APRIL 2015

Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

Patient *Centricity*

Including....

Association of Clinical Research Professionals (ACRP)
www.acrpnet.org

Essential Web Seminars and Publications
for Clinical Research Professionals

10-Week Clinical Research Associate (CRA) On-Boarding Program

March 13 - May 29, 2015
12:00 PM - 3:00 PM Eastern

— & —

June 5 - August 28, 2015
8:30 AM - 11:30 AM Eastern

30-Hour Clinical Project Management Fundamentals Certificate Program

April 7 - May 7, 2015 • 9:00 AM - 12:00 PM Eastern • Tuesday and Thursday mornings

30-Hour Clinical Research Auditing Certification Program

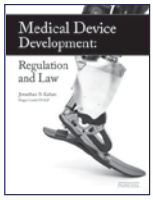
April 9 - June 11, 2015 • 6:00 PM - 9:00 PM Eastern • Thursday nights

Good Clinical Practice: A Question & Answer Reference Guide

This industry-leading guide answers over 1,200 of the most common and difficult questions regarding the interpretation and implementation of US and International GCP standards.

New Drug Development: A Regulatory Overview (8th Edition)

Go inside the drug development and FDA regulatory process with today's most authoritative and popular reference on the topic.



Medical Device Development: Regulation and Law 2014

The "must-have" resource for the novice or veteran medical device regulatory affairs professional. This practical reference provides the most comprehensive and updated analysis of US medical device and diagnostics development and approval requirements anywhere.

Order your copies today. Visit our website at www.barnettinternational.com/publications or call 800 856 2556 or +1 781 972 5402 to place your order.

BARNETT INTERNATIONAL
Leaders in Clinical Research Training

Clinical Researcher™
The Authority in Ethical, Responsible Clinical Research

Patient *Centricity*

CONTENTS

April 2015 • Volume 29, Issue 2 • 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

+1.703.254.8102 (fax)
+1.703.254.8100 (phone)

www.acrpnet.org

DESIGN
TGD Communications
tgdcom.com

GUEST EDITOR'S MESSAGE

Michelle Mocarski, MPH, BA, CCRC

[DOI: 10.14524/CR-15-4062]

Practicing Patience in Patient Centricity

Although it may seem obvious that the ultimate goal of clinical research is to discover new treatments to improve patients' lives, unfortunately, this patient-centric view is sometimes either overlooked or forgotten when it comes time for a trial's actual implementation.

With increasingly complex trial protocols, evolving regulations, and aggressive enrollment targets, perhaps not surprisingly, it can be difficult for sites, clinical research organizations (CROs), and sponsors to step back from timelines and the myriad forms and procedures to determine whether patients' needs are considered within the drug development process.

Thankfully, there has been recognition in recent years that patients should play a larger role in how drugs come to market, since patients will be the ultimate recipients of therapy. As the momentum around patient centricity continues to build, more companies and organizations are trying to determine how to bring the patient perspective to the center of research.

Whether it's the creation of the Patient-Centered Outcomes Research Institute or the growing use of patient-reported outcome measures, we in the field can see the needle moving toward more patient-centered research design already. However, though the concept of patient centricity is important and growing in acceptance, how to apply it in our daily practice can be more challenging.

This issue of *Clinical Researcher* aims to take a practical and actionable approach to understanding how we can all contribute to making our work more patient-centered. The authors approach the challenge from several different angles, and they describe a variety of approaches that can be used not only to make clinical research more patient friendly, but also to streamline and optimize our existing research infrastructure. Their approaches range from simply improving patient satisfaction at the site level by more appropriately managing staff workflow, to perhaps the most challenging—changing organizational culture.

However, the key need to understand patients as individual human beings is at least one "take away" for all readers from this issue, and represents the best starting point for helping to advance the patient centricity movement, regardless of any individual's role.

Understanding the Patient

Before patient centricity can be incorporated into the drug development process, we, as researchers, need to gain a better understanding of the patients we enroll into our studies. Author Kenneth Getz provides a thorough history of the patient centricity movement in his article, "Charting a Course for the Patient Centricity Movement." He makes the case

To read our Article Submission Guidelines, see page 74.

that a shift from product-centric drug development to patient-centric drug development not only results in study findings that are more meaningful to patients, but also has the potential to improve the efficiency of the drug development process. He profiles several ways that the field is successfully moving toward a more patient-centric approach.

The article by Paul Wicks and coauthors, "How Engaging Patients Will Change Clinical Trials for the Better," demonstrates just how willing patients are to be part of the process, and how early engagement can benefit all stakeholders. This piece points out that not only can researchers gain valuable insights from patients regarding acceptability of study elements such as the protocol design, but they can also gain a better understanding of how patients may likely see pipeline products someday fitting into the current treatment regimen. The authors end the article with a case example of how patients have been successfully engaged to provide guidance to one sponsor company's program.

Jeroze Dalal's article, "Factors Influencing Patient Participation in Clinical Trials in India," highlights that there also is unlikely to be a one-size-fits-all answer for how patients view research and patients' willingness to participate. This article presents the results of a survey conducted among patients in India regarding their views of clinical trials and their motivations and concerns about becoming involved. The variation among patients in their views suggests that truly obtaining the patient perspective requires synthesizing several different perspectives and finding the key areas of overlap.

Solutions You Can Use

Another trio of articles provides several practical approaches that can be used by sites, CROs, and sponsors to increase patient centricity.

Ari Gnanasakthy and Carla DeMuro's article, "Logistical Considerations for Integrating Patient-Reported Outcomes in Multiregional Clinical Trials," sheds light on a specific area of patient centricity—collecting data directly from the patient to support endpoints in a clinical trial. The authors point out that, although it may initially seem straightforward to include an existing patient questionnaire into a clinical trial protocol, many considerations must be made to ensure that the data ultimately collected are meaningful, accurate, and complete. This includes fairly obvious activities, such as providing comparable translations of the questionnaire to all anticipated language groups, and those activities perhaps less obvious, such as educating site staff and all individuals supporting the trial on the patient-reported outcome measures, whether from the site, CRO, or sponsor side to ensure that all individuals are on the same page regarding the process of collecting patient data.

Jay Yockelson approaches patient centricity from yet another angle, saying that to truly respect the patients who participate in research, sites must be mindful of selecting the right studies and the right number of studies to conduct. Suggestions are made for how to streamline the process for patients when they are at the site with the aims of ensuring that all study procedures are conducted in the most optimal and efficient way, reducing the time that the patient ultimately must spend at the site, and being respectful of patients' priorities. He then describes how having a "putting patients first" approach can also have the additional benefit of making sites more profitable in the long run.

Finally, Abbe Steel's article, "A Culture of Patient Centricity: Using a Model of Co-Creation to Optimize Clinical Trials," focuses on the many ways that patients can be engaged throughout the drug development cycle. She challenges us all to not only think beyond making small incremental changes (though these are, of course, important), but also to think about how we can change the culture of our organizations so that we are all focusing on the patient every step of the way.

Warm Regards and Happy Reading!

I would like to thank all of the authors for providing such thorough and thought-provoking pieces. I have learned a lot while putting together this issue of *Clinical Researcher,* and I am excited for others to access these articles. I hope they help you to increase the patient focus in clinical research to the benefit of both yourself and your key stakeholders, and that you can find actionable suggestions in the following pages you can put to use in your daily practice.

Michelle Mocarski, MPH, BA, CCRC, (michelle.mocarski@gmail.com) is associate director for health economics and outcomes research with Novo Nordisk, Inc. in Wayne, N.J., and a member of the Editorial Advisory Board for *Clinical Researcher.*

BY THE NUMBERS

Taking stock of some of the ways clinical trial managers and sponsors are or should be communicating with potential and current study volunteers and consumers.

Text messaging campaigns can accelerate enrollment in clinical trials. Use of the approach in a vaccine trial achieved a **1% increase** in subjects enrolled for every **1.5%** increase in text messages sent; 1,541 messages resulted in screening 795 patients and **enrolling 265.**

Source: www.mosio.com/study-text-messaging-enhances-clinical-trial-enrollment-mobile-solutions-mosio/

A survey of **307 consumers** found that knowledge about their own disease and an understanding of the relative advantages of personalized medicine have the most significant influence on patient acceptance of treatment regimens based on the individual's DNA.

