not important limitations to further generalizing the results of the survey to Latin America.

20. What does the survey of education and training needs in Brazil and Peru suggest?
- **A.** Regulatory compliance requires ongoing training in proper GCPs.
- **B.** Individuals who are professionally certified require significantly less training.
- **C.** Training programs and assessment for professional certification in both countries should be based upon competency domains.
- **D.** Site accreditation would reduce the need for continuing professional development.

The Benefits of Sponsor–Site Management Organization Partnerships: An Indian Perspective

21. The ICH GCP and other international guidelines are applicable to which entities within the clinical trial process?
- **A.** Pharmaceutical companies only
- **B.** Investigators only
- **C.** Contract research organizations (CROs) only
- **D.** All stakeholders, including pharmaceutical companies and CROs

22. What is the main aim of the ICH GCP guidelines?
- **A.** Patient safety
- **B.** On-time recruitment
- **C.** Drug development
- **D.** Quality data

23. Which of the following are typically appointed by site management organizations (SMOs)?
- **A.** Principal investigators
- **B.** Clinical research coordinators
- **C.** Clinical research associates
- **D.** Electrocardiograph technicians

24. What is the name of the national regulatory body for pharmaceuticals and medical devices in India?
- **A.** Food and Drug Administration
- **B.** Central Drugs Standard Control Organization
- **C.** Central Drugs Administration
- **D.** Drugs and Cosmetics Administration

25. When were the revised clinical trial guidelines introduced by the government of India?
- **A.** 2014
- **B.** 2000
- **C.** 2012
- **D.** 2013

26. According to the revised clinical trial guidelines in India, what is the timeline for reporting a serious adverse event (SAE) to the Indian regulatory body?
- **A.** 24 hours
- **B.** Fortnight
- **C.** Two days
- **D.** Within an hour of occurrence

27. According to the revised clinical trial guidelines in India, who determines the amount of compensation to be paid in case of an SAE?
- **A.** The patient's nominee
- **B.** The sponsor
- **C.** The Drug Controller General of India (DCGI)
- **D.** The patient

28. According to Indian guidelines, what are the possible consequences for noncompliance with regulations?
1. Warning letters
2. Reject or discontinue clinical trial
3. Debar sponsor from doing any business in India
4. Suspend or cancel clinical trial permission

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

29. What does the success of a sponsor-SMO partnership depend on?
- **A.** Sponsor learning and following SMO rules
- **B.** Training provided to the sponsor
- **C.** Following the partnership guidelines established by the DCGI
- **D.** Establishing and clarifying expectations at the onset for both parties in the partnership

30. What key element is essential to developing a successful partnership between sponsor and SMO?
- **A.** Following international guidelines for clinical trials
- **B.** Following complex protocols exactly
- **C.** Good communication between sponsor and SMO
- **D.** Good recruitment practices by SMO

Gerald J. McDougall

Creating a New Research and Development Future for AMCs

Today, academic medical centers (AMCs) derive about 85% of revenues from providing clinical care.[1] Looking forward, it's clear that major changes are coming in how care is delivered and paid for in the U.S. as healthcare shifts from a model that rewards volume to one that rewards value delivered. These changes have implications for all AMC activities, including research.

Traditional R&D Funding Sources are at Historically Low Levels

The traditional sources of funding for academic research and development (R&D)—notably, federal and institutional dollars—are declining. AMCs are also finding it increasingly difficult to support R&D programs with funding from their clinical revenue streams.

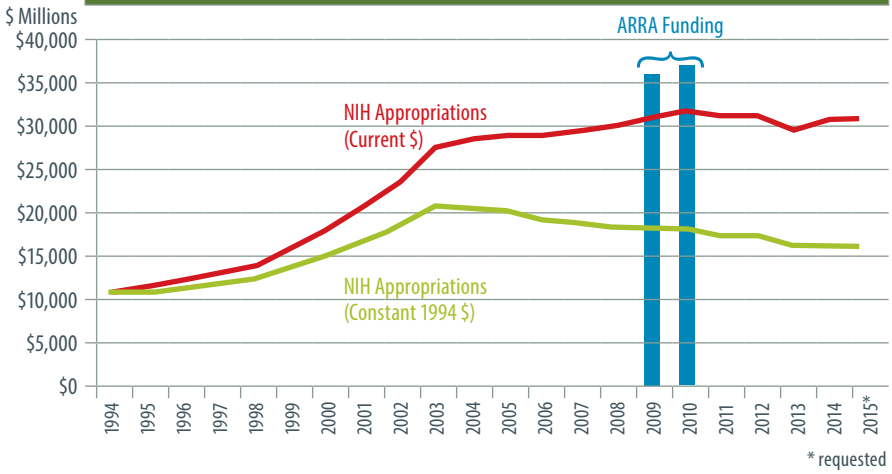
Although any dip in the average 5% operating margins of AMCs would threaten not only hospital operations, but also education and research, Figure 1 shows how dramatically National Institutes of Health (NIH) funding—a mainstay of academic R&D—is falling, especially in constant dollars.

AMCs Need to Rethink Their Models

The historical AMC basic research model—using the NIH's standard independent research grant (the R01)—is a fantastic driver of pure science and needs to continue. However, it is not a model that can address the funding gap being discussed here.

For the leaders of AMCs to attract and grow other sources of financial support, including industry dollars, their institutions also need a base of translational research. Simply put, AMCs will need to supplement their models for identifying funding sources for research. With notable exceptions, the AMC R&D community has not yet established the business development infrastructure that can and should support a growing commercial revenue stream.

FIGURE 1. NIH Appropriations in Current and Constant Dollars



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Congressional Research Service: A History of NIH Funding: Fact Sheet, March 7, 2014

At the end of the day, it will be imperative for AMCs that want to remain competitive as R&D engines to rapidly expand sources of research funding to make up for the shortfall in such traditional sources as NIH grants.

To stay relevant, AMCs must accelerate investment in translational research, which converts basic scientific findings from "bench to bedside," and concertedly push those findings out to the consumer. Success in the "New Health Economy"[2] requires collaboration, innovation, and technology.

Although translational research may result in marketable discoveries, commercialization of AMC intellectual property requires tenacity and business acumen. Bringing a product to market requires the kinds of promotional, fundraising, and relationship-building skills found in the DNA of venture capitalists, entrepreneurs, and corporate executives.

AMCs Must Capitalize on Industry Funding

Today, industry is the largest funder of U.S. R&D, contributing more than $307 billion annually[3]—most, of course, spent inhouse. At the same time, industry is developing new approaches to innovation and has been increasing its investment and partnerships with academic and research institutes. Table 1 presents these points for current relationships between sources of funds and performers of R&D:

- Industry R&D investment in academia and nonprofits is estimated at $5 billion per year.[3]
- Industry is increasingly forming alliances with universities and outsourcing R&D.
- Pharmaceutical industry drug discovery outsourcing is expected to increase 14% per year through 2018, from $13 billion to $25 billion.[4]

TABLE 1. Current Relationships Between Sources of Funds and Performers of R&D[3]

		Performer of R&D					US $ Billions
Source of Funds		Federal Gov't	FFRDC (Gov't)	Industry	Academia	Non-Profit	Total
	Federal Government	$35.7	16.5	27.8	37.1	6.0	123.0
	Industry		0.3	302.5	3.3	1.4	307.5
	Academia		0.1		13.2		13.3
	Other Government		0.0		4.0		4.0
	Non-Profit		0.1		5.3	11.3	16.7
	Total	$35.7	17.0	330.3	62.9	18.7	464.5

Moreover, industry funding of AMC R&D is not evenly distributed. On average, less than 5% of university research is funded by industry, according to National Science Foundation statistics.[5] In contrast, at leading universities that percentage approaches 15%. The potential to narrow that funding gap represents tremendous opportunity for universities and AMCs at the lower end of the range.

To fully capitalize on industry R&D investment, AMCs must develop an environment focused on translating science into commercially viable products.

Solving the Funding Equation: Translational Platform + Venture Funding

One solution to this funding dilemma may lie in new structures—collaborative translational platforms for leveraging regional healthcare and technology expertise, while at the same time enhancing access to area-based foundations, angel investors, and venture capital funding. These platforms can tap another growing source of research dollars—corporate venture funds established by new entrants to the health space, such as high-tech consumer companies exploring disease-monitoring[3] contact lenses and "wearables."

Several successful models of AMC "commercialization collaboratives" already exist around the country. They succeed because they infuse companies' entrepreneurial spirit and business acumen with the scientific knowledge and research skills of AMC teams.

Each side of the model brings needed attributes to the table:

Commercialization Collaborative—A neutral, translational platform within a region that…

- Supports innovation engines and creates new regional economic growth
- Fosters translational/applied programmatic research initiatives (i.e., advanced diagnostics development center, drug commercialization center)
- Pursues proactive and global business development to attract industry funding
- Drives new revenue into universities
- Offers value-adding services across industry sectors
- Seeks large-scale industry relationships
- Promotes smart incubation and startup support/coaching
- Ties into a global startup network (management, diligence, capital)

To fully capitalize on industry R&D investment, AMCs must develop an environment focused on translating science into commercially viable products.

Venture Funding—Smart money, highly leveraged, deep market insight, and resident management with…

- Investment partners who build and operate companies
- Market insight from regional industrial strengths
- Regional corporate co-investment
- Network/knowhow to build successful companies and recruit/grow management talent
- Seed and Series A, B, C scale investments and links to growth capital

From a study of existing collaborative examples, five important characteristics emerge as essentials for a successful collaboration. Collaborations should:

1. **Add Real Value to the Member Institutions by…**
   - Bringing together basic and clinical scientists from institutions with complementary expertise (e.g., basic biologists, clinician scientists, engineers, computational scientists, imaging experts, etc.), for deeper collaborations across institutional boundaries
   - Leveraging combined strengths from multiple institutions to attract investment from private sector partners
   - Hosting state-of-the-art facilities to co-locate collaborating scientists and provide resources and cores not available in any one institution
   - Encouraging "fail fast" entrepreneurial thinking—a different mindset for academics
2. **Avoid Roles that May be Viewed as Competing with its Members by…**
   - Not making primary faculty appointments, and only seeking grants/contracts when the collaborative can be more competitive
   - Avoiding competition between the collaborative and its member institutions

3. **Feature a Nonbiased Governance Structure Under Which…**
   - Governance has a strong commitment and direction provided by "external" (nonmember institution affiliation) board members
   - Member institution interests are highly valued, even when at odds with the collaborative's interests
4. **Garner Faculty Support from the Beginning Through…**
   - Buy-in gained from key faculty leaders at member institutions from the outset
5. **Build Upon Existing Strengths by…**
   - Identifying targeted areas early where a particular collaborative community has specialized strengths (neuroscience, cancer, etc.)
   - Understanding that differentiation is critical to achieve maximal impact

At the end of the day, it will be imperative for AMCs that want to remain competitive as R&D engines to rapidly expand sources of research funding to make up for the shortfall in such traditional sources as NIH grants. Industry's increasing trend to collaborate with academic institutions holds promise as the emerging avenue for addressing the funding gap and building long-term sustainable funding partnerships.

For AMCs at the lower end in terms of the percentage contribution to R&D funding seen from industry, moving even a few percentage points up that ladder can mean tens of millions in additional R&D dollars.

Conclusion

AMCs have long been the training ground for scientists. However, as funding opportunities have shrunk, the average age of principal investigators has risen—now into the 40s. Attracting young innovators requires that they believe sustainable careers are possible. A clear danger is that, unless this funding issue is fixed, the U.S. will likely lose an entire generation of scientists.

Embracing a collaborative, entrepreneurial culture that is open to commercialization will provide an important foundation for enabling the transition to new, sustainable R&D models.

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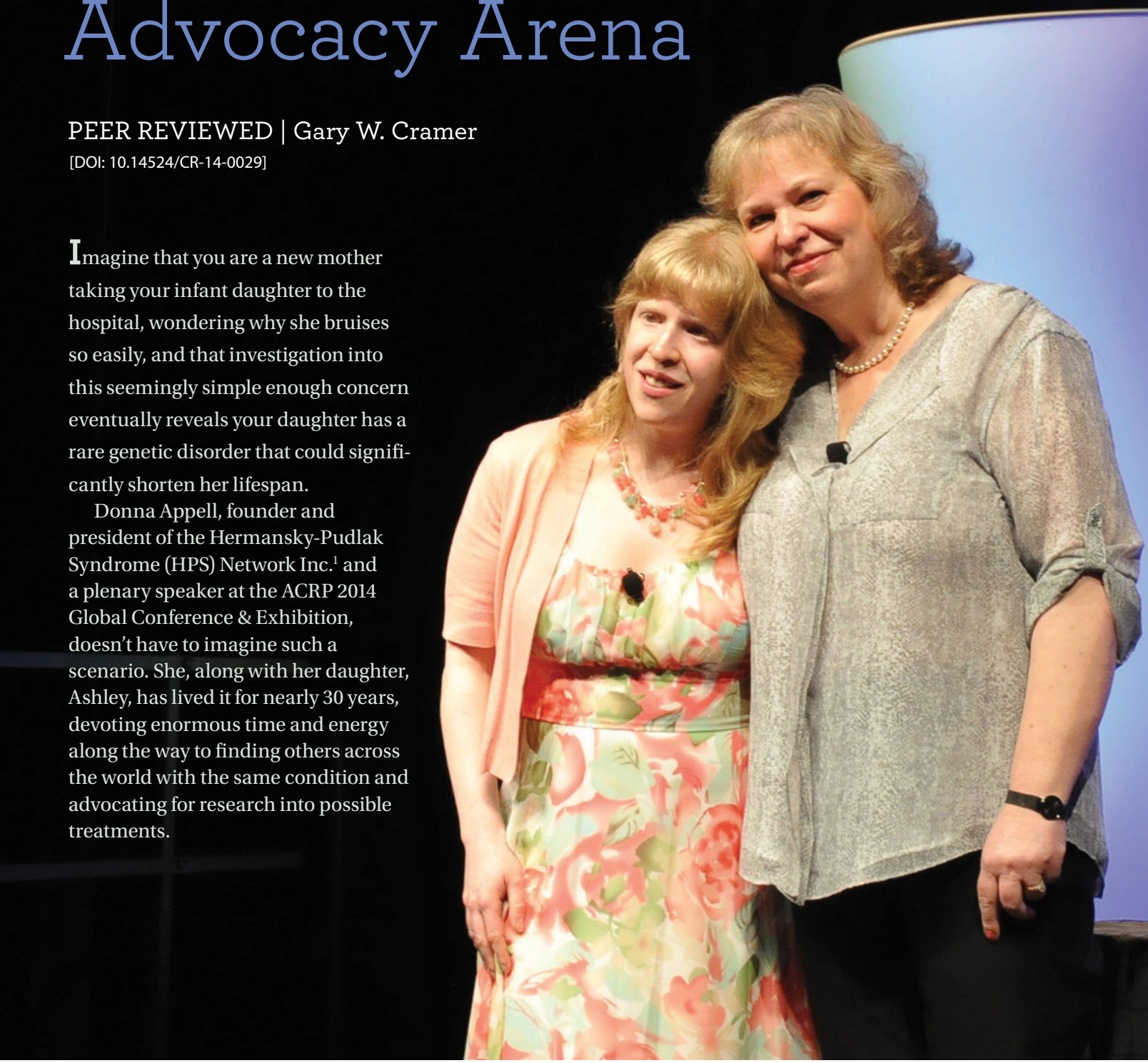
PERSONALITIES AND PROGRAMS in the Evolving Patient Advocacy Arena

PEER REVIEWED | Gary W. Cramer

[DOI: 10.14524/CR-14-0029]



Imagine that you are a new mother taking your infant daughter to the hospital, wondering why she bruises so easily, and that investigation into this seemingly simple enough concern eventually reveals your daughter has a rare genetic disorder that could significantly shorten her lifespan.