Source: www.eurekalert.org/pub_releases/2015-01/cu-hts010615.php

Researchers are suggesting **10 situations** in which it is ethical for a physician to "Google" a patient, including "duty to re-contact/warn patient of possible harm" and "discrepancies between a patient's verbal history and clinical documentation."

Source: www.eurekalert.org/pub_releases/2015-02/ps-pgf020215.php

ACRP
ASSOCIATION OF CLINICAL RESEARCH PROFESSIONALS

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

[DOI: 10.14524/CR-15-4058]

THE LOGIC BEHIND LOGISTICS

In this issue's column, the questions focus on a variety of logistical concerns that may come up during the planning or conduct of clinical trials.

When IRBs do review subject recruitment practices, they primarily review advertisements and incentives paid to subjects, not practices involving sponsor-investigator interactions.

Q: Is it permissible for a clinical site to mail investigational drugs to enrolled subjects?

A: The regulations do not explicitly prohibit the mailing of investigational drugs to study subjects; however, "control" of investigational drugs may be a challenge if the study drug is mailed to subjects. Questions to consider if this approach is contemplated include:

- Does the study protocol allow the investigational product to be used directly by the subject, or must the investigational product be personally administered to the subject (e.g., by injection)?
- Does the product require refrigeration or other special handling?
- Is it a controlled substance, subject to the Controlled Substances Act, and thus, are there additional precautions that must be taken to limit access, theft, or diversion of the substance into illegal channels of distribution? (see 21 CFR 312.69 in the *Code of Federal Regulations*)
- How will the investigator verify that the subject actually receives the product for use and stores it properly?

In rare cases, when a study subject is located a considerable distance from a study site, arrangements could be made to ship the product to the subject or the subject's local physician.

Q: To what degree is there active institutional review board (IRB) oversight of various subject recruitment practices?

A: A 2000 report from the Office of the Inspector General in the Department of Health and Human Services (HHS), "Recruiting Human Subjects: Pressures in Industry-Sponsored Research," concluded that the "oversight of the recruitment of subjects is minimal," and worse, that "IRBs are not reviewing many of the recruitment practices that they and others find most troubling."

The report looked at what HHS identified as the "four main strategies" that sponsors and investigators use to recruit human subjects and encourage timely recruitment:

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 e-mail to: gcp@moriahconsultants.com and I will answer it in an upcoming column.

1. sponsor-offered financial and other incentives to investigators to boost enrollment;
2. investigators "target" their own patients as potential subjects;
3. investigators seek additional subjects from other sources, such as physician referrals and disease registries; and
4. sponsors and investigators advertise and promote their studies.

"Although financial incentives given to investigators by sponsors to boost enrollment are among the recruitment practices that IRBs are most concerned about, 75% of IRBs that responded to our survey do not review any financial arrangements between sponsors and investigators," the report states. When IRBs do review subject recruitment practices, they primarily review advertisements and incentives paid to subjects, not practices involving sponsor-investigator interactions.

The International Conference on Harmonization's (ICH's) Good Clinical Practice E6 guideline states that IRBs or independent ethics committees should review site documents related to subject recruitment procedures (e.g., advertisements) and any written information to be provided to subjects. The finding that a significant percentage of IRBs do not gather basic information about recruitment practices on sites' study applications for review raises the possibility that some IRBs may not be reviewing recruitment practices at all.

The 2000 HHS report found some positive trends, including the fact that IRBs reported devoting increasing attention to recruitment-related issues. In addition, 61% of the surveyed IRBs reported that they had requested changes in the recruitment practices called for by a protocol during the previous three years, and many said that they were requesting more recruitment-related changes than they had three years earlier.

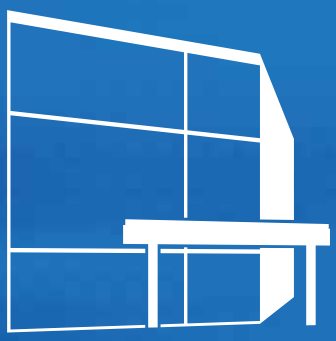
Q: Are IRB review and approval needed for general telephone scripts that the clinical site's receptionist uses to interact with potential study subjects who contact the site to inquire about or express an initial interest in a study?

A: In the U.S. Food and Drug Administration's information sheet on "Recruiting Clinical Subjects," the agency states that, "the first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed (ICH E6, 3.1.2) adequately protect the rights and welfare of the prospective subjects because often personal and sensitive information is gathered about the individual."

Questions the IRB will ask include:

- What happens to personal information if the caller ends the interview or simply hangs up?
- Are the data gathered by a patient recruitment company? If so, are names, etc., sold to others?
- Are names of non-eligible subjects maintained in case they would qualify for another study?
- How are the data captured, and are paper copies of records shredded or are electronic readable copies permanently deleted?

Michael R. Hamrell, PhD, RAC, FRAPS, RQAP-GCP, CCRA, (gcp@moriahconsultants.com) is president of MORIAH Consultants (a regulatory affairs/clinical research consulting firm), holds appointments at several major universities, is a member of the ACRP Editorial Advisory Board, and serves similarly for several other leading clinical research and regulatory affairs journals.



imarc
UNIVERSITY
CLINICAL RESEARCH EDUCATION

Training is in our DNA.

Visit us at booth 618

at the ACRP 2015 Global Conference & Exhibition to learn more about our affordable, online training courses for clinical researchers.

www.imarcresearch.com/university

Suzanne M. Heske, RPh, MS, CCRA, BCNP

[DOI: 10.14524/CR-15-4055]

PATIENT CENTRICITY

ACROSS

1 Patient

2 Patient-reported outcome (abbreviation)

3 _____trials involve smaller number of patients with flexible protocols

7 This is a hot topic with increasing usage of social media (two words)

8 Research study (two words)

9 _____have become more arduous in recent years

10 Subject agrees to participate in a clinical trial by signing an_____(two words)

13 Provide medical care to mitigate disease

15 A core component of quality healthcare (two words)

16 Direct-to-patient is a method of_____

18 Electronic medical record (abbreviation)

19 Patient-Centered Outcomes Research Institute (abbreviation)

20 Examine large datasets (two words)

23 Type of trial design

24 Personal health record (abbreviation)

27 Optimal patient-centric healthcare depends on good_____

28 Actively focused or occupied

DOWN

1 Form of communication that can improve healthcare delivery (two words)

4 Critical data

5 This innovative concept aims to transform healthcare delivery (two words)

6 Consequence

11 Helps ensure consistency or uniformity

12 Component of Good Clinical Practice (two words)

14 Technique or methodology (two words)

15 Patient-reported outcome measure (abbreviation)

17 An aspect of having authority

21 Quality of life (abbreviation)

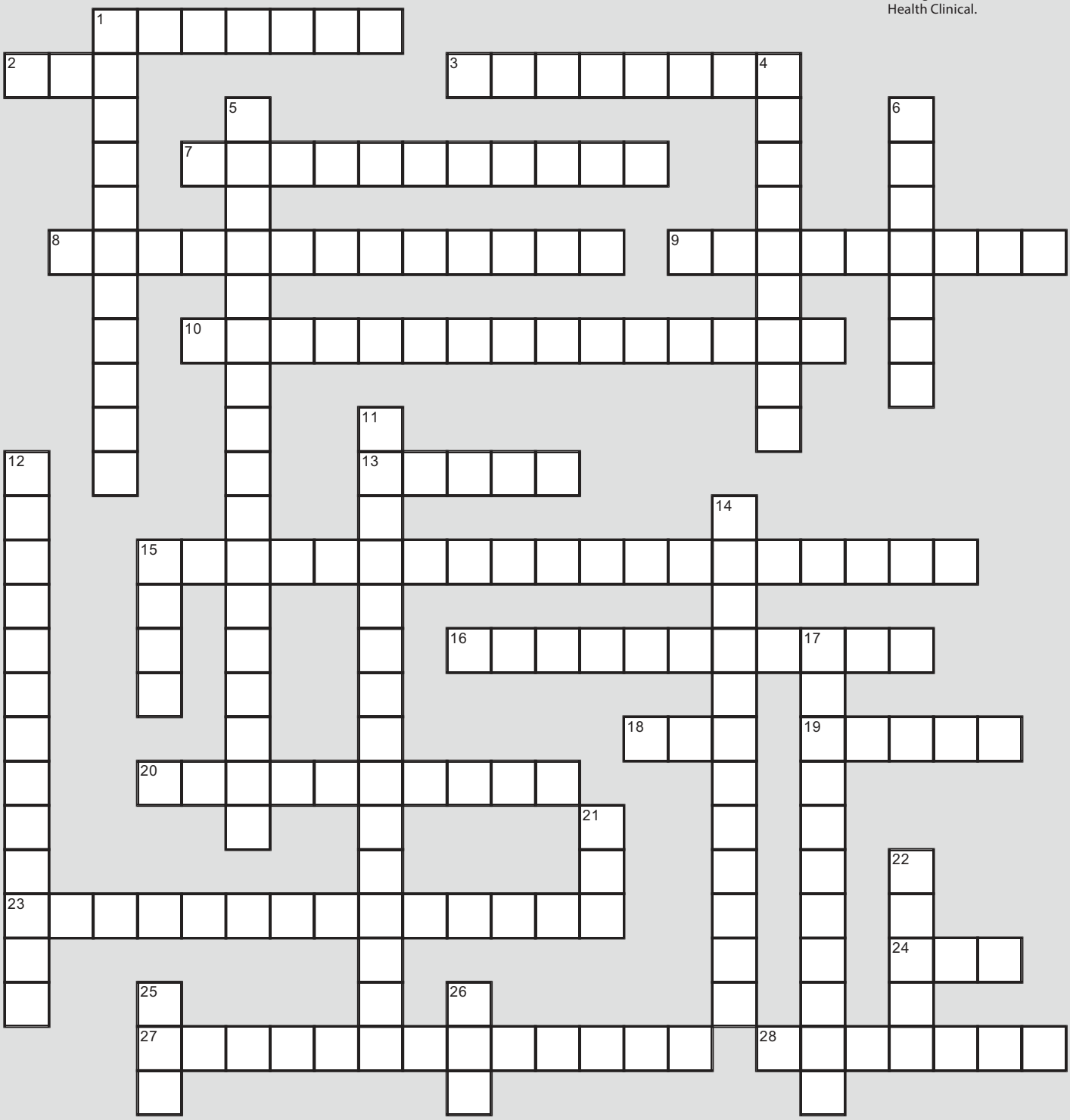
22 Health Insurance Portability and Accountability Act (abbreviation)

25 Affordable Care Act (abbreviation)

26 Good Clinical Practice (abbreviation)

Answers:
ACROSS: 1. Subject, 2. PRO, 3. Adaptive, 7. Data privacy, 8. Clinical trial, 9. Protocols, 10. Informed consent, 13. Treat, 15. Patient centeredness, 16. Recruitment, 18. EMR, 19. PCORI, 20. Data mining, 23. Interventional, 24. PHR, 27. Communication, 28. Engaged
DOWN: 1. Social media, 4. Endpoints, 5. Outcome, 6. Patient centricity, 11. Standardization, 12. Data integrity, 14. Best practice, 15. PROM, 17. Empowerment, 21. QOL, 22. HIPAA, 25. ACA, 26. GCP

Suzanne M. Heske, RPh, MS, CCRA, BCNP, (suzanne.heske@inventivhealth.com) is associate director for operational quality management with inVentiv Health Clinical.



HOME STUDY TEST

Earn 3.0 Continuing Education Credits

This test expires on April 30, 2016

(original release date: 04/01/2015)

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

A**nswers must be submitted using the electronic answer form online (members only, $42).** Those who answer 80% of the questions correctly will receive an electronic statement of credit by e-mail within 24 hours. Those who do not pass can retake the test for no additional fee.

ACRP DISCLOSURE STATEMENT

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

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

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

CONTINUING EDUCATION INFORMATION

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

Contact Hours

The Association of Clinical Research Professionals (ACRP) provides 3.0 contact hours for the completion of this educational activity. These contact hours can be used to meet the certifications maintenance requirement. (ACRP-2015-HMS-004)

Continuing Nursing Education

The California Board of Registered Nursing (Provider Number 11147) approves the Association of Clinical Research Professionals (ACRP) as a provider of continuing nursing education. This activity provides 3.0 nursing education credits. (Program Number 11147-2015-HMS-004)

Continuing Medical Education

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

A Culture of Patient Centricity: *Using a Model of Co-Creation to Optimize Clinical Trials*

PEER REVIEWED | Abbe Steel

[DOI: 10.14524/CR-14-0052]

With nearly 60% of study sites falling short of recruitment goals[1] for clinical trials and patient dropout rates soaring, the need to rethink the trial design process is more urgent than ever. Fortunately, there has never been a better time for sponsors to partner with patients, who can play active roles in this effort.

Patients want to participate in clinical trials designed with their needs in mind, whereas study sponsors in the pharmaceutical industry want to deploy faster, more effective, and less expensive studies.

Patients want to participate in clinical trials designed with their needs in mind, whereas study sponsors in the pharmaceutical industry want to deploy faster, more effective, and less expensive studies. Patient feedback is a promising extension to traditional clinical trials, and with increasing pressure on sponsors to rapidly deploy and complete cost-effective clinical studies, sponsors are looking for new patient-centered business models.

With so many ways to interpret the concept of patient centricity, it's not always clear what a "patient-centric" company should really do. Spend money on patient initiatives? Establish patient engagement as a core focus through social media and mobile technologies? Try to engage patients early in the research process, to align protocols to patients' lives while focusing on meaningful outcomes and fulfilling unmet needs?

All of these strategies are necessary, but perhaps, for a company to fully embrace patient centricity as a core organizational component, the patient must be considered in every major decision—across all therapeutic areas, all departments, all geographies, and all phases of the product life cycle—from Phase I through patent cliff. The changes needed are operational, strategic, and even cultural.

Although such changes can seem daunting, and represent a radical departure from today's more traditional, provider-focused business model, practical steps can be taken to get ahead of the curve and make tangible progress toward fully aligning the business around the patient.

Open the Feedback Loop

Simple feedback mechanisms are the first step in gaining a better understanding of the patients' true feelings and perceptions regarding their illness and its management. Such insights are the building blocks for an effective patient engagement program that covers the entire span of the company/patient relationship.

The feedback loop can start well before drug launch. Patient insights can and should feed directly into protocol design; those insights can be leveraged to support many operational aspects of the trial and shape the clinical endpoints for the study. Thus, sponsors will better understand patient perceptions and treatment preferences related to their illness, its treatments, and its management.

Study designers rarely consider the patient experience as a part of protocol development. Patients have historically been kept at arm's length, due to both privacy concerns and the long-held view among many researchers that patients, lacking the required deep understanding of the clinical

and regulatory space, would not understand either the process or the complexity of designing and running a study.

Instead, the focus is primarily on efficacy, safety, and tolerability of the drug, using quantitative analytical and statistical approaches as part of a structured scientific methodology that includes regulatory, scientific, and statistical considerations. Feedback is sought from a stakeholder group that might include the clinical and operations teams, a steering committee of key opinion leaders, or partners such as a contract research organization or technology provider. Rarely are patients included in that group, and yet the patient is the key customer for a clinical trial—the one who has to agree to a potentially demanding visit schedule, take an unapproved medication or possibly a placebo, keep diaries, and so on.

Often, the requirements of a study are considerably more demanding of time and attention than standard medical care, including increased office visits, extra blood tests and procedures, lengthy questionnaires, hospital stays, or complex dosages. Since the total median procedures per protocol increased from 105.9 from 2000–03 to 166.6 from 2008–11,[2] it's even more important to design trials that fit with patients' lifestyle and medical needs.

The questions sponsors should ask are: Why would a patient with insurance and other treatment options want to participate in the study? Further, how can studies make that question easier to answer, and encourage patients who have enrolled to stay in the study?

The answers are readily available, once sponsors recognize that the patient must be among the key stakeholders. By directly engaging with patients early, sponsors can gain a wealth of valuable information from their customers:

- What they like or dislike about trial requirements
- How the study would affect or disrupt their daily routines
- Which outcomes are most important to them

These are critical topics that can significantly affect recruitment and retention, but they're often overlooked because, too often, the protocol development is driven only by the science at the expense of the patient.

Opening an active communication channel with patients can also give sponsors valuable insights about matters that aren't specific to the clinical trial itself. Sponsors can learn about the barriers and the drivers for using certain therapies, or the factors that influence medication switching. These kinds of topics speak to the overall patient experience; the more sponsors understand about that experience and allow it to drive even a single study requirement as part of the overall design, the closer "the patient" moves toward the center of the business model.