Donna Appell, founder and president of the Hermansky-Pudlak Syndrome (HPS) Network Inc.[1] and a plenary speaker at the ACRP 2014 Global Conference & Exhibition, doesn't have to imagine such a scenario. She, along with her daughter, Ashley, has lived it for nearly 30 years, devoting enormous time and energy along the way to finding others across the world with the same condition and advocating for research into possible treatments.

As detailed in the 2012 documentary film *RARE*,[2] shown during the plenary session to a large and appreciative audience and expanded upon by the mother-daughter duo in a question-and-answer period, HPS manifests in albinism, blindness, pulmonary fibrosis, a bleeding disorder, and a bowel disorder. When Donna, a trained nurse, first learned of the syndrome, there were just 23 known cases of it in the mainland United States. "I want to know who's researching this, and where's the cure," she says in the film, "and I found nothing."

So it was that a drug discovery sequence began in reverse of the usual order of such things. In most cases, it starts with pharmaceutical scientists working directly for a sponsor organization whose leaders want to take any promising drug candidates for relatively common conditions to trial once the scientists advance the candidates to that point. The plans naturally include working with physician investigators and possibly contract research organizations to attract an adequate number of volunteer subjects who are suffering from said conditions to provide statistical reliability to the trials' findings.

What the Appells faced instead was a situation in which the very people with the condition and their families first had to find experts who understood the disease well enough to begin advancing a drug candidate outside the corporate environment. They then had to gather enough volunteers largely on their own initiative to make a trial possible—long before knowing if a company could someday be convinced to invest in any drug that seemed to be proving successful, given the dim prospects for profiting from a product targeting such a rare disease.

"Advocacy groups for rare diseases start out with one strike against them—namely, that there are very few of them," says William A. Gahl, MD, PhD, in the *RARE* film. As clinical director of the National Human Genome Research Institute at the National Institutes of Health (NIH), Gahl is researching HPS in close cooperation with the network. "They don't have much lobbying effort, and other people don't understand why one should study a rare disorder instead of a common disorder. [But we] are really hoping that studying [HPS] will eventually lead to therapies for more common disorders."

Expressions of that sentiment—that a greater good for more common and related conditions will come from breakthroughs treatments for rare diseases—represent just one tactic that patient advocates are wielding in their quest for recognition and support.

Background

The Appells are hardly the first patient advocates to find themselves in such straits. Although individual rare diseases afflict small populations, collectively, more patients are diagnosed with rare diseases than AIDS and cancer combined, and fewer than 400 drugs approved by the U.S. Food and Drug Administration (FDA) are available to treat more than 7,000 rare diseases. Indeed, as it stands now, an estimated 95% of all rare diseases lack FDA-approved treatments.[3]

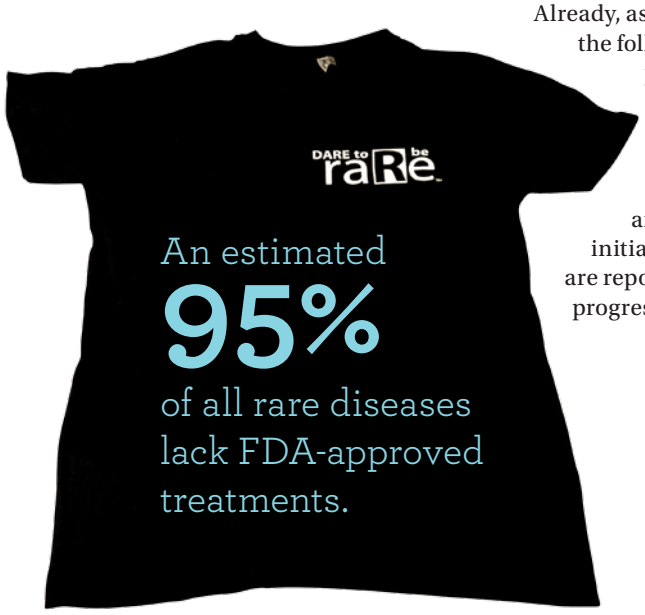
However, in an environment bolstered by growing ranks of volunteers dedicated to specific conditions (rare or otherwise), surging social media outreach now possible on a global scale, and increasing awareness about rare diseases among researchers and the general public, the tide may be turning. According to an analysis published in the July 2014 issue of *Health Affairs* by researchers at Duke Medicine, as more health studies are

PhRMA has developed a participant-focused document on *Principles on Conduct of Clinical Trials: Communication of Clinical Trial Results,* available at www.phrma.org/sites/default/files/pdf/042009_clinical_trial_principles_final.pdf.

driven by "big data" research projects, patients are empowered to become active participants providing real-time information on their symptoms, side effects from the treatments they receive, and clinical outcomes.[4]

Meanwhile, the members of a panel session at the June 2014 BIO International Convention debated the FDA's effectiveness to date in terms of incorporating the patient perspective in the drug review process. Coverage of the event indicated the panelists, who were regulatory experts, think the agency must learn to define medical need "from a more patient-centric perspective. That requires setting metrics to raise the bar in demonstrating how patient engagement actually shapes and drives FDA decisions, especially around the critical underlying construct of benefit-risk, and spilling over to areas like clinical trial design, marketing authorization, or labeling updates to include patient-reported outcomes."[5]

To give a sense of the scope of the issue just in terms of rare diseases (those affecting fewer than 200,000 Americans), the National Organization for Rare Disorders (NORD), a nonprofit that assists more than 180 advocacy organizations, offers a database on 1,200 diseases. In fact, NORD says it "responds to hundreds of thousands of telephone, mail, and e-mail inquiries from individuals, families, teachers, social workers, and medical professionals" each year.[6]



Already, as evidenced by the following examples, more and more patient advocacy groups and related services are tackling new initiatives, and some are reporting significant progress in their efforts.

Who's Out There

In 2013, PatientsLikeMe,[7] an established network for patients who want to monitor their health, improve their outcomes, and contribute to medical research and discovery, was awarded a $1.9 million grant from the Robert Wood Johnson Foundation (RWJF) to create the world's first open-participation research platform for the development of patient-centered health outcome measures. The platform is part of an initiative to put patients at the center of the clinical research process and allow researchers to examine new ways to measure diseases. "This project is really exciting for us because it focuses on data that [are] developed by patients in the real world…as opposed to controlled clinical settings," says Brian Quinn, director of the RWJF team funding the project. "We believe it has the potential to help researchers better understand the course of disease and open up important paths for the development of new therapies. We're eager to see what medical revelations will emerge when researchers focus first on patients' needs and concerns, and openly collaborate with patients and each other."[8]

The doctors behind a medical search engine known as CureCrowd use the platform to conduct online surveys of patients to chart the effectiveness of treatments they've already tried, and to display results comparing all treatments side-by-side. In part, the resource aims to bring "hope to the communities of rare diseases as an ongoing, infinite study to discover what truly works."[3]

With funding from the National Cancer Institute, Pharmatech Oncology,[9] a contract research organization headquartered in Denver, Colo., has been developing a patient-centered approach to enrolling patients with rare forms of cancer in clinical trials. According to the company, the approach uses a "just-in-time"[10] enrollment model that "puts patients first in the research process, prioritizing selection of the most appropriate therapy, and using highly efficient workflow to enroll individual cancer patients into a trial in 10 days or less."[11]

As announced in March 2014, the Pharmaceutical Research and Manufacturers of America (PhRMA) and the National Minority Quality Forum are working with patient advocacy organizations, provider groups, individual physicians, clinical trial sponsors, and researchers to drive awareness and involvement in the "I'm In" campaign,[12] which

aims to increase diversity in clinical trials. The campaign contributes to and supports the National Minority Quality Forum's Clinical Trial Engagement Network for accelerating the inclusion of underrepresented populations in medical studies.[13]

Among other initiatives, the Patient-Centered Outcomes Research Institute (PCORI), an independent, nonprofit organization authorized by the U.S. Congress in 2010, funds large, patient-centered pragmatic clinical studies in the form of comparative effectiveness research (CER), comparing two or more interventions in real-world settings. PCORI calls this an effort to more rapidly and efficiently produce evidence that is generally applicable to a wide spectrum of patients' needs and clinical care settings. "We're dramatically increasing the amount of funding we're investing in patient-centered CER and expect to commit roughly $1 billion over the next two years to support this work," PCORI Executive Director Joe Selby, MD, MPH, said in early 2014.[14] Tufts Medical Center, University of South Florida's Morsani College of Medicine, and a network of seven New York City health systems are among the institutions already using PCORI funding for the advancement of patient-centered research.[15]

In February 2014, Drugs.com, an online clinical drug resource, and TrialReach, a service for connecting patients with clinical research teams, announced their new partnership to provide patients with information and access to treatments that are still under development. According to TrialReach CEO Pablo Graiver:

> Our partnership gives us the opportunity to give many more patients the ability to voice their needs and experiences so researchers can design better treatments and trials in the future. …Everyone is talking about "Big Data," but we have to go beyond data to actionable insights so we can deliver something meaningful to patients. What do patients care about? What are they experiencing? We think that by allowing people to "voice" their knowledge and their experience of clinical trials, either directly on our site or through social media, we can make clinical trial information more up-to-date, more relevant, and more valuable to patients and researchers than ever before.[16]

Research for Her™, a Cedars-Sinai online medical research database aimed at increasing women's participation in clinical studies, is noteworthy for offering an online consent form for registering interest in trials that is just two pages long and written in nontechnical, easy-to-understand language. "By listening to the new ideas and barriers of our target population, we were able to respond and adapt to better meet the needs of women in the community," says Beth Y. Karlan, MD, who directs multiple cancer programs and is chair in Gynecologic Oncology at Cedars-Sinai in Los Angeles, Calif. "Women have responded affirmatively and we have more than quadrupled the monthly enrollment average in our clinical trials."[17]

A University of Michigan Health System team in 2013 won a national prize through PCORI to further the development of its prototype for a web-based, crowdfunding platform called WellSpringboard. This platform could someday allow anyone to propose and donate money for ideas for new patient-focused research studies, and researchers to propose carrying out the studies with the funding if enough dollars are raised. The site would focus on CER studies, and could be used as a registry for volunteers to review proposals and/or to be study subjects. "We want to bring the public's voice into the world of health research, to allow them to ask for answers to questions that are most important to patients of all ages and the people who care for them," explains team leader and health researcher Matthew M. Davis, MD, MAPP. "We also want to make it possible for researchers to join the virtual exchange of ideas that can attract broad public attention and investment."[18]

In 2012, a coalition of community and research groups in Baltimore, Md., led by the University of Maryland School of Pharmacy, released a report on "Integrating Patients' Voices in Study Design Elements,"[19] which encouraged medical researchers to include hard-to-reach patients in future studies and clinical trials. Made possible by a contract with PCORI, the report delivers 10 suggestions for eliciting hard-to-reach patients' perspectives and partnering with patient communities. The insights came from focus groups and interviews with patients (and their parents and/or caregivers) and with physicians and nurses who treated hard-to-reach patients who were:

"Advocacy groups for rare diseases start out with one strike against them—namely, that there are very few of them," says William A. Gahl, MD, PhD, in the *RARE* film.

To hear more from Donna and Ashley Appell about their patient advocacy efforts or to search for ACRP Global Conference sessions on related topics, visit the Online Conference Library at www.prolibraries.com/ACRP. A recording of the Q&A session that followed the showing of *RARE* at the ACRP 2014 Global Conference is available at www.prolibraries.com/acrp/?select=session&sessionID=1307. Full-conference registrants to the 2014 conference may earn up to 8.0 contact hours/credits through the Online Conference Library in the two full years following April 27, 2014.

- African-Americans or bilingual Spanish-speakers, predominantly of low socioeconomic status;
- others who were found through faith-based organizations;
- others who were cognitively impaired; and
- others who were mobility limited, visually impaired, or hearing impaired.

Spurring the project, says study leader Daniel Mullins, PhD, a professor in the Department of Pharmaceutical Health Services Research, was the issue that, "Researchers usually don't [conduct] outreach to some groups of patients, perhaps because it takes more time and effort to include them, but these overlooked people typically have greater health needs."[20]

What's Behind and What's Ahead

Among the variety of special events focused on the ongoing mission of so many people to keep issues related to rare diseases in the public eye, Rare Disease Day has been held February 28 each year since 2008, as organized by EURORDIS (Rare Diseases Europe) in partnership with such organizations as NORD, the Canadian Organization for Rare Disorders, and Genetic Alliance UK. According to a website devoted to the event, "The political momentum resulting from [Rare Disease Day] has…served for advocacy purposes. It has notably contributed to the advancement of national plans and policies for rare diseases in a number of countries."[21]

Similarly, NORD holds a Rare Diseases and Orphan Products Breakthrough Summit, with the next one slated for October 21–22, 2014, in Alexandria, Va. Among the content tracks for this year's event is one dedicated to "Advancing Patient Engagement and Support."[22]

One of two very recent advances for rare disease communities seen in June 2014 was the submission of the first-ever patient advocacy–initiated draft guidance for a rare disease to the FDA to help accelerate development and review of potential therapies for Duchenne muscular dystrophy.[23] The other such advance was the holding of the Dravet Syndrome Foundation's First Biennial Family and Professional Conference in Chicago, Ill., where corporate sponsorship helped bring together affected families and caregivers with clinicians and researchers to discuss new developments in the treatment of the syndrome and associated intractable childhood epilepsies.[24]

The National Organization for Rare Disorders (NORD), a nonprofit that assists more than 180 advocacy organizations, offers a database on 1,200 diseases.

In addition to welcoming financial backing from pharmaceutical firms when it can be had, rare disease organizations such as the Children's Tumor Foundation[25] may find advantages for gaining public attention from having a celebrity spokesperson on their side. Through his friendship with one of the disease's sufferers, Ian Desmond, shortstop for the major-league baseball team Washington Nationals, has championed the cause of neurofibromatosis (NF) awareness and research in recent years. Desmond even went so far as to have his left arm tattooed with a special design that includes the symbol for NF research.[26]

Courtesy of MASN

As for the Appells and their advocacy, the HPS Network's outreach to the NIH and great effort in terms of recruiting subjects eventually led to a small clinical trial of pirfenidone as a drug candidate for the lung condition involved in HPS. Led by the NIH's Gahl, the trial took more than three years to accrue 35 volunteers, and came to a close when an interim analysis showed the futility of the drug.

The political momentum resulting from [Rare Disease Day] has. . .served for advocacy purposes. It has notably contributed to the advancement of national plans and policies for rare diseases in a number of countries.

"[One day, Dr. Gahl told me that] often, founders of disease groups don't reap the benefits of the findings [from clinical trials], and I remember thinking, 'Well, was I smiling too much today for ya?'" says the good-natured Donna in the film, as she balances her blunt and driven side with an obvious streak of the humor that is often key to get people through such life challenges. "I think offering people false hope is not a good thing, but the hope of the search is so necessary."

According to Donna, since the events depicted in the film, the HPS Network has added a new HPS member on an average of one per week. "In the past year, which we count from March to March (at our annual conference), membership increased by 26%. ...It gets us a bit sad to grow our numbers, because it means that there are more people struggling with HPS; but we realize that they are out there, and finding them eliminates their isolation and gives them hope. Our hope presently is in research and our research teams, [but there] is no new targeted therapy under consideration at this moment."