Get By with a Little Help

Patient advisory boards are invaluable in aiding this shift, although the considerations in setting up a proper board can seem overwhelming. These considerations include:

- identifying the size and geographic makeup of the board
- obtaining the required permissions
- defining substantive breakout sessions
- deciding on an opt-in patient database, a pharmacy network, or patient advocacy group
- determining the optimal level of interactivity and the proper use of patient guides, recruitment materials, and more

Fortunately, some organizations specialize in providing exactly these kinds of services, so there's no need for an organization to start from scratch to open channels of patient communication.

Encouraging and maintaining these communication channels fosters trust within the sponsor/patient community. That trust, and sponsors' genuine receptivity to feedback, engender enthusiasm among patients, which can lead to more effective recruitment and more cost-effective, efficacious clinical trials.

Further, it doesn't have to be an "all or nothing" situation. In one trial simulation exercise for a complex, pivotal Phase III clinical trial, researchers discovered that the study drug packaging was confusing to patients in ways that might cause missed doses or medication errors. Because of the patients' feedback, the sponsor modified the printed instructions on the package and provided a separate drug instruction card.

In another study, originally designed with 16 planned visits, patient feedback caused the sponsor to make a portion of the visits home-based, reducing patient burden and having an added advantage of lower site costs.

These examples show that small shifts toward patient-centered designs can go a long way in the improvement of clinical trials.

LEARNING OBJECTIVE

After reading this article, participants should be able to:

- provide clinical development professionals with new, innovative approaches for obtaining patient feedback for protocol design.
- better understand actionable and measurable approaches for involving the patient in clinical development and providing examples of ways to create a culture of patient centricity.
- provide simple, effective tools to capture the patient voice related to lifestyle, health outcomes, and treatment options capturing those measures that matter most to patients.

DISCLOSURES

Abbe Steel: *CEO of HealthiVibe, LLC*

Engage the Right Partners

Patient advocates are often hyper-engaged in their advocacy activities: They have a substantial online presence for blogs and other forums; they may belong to one or more official advocacy groups; and they typically have a significant following. With such factors in mind, sponsors can kick-start their shift toward a patient-centric and patient-friendly model by directly engaging the patient advocates from the start of the drug development process.

Not only will advocates bring much-needed insight into the target patient demographics' specific needs and concerns, the information gleaned will help sponsors identify the most critical factors influencing treatment choices and risk-benefit decisions. These are the building blocks for an effective patient engagement program that can be used throughout a company's relationship with a patient—from protocol design to product launch and beyond. Among the key impacts of obtaining such information are:

- Helping to support the design of clinical trials, so they are operationally in line with patient needs and address those factors that will make it easier for patients to participate.
- Capturing insights around endpoint development and unmet patient needs to provide better alignment with the product label, significantly affecting the drug's commercial viability.

However, capturing feedback from a larger sample of patients through qualitative and quantifiable methods is also important. A patient with hypertension or diabetes is not necessarily engaging in an online community, participating on advisory boards, or speaking out on behalf of an advocacy group.

An organization running a global study with 6,000 diabetes patients in 10 countries, must get a good sense of the everyday person on the street in these countries—the mother taking her kids to school, the man shopping at the local grocer—to make sure the global protocol suits the patients' lifestyles and is specific to the country in which they live. This involves conducting advisory boards and gathering survey responses or other input from such people, and ensures that a more generalizable, representative population is included in the feedback loop.

One organization that has been at the center of involving patients in research is the Patient-Centered Outcomes Research Institute (PCORI), which funded projects in December 2012 hoping to address the questions and concerns most relevant to patients. By encouraging patients and other stakeholders to become integral members of the research process, and by providing a platform to support this effort, PCORI is working to bring the patient perspective and experience into all aspects of the process. This includes not only helping to determine which research topics and outcomes should be studied, but also helping to develop and conduct the studies and sharing the results.[3]

> It's vitally important for any sponsor company to show, above all else, that it is listening and responding to patients; one-off interactions with patients aren't the answer.

The U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development initiative aims to more systematically gather patients' perspectives on their conditions and on available therapies. As part of this commitment, the FDA is holding at least 20 public meetings during the current fifth iteration of the Prescription Drug User Fee Act, each focused on a specific disease area. "Voice of the Patient" reports will summarize the input provided by patients and patient representatives at each of these public meetings.[4]

The FDA has also been soliciting feedback and suggestions from the pharmaceutical and medical device industry on how to increase patient participation in current and future regulatory discussions. With an increased focus on patient-centered designs by both government and nongovernment agencies, there has never been a better time for clinical trial sponsors to take an active role.

Leverage Technology

New technologies can also play a major role in building a trial around the patient's needs, rather than forcing the patient to make adjustments for the sake of the trial.

As of 2013, 95 million Americans were using mobile phones as health tools or to find health-related information—a 27% jump from 2012[5]—and the mobile health application market is booming, with tens of thousands of apps targeting various customer segments and issues such as disease states, nutrition, fitness, and weight management. That number will grow, spurred by new technologies, an aging population, and increased demand for personalized care. The global health market is projected to reach $23 billion by 2017,[6] with monitoring, diagnosis, and treatment-related programs expected to comprise more than half the market.

The emergence and popularity of patient-centric digital programs provides a great opportunity for pharmaceutical manufacturers to engage patients through a direct and customized relationship. Integrating mobile device use into the trial process can improve data accuracy and accelerate the transfer of patient data.

Wireless health devices (e.g., glucose monitors and vital sign recorders) relay information directly to the clinical monitors, possibly eliminating the need for some study-mandated visits. Depending on the protocol, portable hand-held devices that transmit data wirelessly could be considered. Using a wireless scale for a congestive heart failure study can enable the study site staff to monitor a patient's weight in real time, with all other electronic data capture device data being collected in the study. This real-time integration enables on-time analysis and decision making regarding any patient-obtained measurement throughout the trial.

The more sponsors explore and exploit innovative technologies, the more possibilities will open up to clinical trial designers. Not every technology will work with every study or every patient, but engaging patients and asking them about their comfort level with and preference for these technologies should be part of the technology selection process.

There are many opportunities to let patients pilot devices and provide feedback through one-on-one interviews, surveys, and in-the-field/real-time observations. Taking such steps demonstrates an increased recognition of the patient's role at the center of the model, and helps to instill patient centricity in the corporate culture.

Shift the Culture

A company's culture is an intangible thing—hard to define and even harder to change. The operational and strategic steps described above play roles in reinforcing patient centricity in such a way as to create a positive feedback loop of change. However, there are other, more specific ways a company can signify—to its employees, its stakeholders, and its clients—that such cultural shifts are guided by an overarching philosophy and commitment to the patient.

One powerful way to emphasize the company's directional shift is create an executive-level role dedicated to the patient experience. Other approaches include:

- removing silos within the company to share patient information and capture all aspects of the patient journey;
- creating an organizational structure that embeds patient centricity in every business decision;
- tying financials to patient outcomes rather than just product sales;
- ensuring transparency of drug information and clinical trial results; and
- developing compliance, legal, and privacy policies that encourage patient interaction and two-way information sharing.

It's vitally important for any sponsor company to show, above all else, that it is listening and responding to patients; one-off interactions with patients aren't the answer. Programs must facilitate an ongoing relationship with the patient and capture and analyze insights in a substantive and systemic way.

Mechanisms must demonstrate the company's understanding of how valuable the patient's input really is, and the impact it makes within and outside clinical trials. Patients and advocates want to know that their ideas matter and have a real influence on sponsors.

With any new approach, especially one that can be emotionally charged and represents so many constituencies, there will be hurdles. Foremost, for either clinical viability or regulatory reasons, the sponsor may not be able to address the patient concerns in the most direct fashion. Patients might complain about a study visit that lasts six hours. Although the length of the visit might not be open to change, the sponsor might consider providing entertainment (such as reading materials and DVDs), more comfortable seating, and snacks to alleviate some of the burden.

Sponsors and study site staff can certainly think of many new and creative ways to work with patients, but speaking first-person with them captures true insights related to the diagnosis and management of their illnesses and their overall expectations as they look to participate in sponsored studies. Establishing a patient-driven culture that dives deep into the patient experience will change the pharmaceutical landscape and create a win-win experience for everyone involved.

References

1. Lo C. The numbers game: boosting clinical trial enrolment. www.pharmaceutical-technology.com/features/featurethe-numbers-game-boosting-clinical-trial-enrolment-4171654/
2. https://www.medpace.com/PDF/Subject%20Recruitment.MMetzner%20and%20CPierce.pdf
3. Patient-Centered Outcomes Research Institute. PCORnet: The national patient-centered clinical research network. www.pcori.org/content/pcornet-national-patient-centered-clinical-research-network
4. U.S. Food and Drug Administration. The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative. www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm
5. Comstock J. 95M Americans used mobile for health in 2013. *MobiHealthNews* October 29, 2013. http://mobihealthnews.com/26821/95m-americans-used-mobile-for-health-in-2013/
6. Advisory Board Company. What will the global health market look like in 2017? *iHealthBeat.* California HealthCare Foundation, March 25, 2014. www.ihealthbeat.org/picture-of-health/2014/what-will-the-global-mhealth-market-look-like-in-2017

Abbe Steel (abbe.steel@healthivibe.com) is the founder and chief executive officer of HealthiVibe, LLC.

How *Engaging Patients* Will Change Clinical Trials for the Better

PEER REVIEWED
Paul Wicks, PhD
Jeremy Gilbert, MBA
Charles E. Barr, MD, MPH
[DOI: 10.14524/CR-14-0050]

The design, conduct, and successful execution of a clinical trial depend on the input of a multidisciplinary team of scientists, clinicians, contract research organizations (CROs), regulators, and pharmaceutical executives. However, the one group on whom the entire endeavor relies is often missing from the table: patients. The vigorous discussions about treatment priorities, meaningful outcome measures, and risk/benefit tradeoffs rarely include the voice of the patient.

In an ideal world, clinical trial study team members would simply have a red telephone on their desks. Anytime anyone wanted to know what patients think, he or she could pick up the phone and ask, and instantly receive an actionable and reliable answer. In reality, the scenario is more complicated. There needs to be a system connecting to the outside world—a network over which to gather the signal. Further, someone must build the system and maintain it to ensure it works, and the study teams must know how to use the system, that it won't cost them too much, and how to ask the right questions at the right time in the right way.

This article discusses how patients are actively seeking to be involved in trial design, in terms of the levels of engagement as they stand, the potential barriers to patient input, and ways to overcome them. Also shared is a case study detailing how patients were recently and successfully engaged in trial design.

Let Patients Help

Traditionally, the role of patients in research has been passive—as subjects to be studied or as participants to be recruited through a process of informed consent. More recently, today's informed, engaged, and empowered patients are taking an active role in helping to identify and prioritize initiatives for research funding,[1] advising the U.S. Food and Drug Administration (FDA) on the greatest challenges they face in living with disease,[2] acting as peer reviewers of scientific articles,[3] or even conducting their own "citizen science" trials,[4] all while taking an increasingly central role in self-management of their conditions.[5]

When researchers and trial designers invite patients to act as research partners, both parties benefit. For instance, in a trial for women with breast cancer, patient advocates were invited to sit on scientific advisory committees, help design recruitment materials, provide feedback on protocols,[6] and even act as coauthors on scientific manuscripts.[7]

Similarly, the Outcome Measures in Rheumatology (OMERACT) group in rheumatoid arthritis invited increasing numbers of patients to its regular international conferences. Blind spots were illuminated, new research topics were explored, and increasing respect for patients developed throughout the partnership.[8]

These two examples are somewhat unique, being broad-based, long-term collaborations among multiple stakeholders with ambitious goals such as learning how to measure disease and treatment outcomes more effectively or advancing new clinical trial approaches.

In an ideal world, clinical trial study team members would simply have a red telephone on their desks. Anytime anyone wanted to know what patients think, he or she could pick up the phone and ask, and instantly receive an actionable and reliable answer.

HS

LEARNING OBJECTIVE

After reading this article, participants should be able to explain the rationale and barriers for patient involvement in the design of clinical trials, and describe approaches for patient engagement to optimize protocol design, recruitment, and retention.

DISCLOSURES

Paul Wicks, PhD: *Employee of PatientsLikeMe.*
Jeremy Gilbert, MBA: *Employee of PatientsLikeMe and hold stock options in the company.*
Charles E. Barr, MD, MPH: *Employee of Genentech.*

Traditionally, the role of patients in research has been passive—as subjects to be studied or as participants to be recruited through a process of informed consent.

By contrast, patient involvement in individual clinical trial design has traditionally been limited or lacking, with patient outreach considered a priority only when a trial is in "rescue mode" because it failed to reach its recruitment targets.

Studies that are not tailored to the study population's needs and interests could face challenges such as slow recruitment or costly protocol amendments,[9] even when study teams have prior experience with the condition. Given the high cost of protocol amendments and other rescue activities, seeking input from potential participants seems logical to find obstacles in advance, particularly when trials are becoming ever more burdensome with increasing numbers of procedures per protocol.[9]

Despite this, in a recent poll of 67 senior clinical trial executives conducted at the 2014 Avoca Group Quality Consortium Summit (including pharmaceutical sponsors and CROs involved in quality management), just 7% of respondents reported that they drew upon quantified patient research as a source of data and insights to optimize clinical trial design, and just 1% said they interviewed patients directly (see Table 1).

TABLE 1: Answers to "What sources of data and insights do you currently use to design your clinical trials to maximize their chance of success"

Responders	Percentage (%)
Key opinion leader (physician) interviews	21
Physician/site interviews	18
Internal knowledge	18
Literature review	15
Other experts	14
Quantitative patient research	7
Electronic medical record (EMR) data	3
Claims data	3
Patient interviews	1

Poll from the 2014 Avoca Quality Consortium Annual Meeting [n = 67 clinical trial executives]

Although the rallying cry of the engaged patient movement has been "nothing about me without me," 21% of those polled said they interviewed "key opinion leaders" who were supposed to accurately convey patients' views on their behalf. That's akin to designing a smartphone exclusively with insights from the target customer's parents.

However, from the perspective of the pharmaceutical industry (or even academia), such conservatism often makes pragmatic sense, since there may be real regulatory and scientific constraints limiting the flexibility in study design. Further, in the past, finding patients with the expertise to understand complex scientific issues and the willingness to invest the time has been difficult.

The Internet and other technologies have changed everything regarding information availability and ease of participation in research formulation. Patients with chronic or severe diseases can become very knowledgeable about their disease and the effects of treatments, and they want to be consulted.

In a survey of more than 1,600 members with chronic conditions who share their health data online and engage in peer support on the patient-powered research network PatientsLikeMe, 93% said they would welcome the opportunity to help researchers improve the design of their trials,[10] and would volunteer their time to answer researchers' questions. Survey participants also signaled a change in their motivations for participating from the traditional assumption that they volunteer out of altruism (see Table 2). In fact, although 74% of patients reported that helping to improve the health of others was an important factor when deciding whether to consider enrolling, this was less important than other factors such as an opportunity to improve their own health (84%), having their medical expenses covered if an injury occurred resulting from the trial (84%), or the reputation of the researchers involved (76%).

Another highly important factor was receiving the results of the trial after the study had ended (73%). This is an area where trials have failed to deliver the feedback that patients so clearly desire.[11] Thus, to maximize our chances of shared success, we must listen to patients about their specific concerns.

TABLE 2: Proportion of Patient Respondents Reporting a Trial Factor was "Very Important" in Deciding Whether to Participate in a Trial

Responses	Percentage (%)
Opportunity to improve own health	84
Medical bills covered if injured	84
Reputation of researchers	76
Improve health of others	74
Getting results after trial ended	73
Potential negative impact on health	72
Side effects of new treatment	63
Option to stay on treatment after trial	56
Distance traveled to trial visits	56
Keeping my doctor during trial	52
My doctor's recommendation	50
Privacy and confidentiality	50
The friendliness of staff	47
Number of visits and time to participate	46
Possibility of placebo	37
Being paid to participate	16

(n = 1,621). Adapted from Okun et al.[10]

Overcoming Barriers

When the Avoca Group Summit poll respondents were queried on the main reasons why patients were not more involved in helping to design clinical trials, 43% cited a lack of expertise; 36% noted regulatory barriers such as concerns over privacy or adverse event (AE) reporting; and 21% questioned what value patients could provide. These are eminently addressable concerns.