The network has held conferences in both New York and Puerto Rico in recent years. In May 2014 in San Diego, it received the first-ever award from the American Thoracic Society for "Innovations in Health Equality," recognizing success in health equality policy, training, and career development.

Meanwhile, "Ashley continues to make her life look easy," Donna says of her now 27-year-old daughter. "She is in her 14th year of receiving Remicade intravenously for severe colitis every six weeks. She still goes to the NIH for research every four months, and loves going there to see everyone, as it gives her hope. Seeing research and having a relationship with researchers keeps her strong. Her strength is a pebble in the pond for the rest of the community. She is taking college classes, only two at a time because of her challenges, and is doing great! She is the intern singing teacher at a preschool and is in several choirs."

Noting that the *RARE* film showed "how hard it is to be involved in research, and how sad for the research team as well as the families when things don't pan out," Donna added an upbeat closing note. "What a hard job it is for those professionals in research, because they know that the [patients'] families are depending on them for their lives. What a burden! But I hope that they all know how much we appreciate them. We think about them all the time and hope they are OK; feeling our prayers and gratitude."

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ETHICALLY SPEAKING

Stuart Horowitz, PhD, MBA

eConsent: A Technology for the 21st Century?

In July 2014, the U.S. Food and Drug Administration (FDA) released new draft guidance under the title of "Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors."[1] This represents the first update on a topic with great importance to the ethical conduct of clinical research (and one of special, ongoing interest to institutional review boards [IRBs]) in 14 years.

eConsent should enhance the relationship between the research subject and the investigator or coordinator, and the connection the subject has with the study.

At 42 pages in length (with 67 footnotes), the draft guidance is about as long as some informed consent forms (ICFs).

On the matter of how new technologies might influence informed consent, the draft guidance is minimal, stating:

> Traditionally, informed consent has been obtained in a face-to-face interview using paper consent forms. New technologies are becoming available that may serve as an alternative to the paper consent form in the informed consent process. Parties interested in pursuing alternative methods of obtaining informed consent are encouraged to contact FDA. Currently, FDA is considering alternative methods using these new technologies and would be interested in comments on these alternative methods.[1]

On one hand, it is not surprising that FDA does not yet offer specific guidance on this topic. There is relatively little experience with electronic consent (eConsent), and thus a paucity of empirical evidence supporting its use.[2] A face-to-face interview together with a paper form is the tried-and-true method of obtaining informed consent. It works everywhere, and it is simple and inexpensive; so there is little impetus to replace it with other approaches.

On the other hand, in this era of smartphones, tablets, electronic medical/health records (EMRs/EHRs), electronic data capture (EDC), and electronic clinical trial management systems (eCTMSs), it seems anachronistic that the clinical development industry remains wedded to a paper-based process. In fact, our industry is currently exploring eConsent, as several pharmaceutical companies conduct pilot studies to evaluate the potential benefits. Just what the potential benefits are, however, remains an issue of some contention.

More Pros than Cons from eConsent?

First and perhaps most important, a candidate research subject may be better informed and less wary of research if the process includes eConsent, and a fully informed person may be more likely to enroll and remain in research.

To achieve a greater level of informed consent, eConsent cannot merely be a digital version of the paper-based ICF that is served up on a computer or tablet screen, including a verbatim voice-over. Instead, it can and should have the following attributes:

It should be comprehension-driven. Features to support enhanced comprehension should include a built-in dictionary, so that a user can click or tap on any word to bring up its definition

in understandable terms. Embedded video clips describe procedures that may be risky or complex. Intermittent quizzes during the process can measure the level of a candidate's comprehension, so the investigator or coordinator can ascertain whether a person has sufficient, quantifiable understanding of the research to be able to provide valid informed consent.

It should personalize the process of informed consent. eConsent should target the needs of the individual.

- First, eConsent allows for a process that is tailored to the individual subject. For example, the embedded dictionary allows potential subjects to look up words they don't know, without any embarrassment about asking questions they may think are too simple, and to skip the definitions of words or concepts they already understand.
- Second, the testing of comprehension can allow the eConsent process to focus on the areas where a person has limited understanding or misconceptions. eConsent can provide subjects with the option for additional in-depth information and track where individuals spent excessive or minimal time. When the eConsent process identifies areas of unsuccessful communication, the investigator and research staff can step in to provide additional explanation.
- Third, eConsent enhances the individual's opportunity to reflect on the information received. This can first be done comfortably while alone with the eConsent system. Depending on the technology deployed, the individual might take the time to visit hyperlinks and do additional web research before resuming an interview with the investigator. This reflection can help the candidate focus questions for the investigator.

It should be relational. eConsent should enhance the relationship between the research subject and the investigator or coordinator, and the connection the subject has with the study. Through technology, eConsent itself can be interactive, quizzing or testing subjects in an entertaining and educational way. eConsent can be used to provide social connections between subjects and the research staff, or with other subjects who opt-in for social connectivity.

Because eConsent can provide real-time information to both the subject and the investigator or coordinator, it can also drive deeper and more focused discussion. Importantly, eConsent facilitates the ongoing nature of the process of informed consent because it is easily updated and, in some circumstances, can be e-mailed to enrolled individuals who need to understand new risks or potential benefits.

At the conclusion of a study, eConsent can facilitate the reporting of results back to the participant. Using eConsent to allow participants to opt-in to receive the results of the trial reduces the sites' burden of contacting all study participants.

Other Considerations

The complexity of producing eConsent is not trivial. The most sophisticated eConsents involve professional services that may come from information technology experts, voiceover talent or actors, graphic artists, video producers, and, of course, writers and editors, along with the resultant costs of these services.

It is yet unknown if eConsent can reduce the time needed to obtain informed consent from participants. If "a picture is worth a thousand words" (and video even more), in principle, eConsent has the potential to improve the time it takes to obtain informed consent. Moreover, clear knowledge of what a candidate does not understand could help focus follow-up conversations.

However, if the primary goal of eConsent is for the participant to be better informed, it may be reasonable to expect that this will require more time. If the added time is not too great, the efforts required of research staff can remain more focused on leveraging the technology to yield greater enrollment rates and retention and, ultimately, on reducing the time to complete a study. In this light, eConsent will likely be seen as valuable to all stakeholders.

Conclusion

As noted at the outset, FDA does not yet offer specific guidance on eConsent, and it might not for some time to come. Until then, IRBs must interpret how the regulations apply, and should take the opportunity to contact FDA and pose questions.

Due to cost and complexity, early and widespread adoption of eConsent may be limited to large, industry-funded, multicenter clinical trials that are reviewed centrally. Over time, as eConsent becomes more widespread, its related technologies advance, and its costs decrease, smaller-scale deployment—even down to the single-site study—should be achievable. By then, the clinical development industry will have sufficient experience for FDA to develop guidance.

A candidate research subject may be better informed and less wary of research if the process includes eConsent, and a fully informed person may be more likely to enroll and remain in research.

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Audio-Video Informed Consent: *More Than Just a Process*

PEER REVIEWED
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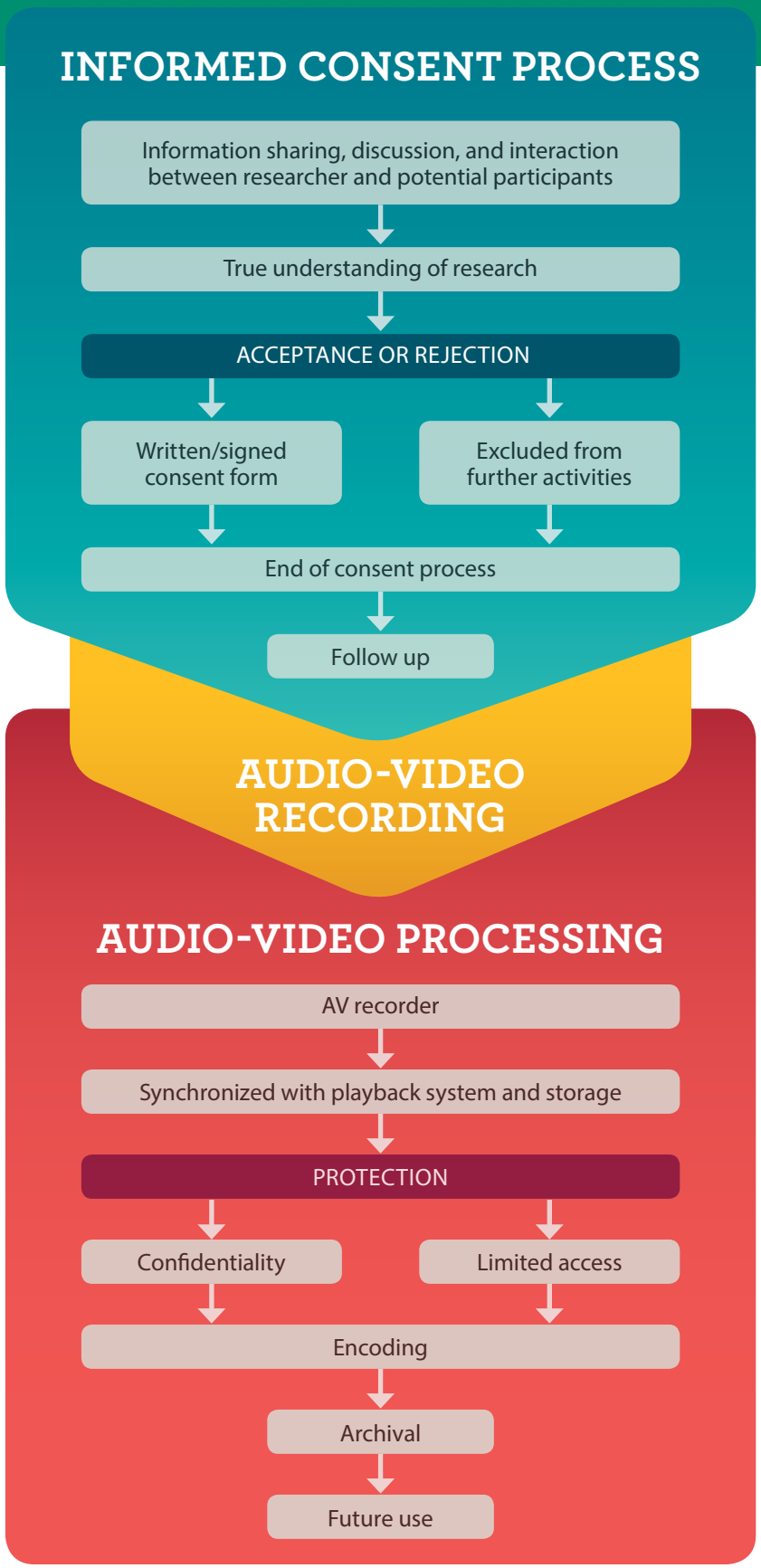
[DOI: 10.14524/CR-14-0014]

Informed consent is a dynamic process by which research participants and the researchers themselves embark on a collaborative relationship optimized via conscientious consent planning, consistent implementation, and complete verification.[1]

The consent process must ensure that all of the applicable study elements are explained and documented, including the probability for participants to be randomly assigned to varying treatments, which could include placebo in some cases.[2] In practice, however, many researchers do not provide detailed information to participants about the risks and benefits of the trial for which they have volunteered. For example, in a placebo-controlled trial, the information that any placebo administered will not have a clinical effect may remain deliberately undisclosed.

For researchers, the significance of the consent process can be difficult to explain, especially to those who are illiterate or who have different cultural backgrounds.[3] Furthermore, at times, the information presented during consenting is overwhelming to participants in terms of its volume and complexity.

FIGURE 1. A Conceptual Framework for the Determinants of Audio-Video Processing and Archiving



Ethical guidelines mainly emphasize the importance of consent[2,4,5]; however, the methods involved in carrying out the consent process and its documentation are rarely described in detail in official materials. An audio-video (AV) recording process will assure that a researcher has provided all the appropriate information to study participants. It may make the investigator more careful, minimize malpractice, and thus enhance credibility for the investigator and/or the study site.

Further, AV recording may make participants more attentive and increase their confidence in the research process. It is one of the important methods that accurately provide information relevant to exercising the participant's decision-making rights. By and large, it will help to increase conformity of the consent process to its expected best practices.[6]

A Framework for the Technical Requirements of AV Recording

Planning to obtain consent through AV recording requires an understanding of the conceptual framework of video processing and its archival requirements. Figure 1 shows a flow of AV processing and the consent process.

Essential Elements of AV Consenting

AV consenting provides an exact picture of counseling provided to a participant by a research team member during the consent discussion. However, prior to the start of the actual study consent process, a separate consent should be obtained to seek permission for the AV recording.

A written consent form should always include information about the AV recording. This information will help participants to understand the concept and importance of AV consent recording (see sidebar on page 50 on essential elements). It will also make the consenting process more transparent and ensure that the ethical principles of human subject protection are not violated in research. Further, this information will help volunteers to understand the AV recording process in detail (i.e., what it is, how it will be done, how the recordings will be used, how long they will be archived, etc.) and to make educated decisions.

A copy of the complete AV record of the actual discussion should be given to the participant, along with the written consent form, and the participant should be provided the opportunity to view the recorded assent as needed at the study site whenever he or she visits.

Ethical and Regulatory Requirements

Ethics and the tenets of good clinical practice state that consent should be obtained before any study-specific procedures are performed.[2,7] The U.S. Food and Drug Administration (FDA) and Department of Health and Human Services regulations require institutional review board (IRB) oversight of all research activities involving human subjects, including those related to informed consent.[8,9]

For every site or institution, the process of the AV recording and the technology used for obtaining consent should be reviewed by the appropriate IRB. Similarly, since these recordings include images and/or voices of research participants, the IRB should review or specify a timeline for archiving and eventually destroying the recordings, in order to help protect participants' privacy.

Regulatory guidelines should be more transparent and strong enough to support AV recording. For example, Indian regulatory authorities decided recently that AV recording of the consent process must be done and the documentation preserved in adherence with the principles of confidentiality.[10] This step will help to ensure that participation is voluntary and that participants can make an educated decision about being involved with a study.

Design Specification

No ethical or regulatory guideline specifies the type of device to be used for AV recording of the consent process. Therefore, for example, the researcher may use mobile phones, digital cameras, or web cameras. However, these devices may have different pixel or resolution power, which will create dissimilarities across trials and may increase regulatory hurdles due to issues with the quality of the videos.

Therefore, any plans to conduct AV recording should be able to fulfill some general hardware and software design requirements, in order to increase the likelihood of acceptance of the recordings by the appropriate authorities (see Table 1). Considering the growing popularity of digitization, the use of digital cameras with high resolution power or high definition video (e.g., HDV with version HDV 1080i and HDV 720p) recorders from known manufacturers like Sony, JVC, Cannon, Nikon, Sharp, and others can serve the purpose.[11]

These cameras should have adequate capability to simultaneously capture the side views, rear view, and facial details of the participant, an impartial witness (if any), and the site staff present during the consent process. The capacity for portable setup is essential if the participant is immovable. Clear and high-quality video is useful as strong evidence in case of any legal conflict during or after the trial.

Storage Device

Recording the consent process requires a storage device. Most high-definition video camcorders use MiniDV cassettes, which provide a maximum of one hour of recording. However, the trend toward tapeless workflow is accelerated with the increased capacity and reduced cost of nonlinear media like hard disk drives, optical discs, and solid-state memory. Other storage devices include pen drives and memory cards. All the stored data should be password protected.