FIRST, within a pharmaceutical company, expertise in engaging with patient groups may reside in the commercial part of the organization (often "fire-walled" off from the clinical research teams). There, patient advocacy colleagues build relationships with patient-centered nonprofits for disease awareness, education, and research collaborations. However, their methods involve individual or small group relationships, ethnography, or market research surveys. Even with their skills in accessing patient networks, such methods do not always have sufficient credibility with the scientific parts of the organization, or fit within the decision framework of a study team.

To overcome the barriers to expertise, patient-informed clinical trial design programs must be accessible to the clinical and scientific research teams. They must leverage internal and external advocacy experience where available, and use scientifically robust methods alongside adequate sample sizes and statistical methods (accounting and controlling for bias). Ultimately, the scientists who design the studies remain responsible for how or when to use the insights generated.

SECOND, the pharmaceutical industry is a highly regulated space, with an array of international, national, and state laws, guidelines, and corporate integrity agreements dictating what company employees and contracted representatives can and cannot do, particularly in terms of relationships with physicians. However, there is less guidance on how to interact with patients, given that such interactions are normally outside the purview of most employees.

Where patient interactions do occur, such as in social settings or at conferences, employees are reminded of the obligations to report possible adverse event (AE) information to their drug safety department for follow-up and documentation, even if the information is only casually mentioned in social situations. The notion of asking hundreds of patients for their views on clinical trials raises the need to have defined procedures for capturing and reporting potential AEs in a compliant and timely manner (within 48 hours for serious AEs).

Although the likelihood of receiving AE data about a marketed product is low when conducting research about trial design with patients, any time a real-world discussion occurs or an open text box is used in a survey (which can generate crucial qualitative insights), patients might mention offhand, for instance, that their interest in a trial was triggered by discontinuing another drug due to a serious side effect that ended in their hospitalization. If the study sponsor marketed this product, there may be a need to report such details promptly.

Given the high cost of protocol amendments and other rescue activities, seeking input from potential participants seems logical to find obstacles in advance, particularly when trials are becoming ever more burdensome in increasing numbers of procedures per protocol.

The usual solution is to contract for the services of a CRO or other outsourced research agency to capture and process all patient-reported information. Such organizations frequently have access to patient networks, have their own scientists trained in survey methodology, and are familiar with the process of clinical trial development.

The exact approach taken will differ according to the regulatory jurisdiction and the company's policy, but sometimes the fear of engaging with this level of regulatory complexity is a barrier to those wanting to learn more from patients directly. Ultimately, researchers must balance the ability to collect useful data that patients want to share, the relevance of the data to inform optimal study design, and the costs and efforts incurred.

THIRD, feedback systems must exist throughout the process—before, during, and after study conduct—to fully gauge the costs and benefits of a patient input program. A one-time engagement is rarely sufficient to yield an enormous step-change in strategy; protocol development and optimization comprise an ongoing and iterative process.

Thus, the greatest potential leverage can be achieved by beginning patient involvement early in the process:

- Confirming there really is an unmet need spontaneously reported by patients,
- Using decision-tradeoff methodologies to see where a new therapeutic option might fit,
- Eliciting patient experience with clinical trials (including pros and cons),
- Defining burdensome aspects of a protocol,
- Refining content of the recruitment materials, and
- Providing insights on what it was like to enroll in the study once it has started.

The performance indicators or benefits of a patient-informed trial program are the speed in addressing questions in a timely manner (using decision committees and advisory boards to guide planning); the credibility of the patient sample drawn upon in terms of its representativeness, generalizability, and similarity to the potential trial sample of interest; the applicability of insights to decisions that can be made within other constraints such as scientific or regulatory standards; and cost.

Case Study:
Patient-Informed Clinical Trial Design

Clinical trials often involve careful measurement with repeated imaging studies, possible invasive procedures, and close monitoring for AEs with long follow-up times to ensure tolerability and safety. Randomized studies are the gold standard in scientific studies for regulatory drug approval; however, the demands of many trials on patients are frequent visits to the clinic, time undergoing diagnostic tests, recurrent needlesticks, invasive procedures, and the risk that experimental treatments may not work as well as hoped for or may result in unknown and possibly serious side effects.

During the development of a Phase II study, the members of a Genentech clinical trial study team became interested in the potential of incorporating patient feedback into their study design. One question of interest was whether an invasive test would be a major barrier to recruitment.

To gauge patient reaction to this and several other aspects of study design, meetings were held with different members of the study team to elicit all of their possible concerns. Scientists with a background in patient-centered research developed these into research questions and survey items to be answered by patients.

Using the Trial Access service on the patient-powered research network PatientsLikeMe, a survey was sent to 2,045 patients who matched the inclusion/exclusion criteria of the study. Of the 697 invitations read within one week, patients provided 387 complete responses (56%). Questions were included on demographics, previous trial experience, and a mixture of quantitative and qualitative reactions to different aspects of the trial protocol.

Overall, 29% of respondents reported that requiring the procedure would "strongly decrease" their interest in participating in the trial—a rate lower than the trial designers had anticipated. Unexpectedly, a much stronger reaction came from patients who had never had this procedure before: Nearly half (47%) said the test would strongly decrease their interest in participating. Thus, fear of the unknown, rather than bad memories, was the greater threat to successful recruitment.

This finding allowed the team to consider optimal ways to train study investigators to write more relevant recruitment materials to better inform patients. Each patient who expressed concern was also given an open text box to explain his or her answer in more detail, and to provide suggestions for how the study designers might address the concerns.

In this example and others, PatientsLikeMe has seen that the counterintuitive findings and the illumination of blind spots are the most useful contributions patients make. Such patient insights enable study teams to proactively address shortfalls in recruitment with foresight of what many of the potential issues might be, rather than having to deduce them after recruitment becomes a challenge.

Also of interest are speed of recruitment, patient retention, and compliance with protocol. There are tensions here, too; for instance, a large and reliable sample of respondents is more expensive to gather and query than a smaller and less reliable one. There are divergent opinions and priorities within study teams: Some team members may be focused more on near-term operational success (the study enrolls and retains well); others may have their eye on ultimate measures of success such as regulatory approval or payer approval further down the road. Sharing and discussing the program frequently with many internal stakeholders will help to ensure their views are included and they feel invested.

Future Steps

We envision a future where fast, reliable, actionable insights can be obtained from patients so easily that they are involved in nearly every key trial decision that affects them. When performed in a thoughtful and compliant manner with the right toolkit, this might lead to better recruitment and retention, faster trial execution, lower patient burden, greater alignment to unmet need, and higher likelihood of approval, market access, and reimbursement.

Once we systematically remove the barriers to listening to patients and produce evidence of welcome results from taking the steps presented below, we will listen as intently to patients as we do to scientists, clinicians, or statisticians when designing our clinical trials:

- Audit current levels of patient engagement in trial design and operations
- Identify barriers and challenges to incorporating patient input and work with stakeholders and experienced vendors to overcome them
- Develop methods to involve patients in every key trial decision that affects them, as early as possible
- Evaluate the impact of patient input on recruitment speed, retention, and product success
- Disseminate results and best practices

Disclosures
The PatientsLikeMe Research Team has received research funding (including conference support and consulting fees) from AbbVie, Accorda, Actelion, Amgen, AstraZeneca, Avanir, Biogen, Boehringer Ingelheim, Genzyme, Janssen, Johnson & Johnson, Merck, Novartis, Sanofi, and UCB. The PatientsLikeMe R&D team has received research grant funding from Kaiser Permanente, the Robert Wood Johnson Foundation, Sage Bionetworks, The AKU Society, and the University of Maryland.

Ultimately, researchers must balance the ability to collect useful data that patients want to share, the relevance of the data to inform optimal study design, and the costs and efforts incurred.

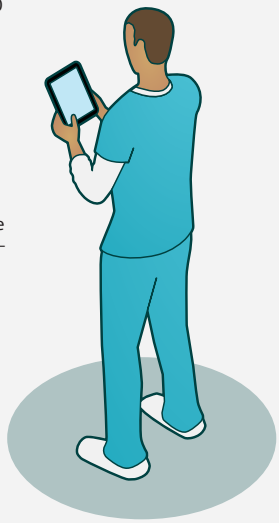
References

1. Fleurence R, Selby JV, Odom-Walker K, Hunt G, Meltzer D, Slutsky JR, et al. How the Patient-Centered Outcomes Research Institute is engaging patients and others in shaping its research agenda. Project HOPE—The People-to-People Health Foundation, Inc. *Health Aff* (Millwood). 2013;32(2):393–400.
2. Mullard A. Patient-focused drug development programme takes first steps. *Nature Rev Drug Disc* 2013(Sep):651–2.
3. Godlee F. Towards the patient revolution. *BMJ* 2014;348(jan29 1):g1209–9.
4. Wicks P, Vaughan T, Heywood J. Subjects no more: what happens when trial participants realize they hold the power? *BMJ* 2014;348:g368.
5. Center for Advancing Health. A New Definition of Patient Engagement: What is Engagement and Why is it Important? Washington, D.C.: 2010.
6. Perlmutter J. Advocate Involvement in I-SPY 2. *Breast Diseases: A Year Book Quarterly* 2011;22(1):21–4.
7. Perlmutter J, Axler S, Baas C, Beckwith BJ, Bonoff A, Brain S, et al. Advocates' perspective: neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 2012;30(36):4586–8, author reply 4588–9.
8. de Wit MPT, Koelewijn-van Loon MS, Collins S, Abma TA, Kirwan J. "If I wasn't this robust": patients' expectations and experiences at the Outcome Measures in Rheumatology Conference 2010. *Patient* 2013;6(3):179–87.
9. Getz KA, Wenger J, Campo RA, Seguine ES, Kaitin KI. Assessing the impact of protocol design changes on clinical trial performance. *Am J Ther* 2008;15(5):450–7.
10. Okun S, Wicks P, Scott M, Gilbert J. Patient-Informed Clinical Trials: Cross-Sectional Survey on a Patient-Powered Research Network. Presented at Drug Information Association, 2014, p. T44.
11. Cox K, Moghaddam N, Bird L, Elkan R. Feedback of trial results to participants: a survey of clinicians and "patients" attitudes and experiences. *Eur J Oncol Nurs* 2011;15(2):124–9.

Paul Wicks, PhD, (pwicks@patientslikeme.com) is vice president of innovation at PatientsLikeMe.

Jeremy Gilbert, MBA, (jgilbert@patientslikeme.com) is vice president of commercial products and strategy at PatientsLikeMe.

Charles E. Barr, MD, MPH, (barr.charles@gene.com) is head of evidence science and innovation and group medical director for U.S. Medical Affairs at Genentech, Inc.



OPINION

PROFIT and the Patient Experience: *Is There Room for Both?*

PEER REVIEWED | Jay Yockelson, MS, CCRA

[DOI: 10.14524/CR-14-0051]

Clinical research is a patient-focused industry. The primary goal behind conducting clinical trials is to identify new, safe, and effective treatments to improve the lives and health of people. However, in the wake of continually decreasing study budgets, investigators are challenged to constantly improve the patient research experience while maintaining profitability.

To achieve both a good patient experience and profitability, targeted planning is critical. This article identifies three key areas—processes, financial matters, and relationship management—where investigators can improve the patient experience in a study while positively affecting the bottom line.

Processes

One of the most effective strategies in creating a patient-focused, yet profitable, research environment is the use of efficient processes. Although regulations do not require official standard operating procedures at research sites, standardized processes are preferred because they streamline practices and avoid wasting staff time.

The processes likely to have the most influence on increasing both the quality of the patient experience and the profitability of the site are those related to time management, specifically time management of study coordinators and investigators. Effective time

LEARNING OBJECTIVE
After reading this article, participants should be able to recognize specific areas to address in order to focus on patient-centered research and remain a profitable research site.

DISCLOSURES
Jay Yockelson, MS, CCRA: *Nothing to Disclose*

management does not mean that less time should be used to perform duties, but that the time spent should be maximized in all respects.

Study Selection

Processes surrounding study selection probably play the most critical role in an investigator's financial success. Comprehensive site selection criteria are important to study success for a sponsor,[1] just as study selection criteria are vitally important to the success of a research site.

Proper study selection is a big predictor of whether research staff will deliver quality patient care. When determining whether to conduct a particular study, the investigator must select those that best fit his or her practice, considering myriad variables at the site level.

For example, study selection should not be based on those studies that are the highest paying, or worse, taken out of desperation to conduct a clinical trial; selecting the wrong study can affect both financial stability of the site and, more critically, patient care.

Further, selecting a study outside the investigator's core experience can increase the time it takes to identify qualified participants. For example, an endocrinologist conducting an irritable bowel syndrome study likely would have to implement an advertising campaign to attract appropriate patients. Instead, this same physician would get more patients and expend fewer resources by conducting a diabetes trial and identifying patients from his or her own database. In turn, patients receive the benefit of a focused and experienced physician providing treatment in his or her own specialty, which enhances the quality of care provided to the patient.

Although an investigator can conduct studies outside his or her core expertise, in doing so, the investigator should account for the extra time needed to keep abreast of the latest information in the indication and to identify qualified patients. Such extra time may prove to make what would otherwise be a profitable study very unprofitable for certain sites. Moreover, studies that allow the site staff to become experts in an indication or type of study can also increase revenue and the patient experience.

Also, allowing a study coordinator to focus on one high-enrolling trial prevents the coordinator from hopping between trials and potentially making costly errors. Therefore, assigning a study coordinator to a manageable number of trials so he or she becomes the internal expert on the study is far more effective.

Proper study selection does not reduce the amount of work for the study coordinator; instead, it allows the coordinator to focus and creates efficiency through familiarity with the trial. The direct result is that, when coordinators are experts on studies, visits generally operate more smoothly for patients, and the time saved can be used by coordinators to enroll more patients, establish relationships with current patients in the study, and otherwise enhance the patient experience.

STUDY VISIT PREPARATION AND CHECKLISTS

Study visit preparation also can affect patient focus and research revenue in a very direct way. Inadequate preparation results in time during the visit being spent on making up for lack of preparedness (i.e., searching for documents or information), which reduces the time that a study coordinator or investigator must conduct a patient visit and complete other tasks associated with a visit. Notwithstanding this fact, and perhaps more dangerously, improper preparation can cause mistakes to be made during the study visit, which increases the time spent documenting and correcting such mistakes, if they can be corrected. In short, it's costly for the site and patient to be unprepared.

One of the simplest and most beneficial strategies for improving process efficiency is the use of a study visit checklist that includes all the items needed before each study visit, and all items to be completed during and after the visit. For example, a pre-visit checklist requires confirmation of how much study medication is expected to be returned, and verifies that previous test assessments were reviewed and procedures were appropriately scheduled during the visit. Checklists also greatly assist backup study coordinators, who may handle duties in the absence of a primary study coordinator, which greatly reduces the chances for making errors and compromising patient safety.

In the wake of continually decreasing study budgets, investigators are challenged to constantly improve the patient research experience while maintaining profitability.

The processes likely to have the most influence on increasing both the quality of the patient experience and the profitability of the site are those related to time management, specifically time management of study coordinators and investigators.

Financial Matters

One of the challenges in planning study budgets is the varying costs incurred by a site during a trial. Some costs are fixed and easy to determine, such as unit costs for physical examinations, whereas others remain variable and difficult to calculate. Here, proper evaluation of a study budget is important up front.

Although a site will negotiate an aggregate per patient payment for any study, that aggregate payment is of no use until a site understands its cost justification for receiving such payment.[2] Often sites understand big, fixed costs, but do not factor in small, additive costs, which, when taken in the aggregate, leave money on the table for sites and can result in less resources being available for patient care, and eventually less profit.

PATIENT REIMBURSEMENT

Although patient reimbursement and/or stipends for patients on a study are known and fixed costs, they are often overlooked as a separate line item expense for the site when negotiating a study budget. Patient stipends should pay patients for the time spent at the visit, and the travel time spent coming to/from a visit. However, more often than not, an initial study budget will not include a line item for patient reimbursement, expecting those funds to come directly from the visit amounts paid to sites.

If a budget includes no line item for patient reimbursements, the investigator should subtract patient reimbursement from the total budget to calculate the total per visit payment. For example, if a study is reimbursing a site $500 for each visit and the patient is being reimbursed $50 per visit, the investigator actually receives $450 as the visit payment by the sponsor. Extrapolating this concept over a study with 10 visits, the total amount not being considered by the site is now $500, so an investigator requiring a minimum of $500 per visit to break even is now losing $50 for each visit conducted.