Compatibility

Different AV recordings made with different devices may not have a consistent frame rate. Similarly, different manufacturers use different methods to maintain a recording's synchronization with a playback system. These methods can falter during format transfers (e.g., from DV to DVD). Often, an audio drift of two-to-four frames after two hours of synchronized DVD playback or a slight echo during regular playback can be observed, which may reduce the quality and extended use of the recordings.

AV consenting provides an exact picture of counseling provided to a participant by a research team member during the consent discussion.

TABLE 1. Design Requirements for AV Recording System

Requirements	Rationale
High image quality	Maximize output resolution, minimize intergenerational loss
High sound quality	Minimize impact of acoustically poor external environment, facilitate audio de-identification
Modularity	Components easily removed and replaced without extensive system disassembly
Reliability	Operate for extended periods with only minor maintenance or repair
Scalability	Designed for expansion without major physical, electrical, or software changes
Ruggedness	Withstand daily transport to and from study site and storage site
Data storage	Minimize physical space and cost of retaining data for subsequent review
Portability	Easily moved and configured by a single operator several times a day
Compatibility	Fit seamlessly into workflow of data collection and storage, minimizing necessary adaptation
Usability	Able to be operated following a minimal amount of specialized training

Essential Elements of AV Recording as Part of a Written Consent Form

- Statement that the research involves the use of AV recording of participant
- How the recordings will be used and how long they will be archived
- Statement indicating who will have access to the recordings
- Permission for the recording to be viewed or heard by anyone other than the research staff
- Participant's opportunity to view (or listen to) the recording after it is completed
- Confidentiality of recording
- Statement indicating where and how recordings will be stored and secured
- Space for participants to indicate whether they want recordings to be destroyed by the timeframe specified, or permit the recordings to be archived for future research within a given research area
- Who will transcribe the records and, if third-party transcriptions will be used, what steps will be taken to protect participant confidentiality

Software Requirements for AV Recording

- Desktop version of the software
- Restricted log accessible only by principal investigator or his/her delegate
- Archival facility at the site server (software developing firm can provide server for long-term archival with mutual contract with site/sponsor)
- Option to upload final signed informed consent form for the respective patients
- Automatic system validation to get detailed audit trail report, which will help to assess the history of activities for a single patient; this will in turn ensure that the patient AV record is not tampered with, and will help site/monitor to track any modifications that were made to patient record at site level (this report should not contain confidential data about the patient)
- Automatic labeling in the AV recording with date, time, patient number, patient initials, study code, etc.
- Multiday/session consenting option: If consenting is carrying out as multiple sessions for a single patient, the software must generate only a single AV recording including all sessions with labels
- Search engine to track patient data
- Capacity to refer the slides of patient information sheet or informed consent form in the software
- Restricted multiple password entries, periodic password change
- Restricted writing of AV records with a counter showing number of attempts
- Calendar showing overall status of consent recording over a month
- Software should be run only in the installed machine
- Multilayer protection to avoid hijacking

Playing an AV recording in different settings may require using different players like VLC, Windows Media, or Real Player. Generally, these media players do not support each other, which can make widespread compliance with any such playback system difficult across study sites. Thus, it is important to synchronize use of recording and playback systems across sites for better compatibility.

Archives Disaster Management

An "archives disaster" is an unexpected event that puts records at risk, such as a fire, natural disaster, or file corruption from a computer virus or dust contamination. Regular backup, "cloud computing," and remote data storage can help to protect records in easy and cost-effective ways. All backup copies should be readable, and at least one set of backup copies should be kept at a different location from the original recordings.

Computer hardware must be kept away from known hazards. Portable storage media such as CDs, DVDs, hard drives, pen drives, and memory cards should not be kept in attics, basements, or other places likely to be affected by volatile chemicals, hazardous materials, or wide variations in temperature, relative humidity, and the like.

All stakeholders in trials should work together to establish a common policy on archiving AV records. For example, Indian regulators, in their recent proposed guidance, state that AV records must be preserved safely for a minimum period of five years, even if they cannot be maintained "permanently."[12] The FDA does not specify any guidance for archiving AV records; however, 21 CFR Part 11 in FDA's *Code of Federal Regulations* defines the requirements for capture, storage, retrieval, maintenance, and security of electronic data.[13] Further, the Clinical Data Interchange Standards Commission has developed models and standards to support various types of electronic data interchange within the clinical trial process.

Confidentiality

Privacy and data protection in relation to trial participants is a worldwide issue for any type of electronic data.[14] All computers containing research data must be in secured areas and accessible only to authorized personnel through multiple levels of strong password protection. Storage devices must be stored in a locked file, itself located in a locked room.

To ensure confidentiality, all identifiable information pertaining to consent takers and participants should be protected. The Health

A copy of the complete AV record of the actual discussion should be given to the participant, along with the written consent form, and the participant should be provided the opportunity to view the recorded assent as needed at the study site whenever he or she visits.

Insurance Portability and Accountability Act (HIPAA) regulations affect research and the consent process, with HIPAA applying to health information created or maintained in electronic records.[15] Because of this, and HIPAA's strong emphasis on confidentiality, AV recording of the consent process is affected. However, with regard to HIPAA regulations, institutional practices and policies may vary significantly.

Additional Information Processing

At different times in the AV consent process, an investigator or expert may wish to review the discussion, or to add or clarify certain points. For example, shortly after gaining a participant's consent, an investigator might view the raw AV footage to determine whether or not an event of special interest has occurred, if any information was missed, and/or if any incorrect information was received by the participant. Such information will be supplemental, and may need to be added as a part of the original AV record. Collection and transfer of all new information to an existing recording—with each data element linked to the video via frame number—is possible; however, depending on the particular details of such circumstances, it should be determined if such modification is ethically acceptable by all stakeholders.

Best Practice for AV Recording

The investigator can delegate activities tied to AV recording to other research team members, although he/she should appoint a skilled person who understands the technical settings of the equipment being used.

As the recording begins, all concerned parties should identify themselves by stating their names, designation, and role in the study. Details of questions asked by the participant, the responses of the investigator, and the participant's understanding of the research project should be recorded. Similarly, the process of signing the consent document should be part of the AV record. At the same time, uninvolved persons should not be included within the recorded scene.

The use of multiple devices with different operating systems for AV recording is costly and technically complex, so the development of user-friendly software with minimum components can save time and expenses (see sidebar). The combined use of a laptop with AV recording software, a camera, a tripod, and a microphone will be ideal for most study sites.

Advantages of AV Recording

AV recording of the consent process will increase transparency in clinical research and will be useful to all stakeholders. Trial participants will be able to view their own records, thus building their confidence in the researchers and studies with which they are involved, and perhaps helping to reduce the overall number of dropouts in clinical studies.

AV recording also will give assurance to investigators that all necessary information was provided to participants, that the participants understood it, and that their decisions to participate were made voluntarily. AV recording will reduce documentation workloads, and ethics committees can use the recordings for reviewing the accuracy of the consent process and taking necessary actions against unethical practices.

In case of any legal matters related to consent, the AV recording can serve as evidence. Similarly, clinical trial monitors will be able to monitor the consent process efficiently. In short, AV recording will reduce ambiguity, thus raising the confidence of society in clinical research.

Practical Issues of AV Recording

Authenticity and Trustworthiness

Despite its many good points, AV consent is susceptible to alteration and corruption, so careful and appropriate handling of the process is required. Providing protection is difficult in the kinds of production or operation environments where most of these records reside. Information technology professionals often claim that the use of authentication technologies such as passwords, personal identification numbers, user identification, biometrics, encryption, and the like. will ensure the protection of the electronic records. Although the use of authentication technologies is critical to the creation of reliable data, we believe it is only a part of the answer.

In addition, the physical storage media (CDs, magnetic tapes, optical disks, etc.) are vulnerable to corruption and degradation with increased time, and thus must be replaced periodically. Furthermore, the records themselves may be altered without leaving any physical evidence. Thus, the technology that makes it so easy to create, use, store, and retrieve AV records also has the potential for making it possible to alter or corrupt the same records.

Privacy and data protection in relation to trial participants is a worldwide issue for any type of electronic data.

Additional Burden on Researchers

Although the consent process is an essential part of clinical research, it can be burdensome for study site staff with so many other things to do, such as recruitment and prescreening procedures, follow-up of potential participants, active participant counseling, documentation of ongoing study results, and more. AV recording and the maintenance of the consent procedure amidst such a heavy workload requires significant staff resources and expertise, to the point that investigators may find it more trouble than it seems worth.

Additionally, the lack of definitive regulatory and ethical guidelines on AV recording makes it a time-consuming and costly process with an air of uncertainty regarding whether the manner in which research teams conduct it now or in the near future will necessarily continue to be considered acceptable by the concerned authorities in the long term.

The Trial Participant's Perspective

In a number of countries, cultural traditions regarding attire may complicate AV recording, such as the burqas women wear in Islamic countries and the scarves (ghunghats) they use to hide their faces in many parts of Asia. Participants following such practices may simply refuse to give consent on camera.

Further, the body language, facial expressions, and voice tones of a person may change when he or she is in front of a camera, due to shyness or unfamiliarity with being filmed. Similarly, an investigator or participant may display different behaviors in front of the camera versus off-camera, which may cause difficulty in the participant's interpretation of information.

In general, participants are not very comfortable with sharing details about their illnesses, even during the routine consent discussion. Therefore, while facing the camera, often they will be reluctant to talk about sexually transmitted diseases, HIV, tuberculosis, or psychological problems. For example, in a study involving patients suffering from mental health problems, participants were more likely to withhold consent for video recording.[16]

Likewise, AV recording for studies enrolling participants being treated in emergency conditions may be difficult, as it also may be in cases where assent is needed from minors. In all such situations, investigators must build confidence in participants about AV recording, its usage, and its importance.

AV recording of the consent process will increase transparency in clinical research and will be useful to all stakeholders.

Infrastructure and Cost

Lack of infrastructure is one of the biggest challenges at many study sites across the world. Many sites are located in remote places where transportation capabilities, the power supply, and Internet services are not sufficient to support AV recording. The seemingly simple preference for using a separate room for the consent process, with adequate lighting and minimum background noise, is sometimes not possible to manage in government hospitals or private clinics.

Furthermore, the costs of building web-based solutions and consistency of Internet services in different regions are some of the major hurdles to be faced in many countries. The cost of the AV recording system itself is an additional burden on the sponsor. Generally, costs increase in late-phase clinical studies because large sample sizes necessitate recording and maintaining many more participants' consent details.

Other Issues

Source documentation is key to monitoring and auditing clinical trials. In cases of written consent, the process narrative is considered source data, whereas in cases of recorded consent, the AV records may act as source data. Thus, during source document verification, a monitor or auditor will review AV recordings.

Original recordings may contain a participant's protected health information (PHI), and therefore problems can arise when site monitors who are not permitted to access PHI need to review the recordings.[17] This problem occurs because there are two

Despite its many good points, AV consent is susceptible to alteration and corruption, so careful and appropriate handling of the process is required.

conflicting regulatory requirements for electronic medical records, one giving monitors a right and obligation to review source documents and the other giving sites a right and obligation to maintain privacy and control access to their records.[13,15,18] Simultaneously meeting these requirements can be a challenge, because there can be different AV recording platforms, and most of them do not feature user-friendly mechanisms for providing limited or temporary access to monitors.

Auditors have limited access to recordings containing information by which a patient may be identified; however, an auditor can verify the technical specification of the AV recording process in terms of recording devices, storage requirements, recording room, and counselor details. Further, an auditor can view an AV recording log or subject form that contains details on whether a subject has given AV recording consent, and if not, the reason for declining. Similarly, an auditor can check a quality log signed by a technician who is an authorized member of that investigator's team; this quality log confirms that each recording is of acceptable quality.

In addition, auditors may face difficulty in understanding whether the AV consent process was performed adequately on camera, especially if he or she is not familiar with the vernacular language used during the recording or requires a translator. Also, an increased time commitment will be needed by auditors to review recordings versus paper forms, which could take hours.

Conclusion

AV recording of the consent process of participants in clinical trials will definitely act as evidence of a well-conducted consent. However, its use is challenging because of a lack of any global initiative to pursue this practice and a lack of technical directives.

For successful implementation, careful consideration is needed in terms of the context in which recorded consent will be obtained, the methods with which it will be used in tandem, and the limitations it may encounter. Also necessary will be development of harmonized guidance for obtaining AV consent and upfront detailed review by ethics committees to determine which approaches will be feasible, depending on the study at hand.

Similarly, a change in attitude from researchers, better cooperation among stakeholders, and improved technology will be required to assure high data integrity and reliability. Only then will the introduction of AV consent be certain to deliver value to the clinical research enterprise.

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Acknowledgment

The authors would like to thank Prakash Ghulanawar and Ashwin Jadhav for their invaluable editorial assistance.

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Safeguards for Minors in Clinical Research: An IRB Perspective

PEER REVIEWED | Mitali Wadekar, MD, CIP | Anil Sharma, MD, MBA | Gina Battaglia, PhD

[DOI: 10.14524/CR-14-0021]

Clinical trials evaluate the effectiveness of one or more interventions in treating, preventing, or diagnosing a disease or condition. A 2013 memo from Robert Temple, the deputy center director for clinical science with the U.S. Food and Drug Administration (FDA), emphasizes the importance of conducting clinical research in the specific populations for which the drug is intended and minimizing unnecessary exclusions,[1] thus helping to assess the treatment risks and benefits in this population.

With this theme in mind, including minors in clinical research is essential, as extrapolation of results from adult studies for application in younger patients is often inaccurate. The pathophysiology, severity, course, and treatment response of conditions such as influenza and certain forms of cancer are different in adults and children. Additionally, some conditions, such as prematurity, are specific to a pediatric population, and other genetic conditions, such as phenylketonuria, could lead to disability or death in childhood if untreated.

Despite the importance of clinical trials, minors are traditionally underrepresented in clinical research because of their higher vulnerability to exploitation and increased protection under federal regulations governing research.[2] Due to the lack of clinical data in minors, physicians often must decide whether it is ethical and beneficial to prescribe a medication "off-label" (intended for a use not included in the approved labeling of the drug) to a child based on adult studies or anecdotal evidence in children.

Although many benefit from off-label prescriptions, others may not because the medicine was ineffective, toxic, or administered at the wrong dose. Physiologically, children are not "little adults," and their inclusion in research is necessary

to establish scientific evidence for safety and efficacy of drugs used in this age group.

Although the passage of the Best Pharmaceuticals for Children Act[3] and the Pediatric Research Equity Act[4] resulted in more than 500 pediatric labeling changes over the past 12 years,[5] only 41% of the molecular entities approved between 2002 and 2008 included pediatric labeling.[6] Improving knowledge about these treatments will help to determine a more effective diagnosis, prevention, and/or treatment of conditions in a wide range of age groups.

However, clinical trial research in minors also presents unique ethical challenges. Institutional review boards (IRBs) must ensure that

- any prospective study involving minors is scientifically necessary to perform in that age group,
- the study intends to increase knowledge about diagnosis, prevention, or treatment of the condition, and
- the risks do not exceed those of other groups.[7]

In most studies, one or both parents or legal guardians must provide informed consent. Minors must also agree to participate in the research if the IRB determines—based on age, maturity, and psychological state—that the participants are capable of providing assent.

This article discusses historical and current trends in clinical research involving minors and provides suggestions on how IRBs should establish additional safeguards to protect minors, while facilitating potentially beneficial clinical research.

Methods and Review

Although the concept of research ethics was not widely addressed until after World War II, medical experimentation involving children dates back several centuries. Physicians often used their own children, their servants' children, and/or institutionalized children to investigate infectious disease or immunization procedures because these children were available and convenient for such experimentation.[8]

As controversy grew regarding questionable 19th- and early 20th-century research practices in children—such as deliberate infection with sexually transmitted diseases, lumbar punctures, and invasive investigation of digestive processes—legislative proposals were implemented requiring legal consent (which minors were unauthorized to provide) to participate in research. This implicitly banned researchers from using children in their studies, although enforcement of such proposals was inconsistent.

Specific guidelines on ethical research in minors were not widely implemented until the 1964 Declaration of Helsinki, which stated that legal guardians must provide consent for child participants.[9] Nevertheless, controversial research practices continued, even in studies in which guardian consent was obtained.

From 1963 to 1966, researchers deliberately infected children at the Willowbrook State School, a state institution for "mentally defective persons" in New York, with hepatitis to study the natural history, prevention, and treatment of the disease.[10] Although the institution was closed to new residents during the course of these studies, parents could still enroll their child in the hepatitis program at the institution. Even though parental consent was technically obtained, many parents were coerced into enrolling because their child's admission to the institution was contingent on study participation.

Such controversial practices led to the development of policy statements by the U.S. Surgeon General in 1966 that required research institutions to have IRB committees to assess study methods for obtaining informed consent, assessing risks and benefits, and ensuring participant welfare.[11]

In 1973, the U.S. Department of Health, Education, and Welfare, now known as the Department of Health and Human Services (HHS), issued a document addressing special protections of children in research trials.[12] The document noted that, in trials, children 6 years or older must provide "assent," an "ethical review board" must review research protocols involving children, and a "protection committee" must monitor the research after it is initiated.

In 1983, the HHS included special regulations for research involving children based on the National Commission report on children issued in 1977 (Subpart D).[13]

The Children's Health Act of 2000 requires the FDA regulations to be consistent with those of the HHS, further increasing the protection of child research participants.[14] This act, which includes a pediatric research initiative in the National Institutes of Health, reflects the trend toward increasing research and treatment of health conditions affecting children and including diverse populations to verify the effectiveness of potential therapies.[14]

This trend has also introduced ethical issues that IRB members must consider in their review process. For example, they should ensure that the investigators effectively communicate (in written and/or verbal form) the research methodology and participation risks and benefits to parents and children,[15,16] and that the parents understand their child is receiving appropriate care when participating in a placebo-controlled or randomized controlled trial.[16]

Committees should also address possible discrepancies between the parent and child in the

Including minors in clinical research is essential, as extrapolation of results from adult studies for application in younger patients is often inaccurate.

desire to participate in the study,[17] and the possible relationship between low verbal communication between the patient and the physician during the informed consent process and difficulty in the patient's understanding of the study.[18]

Finally, the IRB must set standards for financial compensation for parents and children that is sufficient but not substantially coercive.[19]

To promote ethical, efficient clinical research in minors, the IRB must emphasize clear communication of the procedures, risks, benefits, and appropriate compensation in the proposals they receive from investigators, as well as consent/assent documents appropriate for the social, cultural, economic, educational background, age, and psychological capacity of the participants.

Minors are traditionally underrepresented in clinical research because of their higher vulnerability to exploitation and increased protection under federal regulations governing research.

Discussion and Recommendations

The relevant IRB must assess the risks and benefits of any human trial, and the regulations guiding research in children are understandably more stringent than in adults. In fact, Subpart D of the HHS regulations governing research states that any study in children involving greater than minimal risk must:

- provide prospective direct benefits to the participant;
- improve generalized knowledge about a disorder or condition; and/or
- provide an opportunity to understand, prevent, or treat a serious problem affecting the child's health or welfare.[13]

However, IRB committees frequently vary in terms of their definitions of "minimal risk" and "direct benefits," which could be problematic for gaining consistent approval among research institutions in a multisite study. Furthermore, risk assessment of common study procedures, such as blood draws, electromyograms, and allergy skin testing, have been found to vary among IRB chairpersons, as did their identification of direct benefits, such as psychological counseling and participant payment.[20]

Such discrepancies in analyzing risks and benefits are particularly important in multicenter studies, in which variations in the IRB review process may affect study approval and/or patient participation at certain research sites, thus limiting generalizability of the results. In one assessment of the IRB review process for a multicenter observational study in children, the committees varied on their recommendations of approval, conditional approval, and deferral, even though the study protocol was essentially identical across the centers.[21]

The number of days from submission to approval of the IRB application varied from five to 172 days for another multisite health services study.[22] The variability in the IRB review and approval process among the centers may limit potentially valuable research at certain centers if

- such studies cannot receive approval,
- investigators find the review process too burdensome, or
- certain groups of individuals (e.g., low-income) are discouraged from participating.[22]

Therefore, universal criteria of defining minimal risk and direct benefits among IRB committees will help establish consistent methods of assessing the ethical and scientific value of clinical studies in children.

Informed consent and assent procedures should also go beyond simply dispensing information and forms to parents and children. Multiple studies[16,23–25] indicate that parents do not fully understand the proposed treatment their child is about to undergo, even after investigators obtain informed consent from them. Parents often want more decision-making time[26–29] and information about the procedures[26,28] before consenting.

The child's involvement in the decision to participate is important, even if he or she cannot legally provide consent. IRB committees typically require research investigators to obtain assent from children by communicating the prospective procedures at a level appropriate for the child's age, maturity, and psychological state. Greater communication between the physician and child patient is associated with increased understanding of the study procedures in one study; however, levels of patient-to-physician communication are low.[18]

IRB committees should ensure that, after establishing that the consent/assent procedures and information provided are suitable for the target population, researchers provide sufficient opportunity for parents and children to understand the study procedures, communicate their questions and concerns to the investigators, and discuss participation with one another (in the absence of the investigator) before making a decision.

Children who are wards (under the legal custody of the state or other agency, institution, or entity) may not be able to obtain parental consent for research participation. Research that involves a greater than minimal risk and offers no direct benefits can be conducted in wards only if (a) the study is investigating a topic for which their status as wards is required for participation, or (b) the study is conducted in a setting in which most children are not wards (e.g., children under legal custody of the state could participate in a study at a public school that they attend, provided they have a pediatric advocate, because most of the other children in such a setting are under direct custody of a parent or guardian).[13] If these criteria are

met, IRB committees must ensure that pediatric advocates—individuals who have the expertise and competence to act in the best interest of the child and are not otherwise associated with the research study—are appointed throughout the child's participation in the research.

Conclusion

In summary, clinical research in minors is important for establishing efficacy of drugs and other treatments, thus improving therapeutic options in a wide range of pediatric populations. However, the history of exploitative research practices and the vulnerability of children require that additional safeguards be employed before undertaking research in this population. IRB committees should adopt universally consistent and methodical procedures for assessing risks and benefits, evaluate consent/assent processes, and assign pediatric advocates when appropriate to facilitate ethical research that promotes the health, welfare, and interests of children and their families.

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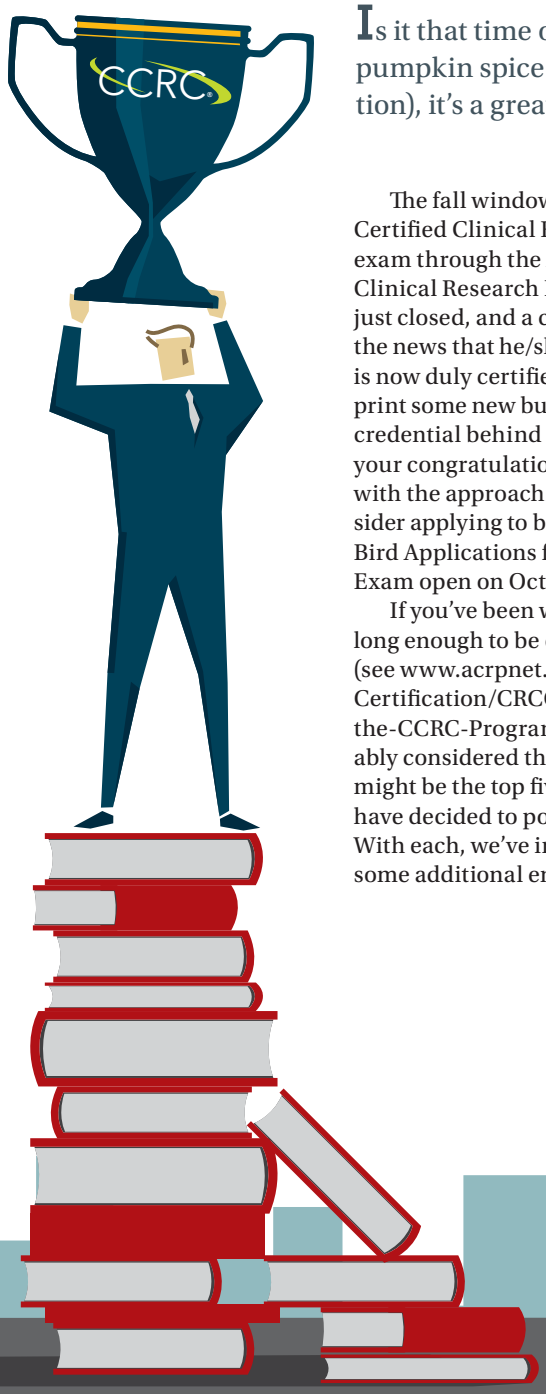
To be, or Not to be, a CCRC



Is it that time of the year again? With the arrival of orange leaves, cool mornings, and pumpkin spice lattes (and while you're still daydreaming about your past summer vacation), it's a great time to make a great decision.

The fall window of opportunity for taking the Certified Clinical Research Coordinator (CCRC®) exam through the ACRP-affiliated Academy of Clinical Research Professionals (the Academy) has just closed, and a colleague of yours has received the news that he/she passed with flying colors and is now duly certified. He/She can hardly wait to print some new business cards that add the CCRC credential behind his/her name. After you offer your congratulations, and before you get too busy with the approaching holidays, you should consider applying to become certified yourself. Early Bird Applications for the March 2015 Certification Exam open on October 1, 2014.

If you've been working in clinical research long enough to be eligible to apply for the exam (see www.acrpnet.org/MainMenuCategory/Certification/CRCCertification/eligibility-for-the-CCRC-Program.aspx for details) you've probably considered the idea. Here are what we think might be the top five reasons you may previously have decided to postpone the decision further. With each, we've included a simple solution or some additional encouragement to make the leap:

1. **You missed the deadline to register.** Well, that won't happen! We're reminding you now, and you have plenty of time.
2. **You decided you were not ready.** Is anyone really ready for anything in life? You're a great and experienced coordinator. Seize the day!
3. **You're not sure you're smart enough, and don't want others to know if you try but fail the exam.** Chances are someone you work with probably did not pass the first time either (it's kind of like taking your driver's test in that way). If you really don't want to, you don't need to share your pursuit with your coworkers until you feel comfortable. You'll get the results right away, and we bet you won't get the same question incorrect on a second attempt! As Bill Cosby once said, "In order to succeed, your desire for success should be greater than your fear of failure."
4. **You don't have time to study or are unsure of what to study.** Find someone to study with or form a study group. (If you are already certified, please consider leading a study group to help your colleagues prepare for the exam.)
5. **You're not sure what value certification will be to you professionally.** This is probably the biggest obstacle to overcome. The exam can be expensive, and how it might help you with your career can seem a bit of a gamble. So we'll look at this one more in depth in the following section.

If you have suggestions for preparing for a certification exam or developing a study group, please send them to **crcperspective@unc.edu**

What's in it (Certification) for Me?

Ours is a WIIFM culture (that is, "What's in it for me?"). In some ways, we need to ask that question when it comes to taking the certification exam.

Depending on your place of employment, the answer may be more or less obvious. At some institutions, achieving certification may provide nothing more than personal pride and a sense of accomplishment. At another, it could be part of a career ladder with certification leading to advancement.

Furthermore, monitors have said that they do take note of certification of coordinators in site selection visits. Better yet, TransCelerate BioPharma Inc., a nonprofit alliance of major pharmaceutical firms, has announced that it considers that the Academy's certificants at sites with which TransCelerate firms place trials have already demonstrated an understanding of Good Clinical Practice (GCP). Therefore, they are not required to retake GCP training for every new trial involving member firms.

By expanding your base of knowledge, you are bound to become a better coordinator. Applying for the exam will afford you the opportunity to become more familiar with the most current regulations and guidelines.

Of course, deciding to test your knowledge of your career can be a scary endeavor. Maybe you won't know as much as you thought you did. Maybe you will fail, but even by failing you will have learned something more about clinical research and about yourself. As a certain Danish proverb goes, "He knows the water best who has waded through it."

A Learning Experience, For Better or Worse

For those of you who have already taken the exam, whether you passed or not, we would venture to guess that it was a good experience. By applying to take the exam and becoming more involved with a larger community of coordinators, you probably learned quite a bit. Learning is such an important part of life.

In Claudia's experience, certification did help her to improve at her job. She found that reading the *Code of Federal Regulations* (CFR) and the International Conference on Harmonization GCP guideline as part of her job duties, and then reading them to study for the test, were really two different kinds of reading. The first time she read through the regulations, she read them because it was part of her job. When studying for the exam, she felt she finally acquired an understanding of the regulations that guide research both in the United States and globally.

Albert Einstein, a pretty smart fellow, once said, "Any fool can know. The point is to understand." With her second reading of the material, what Claudia came to understand was that all of the things that seemed at first to be arbitrarily required by the study sponsor were actually grounded in the CFR. By understanding the regulations, her job duties became even more fulfilling, rather than tedious. *[Editor's Note: ACRP Certification Exams currently do not test FDA regulations. The exams are grounded only in the ICH Guidelines. This column reflects Claudia's experience at the time of her certification.]*

Claudia also admits to being superstitious by noting that she refused to discuss how she thought she did on the exam, as she did not want to jinx herself. When she took the exam, it was a very long six-week wait to get the results; nowadays, the verdict is provided immediately.

Spread the News

If you have already taken the exam and found the experience to be valuable to you, to your study participants, and to the clinical research enterprise as a whole, please encourage your colleagues to apply for the exam. By discussing your experience with them, they may feel more at ease with the idea and the benefits to be gained.

Whether you decide to consider the CCRC exam or another national professional certification, or you are already certified and want to encourage a colleague to sit for the exam: Go for it!

Claudia has been facilitating study groups for the past three years, and is always looking for suggestions on how to improve the study group experience. If you have suggestions for preparing for a certification exam or developing a study group, please send them to crcperspective@unc.edu.

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The NC TraCS Institute at UNC is the academic home of the National Institute of Health's (NIH's) Clinical and Translational Science Awards (CTSA) program, grant number 1UL1TR001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

What Happened to My Labs

PEER REVIEWED | Lynn Petrik, RN, BSN, CCRC

[DOI: 10.14524/CR-13-00053R2.1]

We were finally in position to get a new study off the ground. Our first potential participant arrived for her screening visit, and the first order of business was an in-depth review of the study's informed consent with her. Once this had been signed, the rest of the visit proceeded smoothly. Two hours later, we said our goodbyes with the understanding I would call and confirm her eligibility for participation in the clinical trial after her lab results were received and reviewed.

Preparation of my volunteer's specimens required a fair amount of concentration. The sponsor of this study was based in Israel, making our site, in the United States, a foreign site. As a further complication, the laboratory selected for processing our samples was located in Canada.

Since this was my first experience preparing samples for shipment to a lab outside the United States, I had poured over the lab manual in advance. Although the processing followed the usual steps, the completion of shipping documents was more onerous than usual, because it required the completion of customs declaration forms detailing the number of milliliters of plasma, serum, and whole blood samples being sent.

Also, because the screening visit occurred on a Friday, I placed the necessary "Saturday Delivery" sticker on each package to ensure next-day delivery. After faxing the declaration forms to the lab to give staff there advance notice the samples were being sent, I called the courier and made arrangements for pickup.

An Unwelcome Surprise

You can imagine my surprise when I received an e-mail the following week informing me that the lab had not received the samples until Tuesday. Consequently, neither the frozen samples nor the ambient samples could be processed. The e-mail, which contained no explanation for the delay, requested I ask our subject to return to our site as soon as possible to have all samples re-drawn.

I decided not to schedule the follow-up appointment until I knew what had caused the delay. I assumed the error was mine: Had I completed the shipping documents incorrectly? Had I forgotten to attach a particular label to the packages? I knew that deliveries would not be made by the courier on the Monday following my subject's visit due to a national holiday; however, the lab samples were supposed to be delivered on the Saturday before the holiday.

In short, if the error had been mine, I needed to know what actions to correct.

On the Trail of What Went Wrong

A week later, I discovered what had happened: The packages containing the lab samples had been held by customs officials in the receiving country and thoroughly inspected. This turn of events came as a complete surprise to me. I was troubled by the

image of people rummaging through my volunteer's blood and urine samples; though there was no identifying information on the lab samples, I felt as though I had betrayed her trust.

Adding to my frustration, the original e-mail informing me of the ruined lab samples offered no polite apology on behalf of the lab or sponsor to our participant. There was no acknowledgment that their urgent request to repeat the screening labs posed additional risk, time, and substantial inconvenience to our potential study subject. So this got me thinking: When using a foreign laboratory, what are the implications pertaining to protection of our subjects during the course of a research study?

The natural place to begin was with the study's informed consent. Though I had carefully reviewed the consent with our volunteer, perhaps I had overlooked information regarding lab samples. A thorough review of the consent signed by our would-be participant revealed nothing that addressed the shipment of lab samples outside the borders of the United States and the related potential risks.

Then I reviewed the role of customs and border protection agencies. I visited the Canada Border Services Agency (CBSA) website and learned its mission is to "ensure Canada's security and prosperity by managing the access of people and goods to and from Canada."[1] To carry out this charge, CBSA personnel staff 119 border crossings and 13 international airport sites.[2] They are responsible for, among other things, preventing the entry of illegal goods in order to protect the health and resources of Canada.

A review of statistics from January 1, 2013, to March 31, 2013, offers a glimpse of the CBSA's sizable workload. In three short months, CBSA personnel facilitated the passage of 21,704,302 travelers, 8,113,076 vehicles, and 8,447,661 courier shipments.[3] Inspectors seized 1,280 firearms and weapons, $76,723,099 worth of drugs, $8,321,287 worth of contraband tobacco, and $3,311,142 in undeclared or illicit currency.[4]

Missing Pieces to the Puzzle

As I suspected, customs and border personnel have the responsibility and the right to inspect any package that arrives at their border in an effort to protect the people of their country. Still, what about my volunteer who agreed to participate in a research study and was unaware her blood samples could be held up in customs, as well as opened and inspected by border officials? There was no mention of this in the informed consent and no mention that, in the event this occurred, she would be asked to repeat the labwork. Finally, there was no mention of financial compensation, if any, for the visit required to redraw the lab specimens.

A number of documents eloquently guide professionals who are engaged in the clinical research enterprise. The Nuremberg Code, the International Conference on Harmonization's Guideline for Good Clinical Practice (ICH GCP), the Declaration of Helsinki, and the Belmont Report are important sources we use to determine how we ought to proceed in human subjects research.

The first point in the Nuremberg Code states, "The voluntary consent of the human subject is absolutely essential.... Before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment conducted, all inconveniences and hazards reasonable to be expected...."[5]

ICH GCP section 2.3 states, "The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." Additionally, under "Informed Consent of Trial Subjects," item 4.8.10 identifies information that should be provided subjects, including (d) "the trial procedures to be followed, including all invasive procedures" and (g) "the reasonable foreseeable risks or inconveniences to the subject...."[6]

Recognizing the Risks

Organizing a multinational clinical trial is unmistakably a daunting task and, understandably, it is impossible for a sponsor to be able to anticipate all potential problems and risks that could arise throughout the course of a study. Thus, it must follow that an informed consent cannot possibly identify every potential risk.

There are, of course, different kinds of risks, including those that are known, such as previously identified side effects of a study drug and potential harms from failures associated with procedures and devices. These are standard and appropriate to include in an informed consent.

Then there are the unexpected problems that might affect study subjects, such as a courier truck transporting lab samples breaking down and delaying their arrival, a study drug not being delivered to a site in time for a participant's scheduled visit, severe weather conditions and power outages affecting study visit windows or a subject's ability to enter lifestyle data into a computer, and so on. These kinds of unpredictable, mundane occurrences, if you will, are not the sorts of problems and risks commonly identified in informed consents.

However, the situation I encountered with lab samples held and thoroughly inspected at a foreign border seems different to me, and rises to a level where it ought to be identified as a potential risk in an informed consent. My volunteer's labs were opened by an entity that was not part of the normal

My volunteer's labs were opened by an entity that was not part of the normal research protocol for handling samples, and this occurrence was no mere fluke or accident, for such an event is an inherent potential feature of transporting samples across international borders.

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research protocol for handling samples, and this occurrence was no mere fluke or accident, for such an event is an inherent potential feature of transporting samples across international borders.

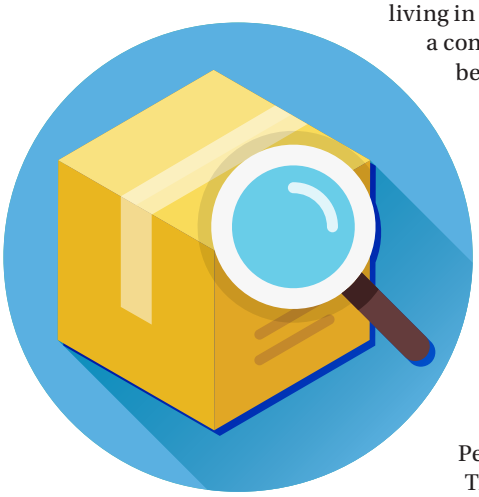
The introduction of the Declaration of Helsinki, section A.10, states, "Physicians should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration."[7]

One way to avoid the situation we encountered is never to participate in a study in which yours is a "foreign site" using a laboratory outside your country. This solution, of course, is not reasonable or practical; many important and valuable research studies are conducted all over the world, and our site is eager to contribute to such research.

Meanwhile, sponsors choose their vendors for a wide range of reasons. Study laboratories might be selected for their expertise in working with clinical trials, their ability to process special types of lab samples and/or ensure consistency with sample processing, their convenient location, or their rock bottom price. Thus, if we are to participate in clinical trials, we must adapt and work with the vendors selected to carry out the trial procedures.

Considering the Subject's Perspective

These considerations, though valid, did not directly address the concerns I had for the study participant in the situation at hand. The delay of her lab samples, though unexpected, added an extra burden and risk. Our participant resided in a southeastern Ohio county that is known as much for its natural beauty as for its high rate of poverty. Many of our study participants are part of this same region's underserved population, living in rural communities and traveling a considerable distance in hope of benefitting from clinical trials.



Our participant, additionally, had three young children to consider. To return to our site to repeat the labwork presented a number of substantial burdens for her. Thinking about these burdens prompted me to look to the Belmont Report, which explains the three ethical principles applicable to human subjects research: Respect for Persons, Beneficence, and Justice. Treating these principles in reverse order, considerations of Justice highlight an important reason why I was troubled by the extra visit required of my patient—namely, the fact that the burdens imposed upon study subjects by a particular visit are not all equal. They depend not only upon the mechanics of the visit itself, but also upon the subject's life circumstances. In this case, "fairly" evaluating the extent of the burden imposed on the subject involved recognizing that the "visit" was, in fact, no small undertaking.

The principle of Beneficence, for its part, requires us to understand the notion of harms and benefits as they pertain to our study participants. With respect to the situation encountered by my study subject, one way sponsors might minimize the risk of this sort of situation would be to adopt enhanced packing procedures that would extend the "life" of samples during shipping. (I thank an anonymous peer reviewer for bringing this possibility to my attention.) Whether such shipping measures would be financially and practically feasible, however, could be decided only by the sponsors on a case-by-case basis.

Though Justice and Beneficence are certainly relevant, it is Respect for Persons that strikes me as most key in this situation. Respect for Persons requires us to treat our study participants as rational and autonomous agents who deserve full information to make decisions about their own lives and welfare. An inadequate informed consent process can be seen as a failure of respect for our subjects.

I believe, therefore, that the remedy to this problem lies in the informed consent—the transparent process by which would-be participants are given the best information we have, so they can make fully informed decisions affecting their health and welfare.

New Practices for Protecting Patients

The surprise situation we encountered when our subject's lab samples were held and inspected by customs personnel prompted our research site to implement new practices for participating in studies that use international central laboratories.

First, we will negotiate contracts that contain provisions for mitigating the potential effects of delays resulting from customs inspection. Such contracts could include:

- reimbursement for subjects and the research site if repeat labs are necessary due to customs delays; and
- funds sufficient to use enhanced shipping methods able to withstand the longer shipping times that can result from border inspection.

Second, we are adding language to the informed consent explaining the risks associated with sending lab samples across international borders.

Conclusion

Truth be told, I debated whether or not this was a situation worthy of such heavy consideration. After all, how often could it possibly happen? I suspect it may not be a common occurrence. Certainly, in my nine years of work as a clinical research coordinator, I had never encountered a situation like this before.

However, this was our first experience in a study that used a foreign laboratory. Though this may not be a common occurrence, the very first time I sent lab samples across the border, they were held for inspection and not delivered within the appropriate timeframe. Whether or not this happens often is not relevant; it happened to my participant.

If I am to be faithful to the spirit of informed consent and adhere to the principle of Respect for Persons, though this mishap was unusual, it was significant. Thus, it was something our future participants deserve to know in advance and which a study site should strive to make as unlikely as possible.

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An Interview with Valerie D. Willetts, RN, BSN, CCRA

Valerie D. Willetts, RN, BSN, CCRA, is well known to many ACRP members through her long-term and significant contributions as a volunteer on many committees, including her year as chair of the Board of Trustees in 2011. She is currently a senior clinical research associate with PAREXEL International, a global contract research organization (CRO), and has accepted a position in San Diego, Calif., on the global monitoring operations management team.

I'm privileged to work with exceptionally talented colleagues who share a common interest in recognizing and supporting basic human rights as patient advocates.

Q: How did you first became interested in clinical research, and can you describe a little bit about the path you took in your clinical research career?

A: My career as a clinical research professional started during my nursing career, when I learned about an opportunity to make a difference in the lives of the patients that I was caring for through working in the clinical research arena as a study coordinator. It seemed like a chance to give back to the healthcare community—the patients—through sharing my skills and knowledge and, above all, supporting their wellbeing. So, it was a bit of a serendipitous transition from nurse to study coordinator.

Q: Can you tell us a bit more about the different roles you've held since your transition from nurse to study coordinator?

A: It's been a long and winding road with many interesting turns, and I'm looking forward to wherever the pathway will lead me next. After my time as a study coordinator, the next steps in my career path included quality management and monitoring roles. They enabled me to teach good clinical practice, rules, and regulations for site management and monitoring; develop learning modules for clinical research associates (CRAs) and project managers; develop a network of research professionals in Canada that became ASKA Research; and develop strategic alliances with other CROs internationally.

I joined PAREXEL International after a couple of decades in the entrepreneurial realm of clinical research services, and I'm enjoying the positive changes and challenges in the corporate world. I'm privileged to work with exceptionally talented colleagues who share a common interest in recognizing and supporting basic human rights as patient advocates.

Q: When did you first get involved in ACRP, and what benefits have you reaped from being a member?

A: I joined the association at the time that Canada first formed an ACRP Chapter. ACRP offered an opportunity to become a volunteer and advocate for the Canadian Chapter. It's been a privilege to volunteer and serve on many ACRP committees, including (to name a few) Education, Regulatory Affairs, Ethics and Human Subject Protection, and Finance. I've also chaired the Canadian Chapter, been overall chapter chair for North America, and served as chair of the Association Board of Trustees in 2011. The benefits of membership have been amazing; I can't even begin to count the blessings and the learning gained from the wisdom and the sharing with and by my colleagues.

Q: Since your career has spanned many years and you have no doubt seen many changes, what is the most significant change (or top changes) you have seen? How has this affected the industry, either positively or negatively?

A: Sabrina Geremia, Google's managing director of integrated solutions, has written in her book on *Habits of Highly Successful People* that the next 10 years of change will be greater than the previous 100 years. We live in interesting times, for sure! Personalized targeted therapies, electronic data capture and clinical trial management system technologies, regulatory requirements, and recognition of the importance of ethical management in all aspects of clinical trials have presented us with new challenges, in particular with regard to informed consent and distribution of healthcare information.

While the clinical research community has been affected by many changes, it's our willingness to embrace change that lends itself to interpretations of what is positive or negative about our evolving research environment. It's important to keep moving forward, keeping in mind that, "The more things change, the more they stay the same" (Hugh Prather). The new "same" becomes the new benchmark.

Q: With this issue's theme of patient advocacy in mind, how has your role as a patient advocate evolved over the years, and what do you believe clinical researchers need to do to endeavor to promote patient advocacy?

A: I'm convinced that healthcare professionals are better caregivers when they have been patients. My experience in nursing was a good foundation for learning about new care options and how to describe them to potential study subjects, while gaining a better understanding about what they needed during clinical trial participation. Wellbeing, healthcare, and human rights advocacy has been a consistent theme throughout my personal and professional life.

I believe it is important to remember why we are involved in clinical research in the first place. As patient advocates, we have a tremendous accountability to deliver the best! A positive and proactive attitude with discretion brings strength and respect, and attracts more energy and light than you can possibly generate on your own. Synergy builds energy, new ideas, and empowerment to make a difference in the lives of others, as well as your own. Stay centered on why we do what we do; we're critical in the lives and wellbeing of the patients we seek to empower.

Q: What advice do you have for clinical research professionals on how to advance their careers?

A: I'll quote Chris Allen, from his APCR President's Message in the October 2013 issue of *The Monitor*: "Trying to anticipate the future is hard, but active management and adaptation does allow a sense of control." One particular point that Chris made resonates with me: "Learn to persevere, as everything can look like a failure in the middle." Be sure to network and learn from the associations that you establish; be disciplined; be willing to change. We need to be chameleons to achieve our goals, to move with the times, and to take advantage of the opportunities as they are presented to us.

Q: As you think about the future generation of clinical research professionals, what three "lessons learned" would you like to share?

A: Three lessons learned; there are so many more than three!

Stephen M. R. Covey describes the principle of contribution in his book, *The Speed of Trust*: It's the intent to create value instead of destroy it, to give back instead of take. More and more, people are realizing how important contribution—and the causes it inspires—are to a healthy society.

Be sure to listen carefully and consider your options in response to what you hear and read and see. Stay informed about the changing climate in the clinical research professional world with your intuitive senses attuned to the need to acquire new skills to ensure that you will have the qualities needed by present and future employers.

Always give back more than you seek to gain; the return on investment is tenfold and more! It is so very important to be curious and seek new perspectives and share what you learn, what you're thinking, and what you want to know, and to keep in mind that giving back brings many blessings.

Q: Do you have any closing thoughts you would like to share?

A: I have been blessed with so many positive influences throughout my career path. I am pleased to acknowledge that this is not only thanks to the leadership and support of my colleagues—many of whom have become friends—but also thanks to the influence of the patients and study subjects with whom I have met and for whom I have cared. I'd also like to end with a quote from the acclaimed author and poet, Dr. Maya Angelou: "I've learned that people will forget what you said, [and] people will forget what you did, but people will never forget how you made them feel."

Val, thank you for sharing your passions and perspectives on patient advocacy, clinical research, and a long and successful career. You clearly live by your words of giving back. On behalf of the patients and ACRP members whose lives you have touched, I am confident they have all gained from your knowledge, wisdom, and compassion.

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The Investigator's BROCHURE: A Real Aid for Drug, Device, and Food Product Trials

PEER REVIEWED | Matthew J. Harris, BA | Joy L. Frestedt, PhD, CCTI, RAC, FRAPS

[DOI: 10.14524/CR-13-00052.1]

The investigator's brochure (IB) is a critical tool used by principal investigators (PIs) to analyze the risks and benefits of an investigational product. The requirements associated with the IB for pharmaceutical studies have been documented in international standards, including the International Conference on Harmonization (ICH) Common Technical Document,[1] and are clearly defined in regulations, including those covering U.S. Food and Drug Administration (FDA) inspections of institutional review board (IRB) oversight responsibility for tracking IBs along with protocols and informed consent forms for a given investigation.[2]

Currently, an IB is also required for medical device clinical trials under the Medical Device Directives guideline MedDev 2.7.2[3] in the European Union and for all companies claiming conformity to the ISO14155:2011 standard from the International Organization for Standardization.[4]

Although IBs are commonly used in drug trials, the medical device industry has only recently started to use IBs more often to convey information to PIs conducting device clinical trials, and IBs are expected to become more commonly used for other types of investigational products in the near future.

The use of the IB for food-related studies is a novel concept; however, after reviewing hundreds of trials in foods, food ingredients, and dietary supplements, the use of food-related IBs can be recommended and should mirror the style and content of pharmaceutical and device IBs.

Although food-related trials do not carry the same risk:benefit ratios as drug and device trials (i.e., some food-related trials are simple observational studies designed to evaluate effects of a food in a small population of rather healthy individuals[5]), the PI will still benefit from having all of the relevant, product-specific data analyzed, documented clearly, and available for review prior to and during the clinical trial.

As a living document, the IB needs to be updated with appropriate changes as new safety and efficacy information becomes available throughout the product lifecycle.

Setting the Standard

The ISO14155:2011[4] standard for good clinical practices when conducting clinical trials for medical devices defines the IB as a "…compilation of the current clinical and nonclinical information on the investigational medical device(s) relevant to the clinical investigation." This standard goes on to state that the purpose of the IB is to provide the PI with sufficient safety or performance data from preclinical or clinical investigations to justify human exposure to the investigational device in the clinical trial.

Further, "The IB shall be updated throughout the course of the clinical investigation as significant new information becomes available (e.g., a significant change in risk, etc.)," and the PI needs to "acknowledge the receipt of the IB and all subsequent amendments."

IB development can be a complicated project when multiple countries are involved in the nonclinical and clinical development of the new (or modified) product. The production of an IB can also be complex if the investigational product includes several different components (e.g., drugs, devices, botanicals, tissues, and/or foods).

Five Key Elements

IBs are designed to provide investigators with the information necessary to facilitate their understanding of the key features of the investigational product relevant to the clinical trial. In addition, the IB should enable clinicians/investigators to make their own decisions regarding the risks versus benefits when using the proposed investigational product in study subjects.

To aid these goals, the initial and ongoing development of the IB should be:

- Concise,
- Simple,
- Objective,
- Balanced, and
- Nonpromotional.

These five key elements are considered essential to the development of all IBs.

Once developed, the IB is a critical component to be thoroughly reviewed before starting a clinical trial and used as a quick reference during the trial, especially to understand safety, efficacy, or performance issues related to the investigational product.

The IB should include any warnings, precautions, and instructions regarding the appropriate use of the investigational product as intended by the manufacturer. Often, the early safety and efficacy language in the IB becomes a part of the required labeling for the product in its postapproval use.

As a living document, the IB needs to be updated with appropriate changes as new safety and efficacy information becomes available throughout the product lifecycle. The IB must be maintained with appropriate editing to reduce redundancy and to clarify the product risks and benefits.

Reasons to update an IB may include newly discovered details on a drug's pharmacokinetics and/or pharmacodynamics, design changes to medical devices, alerts regarding food sensitivities and/or biocompatibilities, and new data related to the safety, efficacy, performance, or tolerability of the product.

Furthermore, if a marketed product is being studied for a new use, an IB specific to the new use is required.[1]

Required IB Contents

Many sources present information about the required contents, including, but not limited to, the ISO14155:2011,[4] ICH-E6,[1] and 21 CFR 312.23[6] (in the *Code of Federal Regulations*) documents.

Although the specific investigational product data may differ in the IBs for different products, a general Table of Contents can be used to guide IB development of a pharmaceutical product (Table 1) or medical device (Table 2). These Tables of Contents have a similar structure, including three basic sections of an IB in common:

1. a general information section (to identify the device and sponsor and to provide device information);
2. a data section (to provide both preclinical testing and existing clinical data); and
3. a risk section (to describe risk management plans as well as regulatory plans and other risk analysis references).

TABLE 1. General Outline of an IB for a Pharmaceutical Product[1]

TO BE INCLUDED	DESCRIPTION
Title Page	Sponsor's name, identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name), release date, edition number, and number and date of the edition it supersedes.
Confidentiality Statement	Statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and IRB/IEC.
Signature Page	Author and reviewers should sign and date the IB.
List of Abbreviations	Acronyms and abbreviations should be defined.
Table of Contents	Sections and page numbers should be tabulated.
Executive Summary	Brief summary highlighting significant results from the proceeding sections.
Introduction -General Information	Brief introductory statement with the chemical, generic and trade names, all active components/ingredients, pharmacological class, and expected position within the class. Provide the general approach to be followed in evaluating the investigational product.
Product Description	Physical, chemical, and pharmaceutical properties and formulation.
Nonclinical Studies	Summary of data from all nonclinical (e.g., animal) pharmacology, toxicology, pharmacokinetic, metabolic, toxicologic studies addressing the methods, results, and relevance of the findings to the investigational product, including: • Nonclinical Pharmacology • Pharmacokinetics and Product Metabolism in Animals • Toxicology
Effects in Humans	Summary of data from all clinical studies of pharmacokinetics, biotransformation, safety and efficacy in humans; data on postmarketing experience if the product under investigation has been already approved for use for other indications, including: • Pharmacokinetics and Product Metabolism in Humans • Safety and Efficacy • Marketing Experience
Guidance and Risk Management	Summary of the data and guidance for the investigator—Describe the possible risks, adverse reactions, and/or specific tests, observations, and precautions that may be needed for a clinical trial.
References and Regulatory Conformity	Provide references at the end of each section.
Appendices	Additional helpful information should be included.

The risk section should review all known risks from uses of the investigational product itself, as well as from products with similar characteristics.

GENERAL INFORMATION SECTION

The general information section should provide the name of the investigational product, the name and address of the sponsor and/or manufacturer, the document reference number, the version or date of the IB, a confidentiality statement, a version or issue number, and a reference number. The IB should be paginated with a page number and total number of pages on each page, and the IB should be signed and dated.

The body of the IB should start out with a summary briefly describing the investigational product and providing an overview of the scientific background and contents of the entire IB. The introduction should provide a detailed overview of the studies conducted, the rationale for the intended use of the investigational product, and a comprehensive scientific background about the investigational product complete with a full bibliography. The methods used to evaluate the investigational product should be noted in the introduction.

DATA SECTION

The data section often begins with the physical, chemical, and pharmaceutical or engineering properties of the investigational product. The safety measures and instructions for storage and handling of the investigational product need to be included, as well.

The nonclinical studies data should contain summaries of all the studies conducted involving the investigational product. The summaries of the studies should include a description of the methods used and any relevant tables and/or figures. Within the nonclinical studies section, data should be represented as they relate to pharmacology, pharmacokinetics, and toxicology for drug products.

For medical devices, the nonclinical testing section of the IB should review such factors as the manufacturing details as well as the design calculations; *in vitro, ex vivo*, and cadaveric tests; mechanical and electrical tests; reliability tests; software validation (especially if related to the function of the device); performance tests; and biocompatibility and biological safety tests.

Clinical data should also be summarized, showing the effects of the investigational product in humans. Benefits and risks including all adverse events should be tabulated and explained in sufficient detail to guide the investigator. The clinical data section will also include information

TABLE 2. General Outline of an IB for a Medical Device[1,3,4]

TO BE INCLUDED	DESCRIPTION
Summary of the Literature and a History of Prior Uses	Include a rationale supporting the design and intended use. This will be similar to a clinical evaluation report.
Regulatory Classification	A statement disclosing the regulatory classification as well as status.
Compliance with International Standards	A statement of compliance with specific international standards, if any, were complied with during the design, manufacturing, and use of the product (may include a statement of conformity with national regulations, where appropriate).
Proposed Mechanism of Action	Include a description of the intended performance/action referencing the supporting scientific literature.
Relevant Manufacturing Details	Include chemical analysis properties (e.g., components, materials, drug substances, and finished product details) and related validation/verification activities, lower limits of quantification, etc.
Testing Results	Include data from nonclinical studies, clinical trials, and summaries of clinical use information (including postmarketing data if product is already on the market).
Justification of Product Use	An evaluation of the data provided justifying the product use in the appropriately selected study subjects.
Risk:Benefit	Include risk management information (i.e., summary of benefits as well as adverse events including serious adverse events, adverse device effects, etc.); should include a discussion about why the benefits would be expected to outweigh the risks for the intended use in the intended population and a discussion about how the residual risks will be mitigated.
Performance and Tolerability Issues	Summarize any device malfunctions, complaints, or compatibility issues.
Instruction for Use	Include information regarding installation/preparation, storage and handling, sterilization and reuse, pre-use safety or performance or sterility checks, precautions and warnings, disposal, etc.
List of References	Include appropriate citations in the text and a full reference list, including all citations.

IBs are designed to provide investigators with the information necessary to facilitate their understanding of the key features of the investigational product relevant to the clinical trial.

on marketing experiences, as well as relevant information from the global literature about the investigational product.

Likely, the IB will include many different study reports grouped into appropriate sections of key findings.

RISK SECTION

The risk section should review all known risks from uses of the investigational product itself, as well as from products with similar characteristics. The determination of equivalence among the different products should be made clear in the discussion of the benefits and risks. A thorough and carefully constructed risk:benefit analysis will consider products with other intended uses if one can reasonably assume the presence of a benefit or risk will be expected with the product of interest.

The goal of the IB is to provide an overview of what is known about the investigative product along with appropriate background information clearly laying out the appropriate patient populations, possible benefits and risks, adverse reactions, observations, and precautions to be taken during a clinical trial.

IB Lifecycle

An IB should be reviewed at least annually, and revised when necessary in compliance with a sponsor's written procedures and in response to any changes in safety or performance. The frequency of revisions depends on the investigative product's stage of development, as well as on the amount of incoming relevant new data (both clinical and nonclinical).

As new information regarding the investigative product becomes available, the IB must be updated to serve its full purpose. For example, as each trial is completed, the new data from the trial need to be added to the IB.

Integrating the safety, efficacy, and performance data from all the clinical evidence (including internal bench and clinical data, as well as data from the literature) is critical to the synthesis of the IB. Generally, the sponsor is responsible for ensuring the IB is up-to-date and available to the investigator(s), whereas the investigators are responsible for providing the up-to-date IB to the responsible IRBs or independent ethics committees (IECs).[1,2]

IB Warning Letters

The development of the IB has been a common practice in the pharmaceutical industry, and the use of IBs is expanding among medical device manufacturers and others; however, problems still exist. A recent review of the FDA's Warning Letter website showed six Warning Letters were issued regarding IBs between 2001 and 2014.[2] These letters included warnings to sponsors about failing to provide each investigator with an IB, failing to obtain investigator statements indicating the investigators have read and understand the IB, and failing to maintain a current IB.

Warning Letters were also issued to IRBs after members who voted on IBs were discovered to be PIs on studies of related products and when IRBs did not document reviews of IBs. Sponsors need to be fully aware of the regulations surrounding IBs to avoid receiving Warning Letters.

Conclusion

This article reviewed the contents expected when developing or reviewing an IB, including specific issues related to pharmaceutical, medical device, and food-related IBs. These brochures play an integral role in clinical research to keep all investigators aware of the latest data on a product under development, or for which a new indication is being considered.

As new information regarding the investigative product becomes available, the IB must be updated to serve its full purpose.

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Going in Depth on Informed Consent

In this issue's column, questions are addressed regarding one of the most important and often confusing issues in clinical trials—the process of informed consent. Almost 10% of the time, inspection outcomes include a finding related to how informed consent is conducted at the inspected research site (see: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM256376.pdf).

A review of recent Warning Letters from the U.S. Food and Drug Administration (FDA) confirms that a variety of informed consent problems can occur during clinical trials. The questions in this issue relate to some procedural aspects of human subjects protection and informed consent.

A review of recent Warning Letters from the U.S. Food and Drug Administration confirms that a variety of informed consent problems can occur during clinical trials.

Q: Does the FDA require that a subject initial and/or date each page of the informed consent form (ICF)?

A: According to the agency's guidance on informed consent procedures listed on its website, as well as 21 CFR 50.25 in the *Code of Federal Regulations*, there is no requirement that each page of the consent form be initialed/dated by the subject. However, some sponsors and institutional review boards (IRBs) have been known to require this practice during informed consent.

If an IRB communicates certain expectations for documentation of an ICF, such as having the subject initial and/or date each page of the form, and approves the ICF template with this feature, then failure to perform those actions would mean that informed consent was not properly obtained. Whether or not this needs to be reported to the IRB as a protocol violation—and whether the subject needs to be re-consented—are decisions to be made by the IRB.

Q: If a subject is a minor at the beginning of a study and then reaches the age of majority during the course of the clinical study, should the subject be consented or re-consented as an adult (i.e., at the next visit after reaching majority)?

A: The FDA has indicated that the subject should be re-consented as an adult. FDA's regulations at 21 CFR 50.20 requires an investigator to obtain "the legally effective informed consent of the subject or the subject's legally authorized representative." Once a child-subject reaches the age of majority (which will vary according to state law), the parent's permission for the child to participate in the trial would no longer constitute "legally effective informed consent" for research activities that take place in the future because the subject, who is now an adult, can make decisions for him/herself and should be offered the opportunity to do so.

Q: If there is a signed ICF, is additional source documentation necessary to record informed consent?

A: According to FDA Good Clinical Practice (GCP) regulations at 21 CFR 312.62(b), "the case history for each individual shall document that informed consent was obtained prior to participation in the study." Interestingly, the International Conference on Harmonization (ICH) GCP guideline does not specify that the obtaining of informed consent be documented anywhere other than in the consent forms themselves.

In order to satisfy and be consistent with other GCP standards and guidelines, all data on the case report form (CRF) should be supported or be verifiable from source data. To satisfy the FDA requirement, site staff may either write a progress note about the consenting process or complete a data item on the CRF that records the date of the consent. Best practices, however, call for a "contextual" statement in a source document regarding exactly how and when the consenting process occurred.

Generally, it is far better to document the consent in the medical record, which, as a primary document, can easily capture the particulars of the consenting process.

Q: Is an approval stamp from the IRB required to be placed on an ICF?

A: Although it is common practice for some IRBs to place a stamp on the ICF—either on the cover page or on every page indicating that the form is "IRB approved"—this is not a requirement. Other IRBs do not do this, instead relying on the date and version control performed by the submitter to know which version is the most current approved version.

Some concern has been raised that a stamp on the ICF indicating the word "approved" might imply to a potential subject that the IRB considers the study to be safe, or otherwise could be misinterpreted as an endorsement of the trial. In addition, in several Warning Letters to IRBs over the years, the FDA has actually suggested the IRB adopt the use of a stamp to assure that the most current version is used. In one Warning Letter, the FDA indicated that, "This is not required by regulation, but it is considered to be a good practice."

The ICH GCP Guideline only specifies that there be documented approval by the relevant IRB or ethics committee, but provides no mention that the IRB or committee should stamp the consent form itself.

Do you have a GCP question or an issue that has come up at your site or company? If you are not sure of how to proceed, please send an email to: gcp@moriahconsultants.com and I will answer it in an upcoming column.

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Using Electronic Medical Records to Facilitate Principal Investigator Involvement

PEER REVIEWED | Rebecca Stock, MSN, WHNP-C, CCRC

[DOI: 10.14524/CR-13-00067R1.1]

Principal investigators (PIs), by virtue of their education, training, and experience, assume responsibility for the entire conduct of a clinical trial, as well as the conduct of its staff members.

The U.S. Food and Drug Administration's (FDA) *Code of Federal Regulations* (CFR) clearly delineates PI responsibilities in 21 CFR Part 312[1] for clinical investigations of drugs or biologics and in 21 CFR Part 812[2] for clinical investigations of medical devices.

Investigators should have sufficient time to conduct and properly supervise a clinical trial and its subject population. However, for many PIs, research duties are often juggled between multiple sites, patient office hours, medical committee responsibilities, and hospital and on-call coverage. Thus, the intensity and timeliness of this supervision may vary from site to site.

To satisfy sponsor and IRB requirements, electronic medical records can be a valuable tool in documenting the oversight process, especially when PIs are not present at a subject's site visit.

The Scope of Supervision

Increasingly, sponsors are developing standard operating procedures (SOPs) requiring documentation of a PI's involvement in a trial, specifically PI supervision of study conduct in accordance with the current protocol. Despite the delegation of many trial activities to sub-investigators and study coordinators, sponsors and institutional review boards (IRBs) now expect well-documented verification of PI oversight. The PI must be available for consultation with study staff and to provide study subjects with satisfactory medical care for any problems that may arise from study participation.

In a survey of more than 500 study coordinators regarding their PI's involvement in clinical studies, conducted by Elizabeth Moench of MediciGroup,[3] coordinator responses included "practically invisible" and "partially involved" when describing their PIs. Strikingly, results showed that only 5% of physicians routinely saw subjects during their study visits.

Furthermore, though it may be unnecessary for the physician to be present at every study visit, a critical study element is to demonstrate adequate PI supervision of and involvement in these visits and the ongoing conduct of the study through thorough documentation. We have often heard the phrase, "Saying and documenting are two different things." Despite continued reference to the importance of adequate record-keeping, many sites may still be lacking in effective documentation showing oversight and involvement by their PI.

To satisfy sponsor and IRB requirements, electronic medical records (EMRs) can be a valuable tool in documenting the oversight process, especially when PIs are not present at a subject's site visit.

Leveraging EMRs for Oversight

Currently, institutions may choose from a number of EMR systems on the market that satisfy FDA guidelines on electronic records and electronic signatures. 21 CFR Part 11 Section 11.1 (a),[4] or Part 11 as it is commonly called, defines the criteria under which electronic records and electronic signatures are considered to be trustworthy, reliable, and equivalent to paper records.

Each individual site's SOPs determine who will have access to the EMR system and how staff will be trained. "Read-only" access is available in most systems for both institutional and noninstitutional personnel, such as clinical research associates (CRAs) who make monitoring visits to sites and must provide verification of electronic documentation to sponsors of the trials to which they are assigned.

With a reliable EMR system in place, the following are simple strategies that illustrate how this can be advantageous in satisfying sponsor and IRB requirements for documenting PI involvement:

- Remote Access to Subject Charts—EMRs can provide secure, 24-hour, remote access to users. Regardless of time of day or PI location, remote entry into a subject's electronic chart allows for review of subject data and swift response to any issues related to the subject with PI verification by unique electronic signature, date, and time stamp.
- Enrollment Decisions—With subjects' medical histories available in a clear concise format within their EMR, the PI is able to confirm inclusion/exclusion criteria based on documented information.
  - »Often, multiple providers have input into a single medical record, creating a comprehensive, centralized file.
  - »In some cases, subjects may not be able to recall their health history with the level of certainty and detail required. Having access to their electronic chart may provide the necessary information to assist the PI in making a proper enrollment decision.
- Prompt Review of Subject Visit Notes—The study team member conducting the visit can use EMRs to electronically send subjects' visit notes directly to the PI, often within minutes of completion of the subject visit.
  - »This action allows review of all subject data and, in particular, any new physical findings, which can be verified by the PI's electronic signature, date, and time stamp.
  - »This also gives the PI an opportunity for immediate follow up with any questions or additional tests and orders.
- High-Priority Notification of Adverse Events—Any new onset of an adverse event or serious adverse event (SAE), or any change in an existing adverse event can be relayed electronically to the PI, with most systems allowing a designation of the incident, from the sender, as "high priority."
  - »By direct transmission of this information, the PI can obtain all necessary data in order to make a determination regarding care of the subject, follow up, and event causality, and can transmit recommendations and orders back to the sub-investigator or research coordinator without delay.
  - »Rapid electronic transmission of data between PI and study staff also facilitates mandatory SAE and endpoint reporting to sponsors and IRBs.
- Notification of Clinically Significant Laboratory Abnormalities—All lab reports can be scanned into the subject's electronic chart and immediately transmitted to the PI for evaluation and intervention of clinically significant abnormalities.

- Keeping the Subject's Primary Doctor and Other Providers in the Medical Loop—Subjects may be required to follow up with their primary doctor or other medical providers for evaluation and treatment of clinically significant laboratory, pathology, or electrocardiogram abnormalities detected during study participation.
  - »An EMR note, signed by the study coordinator and PI, identifies continuity of care as well as PI oversight of the issue and maintains healthcare coordination with all associated providers.

Clearly, in an ideal situation, PIs would be present to conduct all subject visits face to face. However, just as unrealistic as this expectation might be, EMR documentation has demonstrated itself as an effective conduit between the PI and all study team members, in terms of maximizing adherence to the protocol and minimizing risks to the subject.

Conclusion

In summary, it is essential for the conduct of the study, as well as for all members of the research team, that the sponsor maintain communication with the PI on a regular, ongoing basis. Until recently, investigator oversight was left to the discretion of the site, with no clearcut standards or policies in place. Recently, this has begun to change, with sponsors and IRBs demanding documented evidence of PIs' accountability in their execution of the FDA's mandated clinical investigator responsibilities.

Ultimately, the named investigator has the personal responsibility to ensure the study is conducted in accordance with the study protocol and all IRB requirements, and to protect the safety, rights, and welfare of investigational subjects. All sites should recognize the fact that robust site documentation of a PI's study involvement has now become an integral component of a successful clinical endeavor. Using an EMR system may prove beneficial in accomplishing this objective.

References

1. Food and Drug Administration 21 CFR Part 312.
2. Food and Drug Administration 21 CFR Part 812.
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Nonsignificant Risk

Medical Device Investigations

The Investigational Device Exemption (IDE) regulations at 21 CFR Part 812 in the *Code of Federal Regulations* describe three types of medical device studies: significant risk, nonsignificant risk (NSR), and exempt studies.[1] An NSR medical device investigation may proceed without approval by the U.S. Food and Drug Administration (FDA), and is therefore an attractive avenue toward commercialization for a manufacturer of a device that does not pose a significant risk. However, there are specific record and reporting requirements for NSR device investigations.

What is a Device?

A "device," within the meaning of the Federal Food, Drug, and Cosmetic Act (FDCA), is "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory" that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals," Sec. 201(h).[2]

A simple analogy is that a popsicle stick is not a device within the meaning of the FDCA, and anyone can make and sell popsicle sticks without premarket approval or registration with the FDA. However, if a manufacturer wanted to market a popsicle stick as a tongue depressor, then this "intended use" would make it a device within the meaning of the FDCA, and the manufacturer would be subject to at least general controls and registration with the FDA. Sometimes the distinction is unclear, and the FDA will respond to an inquiry whether an intended use of a device puts it into an exempt, NSR, or significant risk category.[3]

What is an NSR Device?

An NSR[4] device is one that does not meet the definition for a *significant risk device* at 21 CFR 812.3(m), which defines a significant risk device as an investigational device that:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

There is a regulatory incentive for an NSR determination: If a sponsor can get an institutional review board (IRB) to agree with an NSR determination, it may proceed with a clinical investigation without having an IDE application approved by the FDA.

In its "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors—Significant Risk and Nonsignificant Risk Medical Device Studies," the FDA stresses that "An IRB's NSR determination is important because the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies."[1]

Although an NSR device investigation may proceed without FDA notification, it is not free from regulatory compliance. An NSR device study must comply with the abbreviated NSR requirements at 21 CFR 812.2(b).

Abbreviated NSR Requirements

Among the abbreviated NSR requirements is a mandate that an NSR device be labeled in accordance with 21 CFR 812.5 and a prohibition against unauthorized claims of safety and effectiveness. Additionally, the device must be labeled with: "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use."

The abbreviated regulations also call for compliance with the monitoring requirements of 21 CFR 812.46, which task the sponsor who discovers an investigator who is not complying with "any condition of approval imposed by the reviewing IRB or FDA [with] promptly either [securing] compliance, or [discontinuing] shipment of the device to the investigator and [terminating] the investigator's participation," 21 CFR 812.46(a). A terminated NSR study may not resume without IRB approval, 21 CFR 812.46(c).

Informed consent must be documented for each subject, and the subject's case history[5] must document that informed consent was obtained prior to participation in the study, 21 CFR 812.140(a)(3)(i). Additional records that must be kept and maintained for an NSR study include sponsor records at 21 CFR 812.140(b) (4) and (5) and reports required under 812.150(b) (1) through (3) and (5) through (10), 21 CFR 812.2(b)(1)(v).

The investigator must report unanticipated adverse device effects (812.150(a)(1)), withdrawal of IRB approval (812.150(a)(2)), and any use of the NSR device without consent (812.150(a)(5)). The sponsor must prepare and submit reports of unanticipated adverse device effects to the FDA and IRBs (812.150(b)(1)), any withdrawal of IRB (812.150(b)(2)) or FDA approval (812.150(b)(3)), and various matters required under 812.150(b) (5) through (10).

An NSR investigation must also comply with the prohibitions in 21 CFR 812.7, which block commercialization of the device before the FDA has approved it for distribution, 21 CFR 812.2(b)(vii).

Conclusion

Sponsors, investigators, and IRBs have certain abbreviated requirements when investigating a device that poses an NSR. Included is the requirement to obtain and maintain IRB approval, document informed consent, and appropriately label the device as investigational. Additionally, an NSR device cannot be commercialized until after the FDA has approved the device for commercial distribution.

Before marketing an NSR device, a manufacturer must classify the device and then choose, prepare, and submit the correct premarket submission. Finally, owners or operators of device establishments or facilities that are involved in the production and distribution of medical devices must register with the FDA and list their devices.[6]

If you have a research compliance issue you would like covered in this column, please send an e-mail to the author at **ibataba@gmail.com**.

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1. U.S. FDA, Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors—Significant Risk and Nonsignificant Risk Medical Device Studies (January 2006).
2. 21 U.S.C. § 321(h).
3. U.S. FDA, Procedures for Handling Inquiries Regarding the Need for an Investigational Device Exemptions Application for Research Involving Medical Devices (October 26, 2001) (#D01-01).
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5. 21 CFR 812.140(a)(3).
6. U.S. FDA, How to Market Your Device, at www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/default.htm

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Human Subjects Protection: **Vulnerable Populations**

This is a topic near and dear to my heart. The U.S. *Code of Federal Regulations* (CFR) 56.111 defines vulnerable populations as "children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons." It goes on to clarify that when some or all of the subjects "are likely to be vulnerable to coercion or undue influence, additional safeguards [must be] included in the study to protect the rights and welfare of these subjects."

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Beyond the Basics

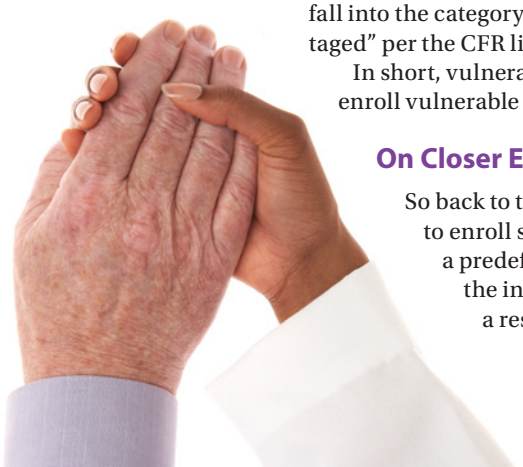
However, there are many more vulnerable populations than those listed in the Code. Terminally ill patients are certainly vulnerable; I don't think I would lump them into the category of "handicapped." Then there are the employees at research sites of any kind, and the students at academic medical centers where research is being conducted.

Further, vulnerability is most often not a visible, objective state of being like being pregnant. Far more often, it's a subtle, transient experience. It's the result of a specific interaction between two particular individuals.

Any patient on the lower end of a real or perceived significant power differential can become vulnerable. Employees are a prime example, and elderly patients (of an age where they are blankly accepting of the physician's judgment), when paired with a physician with a strong personality, would be another.

Some people become vulnerable when confronted by a father figure. For others, their vulnerability may present itself when faced with someone with much more education, even if that patient is very well educated him or herself and would never fall into the category of "educationally disadvantaged" per the CFR list of vulnerabilities.

In short, vulnerability is everywhere, and we enroll vulnerable patients every day.



On Closer Examination…

So back to the CFR definition: If you want to enroll someone who is a member of a predefined vulnerable population, the institutional review board has a responsibility to put in place additional safeguards and to pay closer attention. If you want to enroll someone who is not vulnerable to coercion or undue influence, then we can all assume he or she is capable of understanding the standard informed consent and capable of making this decision. Right?

When I read CFR 56.111, it sounds perfectly reasonable. When I restate it as above, it sounds completely inadequate to protect research subjects. Who is *not* vulnerable?

I did surgical rotations during my residency at a trauma center. There, a very wise surgeon made an impact on me that I never forgot. During these rotations, we would occasionally get a "very important person" (VIP), such as a senator or, worse yet, a personal injury lawyer as a trauma patient. The emergency department would begin buzzing about this person and people would warn one another to pay close attention because so-and-so is in Trauma Bay 3.

Dr. Jenks, however, would always chide us with the same reminder: "Give him exactly the same high level of care you would give to anyone else." If it's possible for you to up your game for a VIP, then why aren't you doing that for everyone? I use this same approach with vulnerable populations.

Do Unto Others

Sometimes it's easy to see that you have a vulnerable patient, such as a prisoner in an orange jumpsuit, someone in a coma, or a child, but every patient is potentially a vulnerable patient. The only way to protect the patient is to remember the wisdom of Dr. Jenks, and treat *every patient* with the same high level of care you would give to a "vulnerable patient." Everyone wins.

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