Although the cost for patient reimbursements seems obvious, time and time again sites do not consider this cost when negotiating study budgets. The net effect is that the site must make a choice—lose money by providing stipends to patients, or see a decrease in enrollment due to no or low stipends provided. All of this results in less money available to the site for research, which affects resourcing and, presumably, the level of quality available to research patients.

MEDICAL RECORDS

Although obtaining necessary medical records on a patient is an ethical obligation for researchers, it is an often overlooked cost during the negotiation stage of a study budget. Investigators use medical records, among other tools, to determine patient eligibility, especially when the patient is not a regular visitor to the investigator's practice. Most often, there is a fee to obtain the records.

The costs to the site, however, include both the hard costs charged by the provider for the medical records themselves, and the time spent by staff obtaining the records. For example, medical records generally cost between $25 and $50 per patient to obtain, and it is not uncommon for the investigator's staff to have to request such records multiple times, using up additional staff time that could be spent on other matters.

Thus, a study with 20 patients would cost the investigator between $500 and $700 as a base cost, and then a variable cost for research staff to request such records and provide any necessary follow-up. For this reason, an investigator should track the costs and time spent on medical records so he or she can properly negotiate the next budget with more information.

Determining the costs of obtaining medical records directly ties into the patient experience, because an investigator can make better decisions on a patient's behalf when in possession of complete records; this equates to better patient care all the way around.

Relationship Management

The basic tenets of customer service governing other industries to make a profit apply equally to conducting clinical research. These concepts, when applied properly, can improve patient satisfaction with an investigator. In turn, patient satisfaction results in patients who are more compliant with study procedures and requirements, more open with medical history and information, and more willing to participate in future trials. All three items allow investigators and their staff to perform their jobs better, and each is fundamental to the long-term financial stability of a site.

Patients who are more satisfied with their physicians are more compliant,[3] which can include showing up for scheduled appointments,

Study selection should not be based on those studies that are the highest paying, or worse, taken out of desperation to conduct a clinical trial; selecting the wrong study can affect both financial stability of the site and, more critically, patient care.

administering study drugs appropriately, and completing studies in full. This results in fewer screen failures and more randomized patients, which makes a site more profitable.

Moreover, patients who are satisfied may be more likely to participate in future trials. This significantly reduces the site's operating costs for patient recruitment, which includes both the hard costs of marketing dollars and the soft costs of extensive staff and investigator time dedicated to recruitment.

The trick for many sites, then, is how to build patient satisfaction and loyalty to reap the rewards from such efforts. Many strategies can be used to develop a positive relationship with study patients, but of utmost importance are those emphasizing availability and providing a personal touch.

AVAILABILITY

Often, building patient satisfaction is as simple as having the right people available when patients need them. Patients develop trust in the investigative staff members when they can reach them; thus, patients always should be provided with an emergency number to contact a research staff member, and if used, the research staff should be available to react to the patients' needs as soon as possible.

Although patients can feel uncomfortable about contacting research staff members after business hours, the patients should be encouraged to use the number for emergency questions or other immediate study-related needs. Maintaining this open communication shows the patients that the site staff are dedicated to them, and in turn makes patients more likely to continue in the study.

Availability, however, has a second component, schedule availability. One of the challenges to enrollment is that many research sites operate only during normal business hours, but many patients in research studies work full time and cannot always attend multiple study visits during business hours. Therefore, an investigator would be wise to consider whether it would be beneficial to have flexible scheduling for research patients outside business hours (i.e., nights and weekends), which would allow patients to participate in research without having to sacrifice work hours to do so.

PERSONAL TOUCH

As trials continue to use a variety of new technologies, the investigative staff members should be sensitive that, in using such technologies, they do not take away the human experience or "personal touch" from the typical research visit. For example, many studies now use automated visit alerts that text or call patients to remind them of a scheduled study visit appointment. Although this may increase compliance for attending study visits, it should not replace human interactions or calls by the investigative staff when needed.

Moreover, patients often have to discuss uncomfortable medical conditions with study coordinators. Thus, the study coordinator or investigator must set the tone of a positive relationship early, so that a patient feels comfortable providing critical information needed by the investigator and/or staff to determine enrollment issues, adverse events, and other possible areas of concern.

Additionally, growing positive relationships with patients translates into more patients in studies completing the items needed, which turns into profits for sites. To this end, staff should strive to understand a patient's background, family, and other interesting personal facts; not only will it help with patient treatment, but marketing tenets tell us it is the easiest way to build brand loyalty, which builds repeat customers.

Conclusion

The success of every clinical research center hinges on the ability for the investigative site staff to evolve as the industry changes. Nowhere is this more apparent than in the areas of processes, finances, and relationship management. Done right, focusing on these three areas can improve patient care dramatically, while driving a very profitable business.

References

1. Warden D, Trivedi MH, Greer TL, Nunes E, Grannemann BD, Horigian VE, et al. Rationale and methods for site selection for a trial using a novel intervention to treat stimulant abuse. *Contemp Clin Trials* 2011;33(1):29-37.
2. Neuer A. Budget woes stall clinical trials and stymie sites. *Bio-IT World,* February 21, 2012 (accessed December 10, 2014): www.bio-itworld.com/2012/02/21/budget-woes-stall-clinical-trials-stymie-sites.html
3. Pawar M. Five tips for generating patient satisfaction and compliance. *Fam Prac Manage* 2005;12(6):44-6.

Jay Yockelson, MS, CCRA, (jay@clinicaltrialsnc.com) is president of Clinical Trials of North Carolina, LLC.

HOME STUDY HS

Patient Centricity

OPEN BOOK TEST

This test expires on April 30, 2016

(original release date: 04/01/2015)

A Culture of Patient Centricity: Using a Model of Co-Creation to Optimize Clinical Trials

1. What is a promising extension to traditional clinical trials?

A. Greater funding from insurers
B. Less geographic focus
C. Increased patient feedback
D. Less expensive studies

2. What are three ways to increase patient centricity discussed in this article?

1. Open the feedback loop
2. Engage the right partners
3. Provider-focused business models
4. Leverage technology

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. What will help sponsors better understand patient perceptions and treatment preferences related to their illness, its treatments, and its management?

A. Patient insights into protocol design
B. A structured scientific methodology
C. A provider-focused business model
D. Increase funding to insurers

4. Why is it important to design trials that fit with a patient's lifestyle and medical needs?

A. It can significantly improve recruitment and retention.
B. It can enhance the site experience.
C. It can help a contract research organization's bottom line.
D. It results in greater insurance coverage.

5. What is an example of how patient feedback resulted in an improved clinical trial?

A. Decreased prescription copays
B. Elimination of mobile technologies
C. Decreased patient engagement
D. Modification of a confusing package design

6. What is one of the ways patient advocates can help pharmaceutical companies support the design of clinical trials?

A. Aid in the development of large, multicenter global studies.
B. Identify factors that will make it easier for patients to participate
C. Disrupt a relationship between sponsors and the patient by getting too involved
D. Lower site costs for clinical trials so more investigators are inclined to participate

7. How is the Patient-Centered Outcomes Research Institute (PCORI) helping to bring the patient perspective and experience to all aspects of the research process?

A. By holding at least 20 public meetings during the current fifth iteration of the Prescription Drug User Fee Act
B. By soliciting feedback on how to increase participation in regulatory decisions
C. By encouraging patients and other stakeholders to become integral members of the research process
D. By soliciting feedback and suggestions from the pharmaceutical and medical device industry

8. How is technology helping pharmaceutical manufacturers engage patients?

A. By forcing the patient to make adjustments for the sake of the trial
B. By increasing the need for study-mandated visits
C. Through one-on-one interviews with patients
D. Through direct and customized patient-centric digital programs

9. How can sponsors reinforce their commitment to the patient?

1. Create executive-level role dedicated to the patient experience
2. Create an organizational structure that embeds patient centricity in every business decision
3. Add patients' photos to their marketing materials for a more personal touch
4. Tie financials to patient outcomes rather than just product sales

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

10. What is one of the new, creative ways to work with patients and alleviate some of the burden of clinical trials?

A. Provide entertainment at the site
B. Increase the number physician visits
C. Decrease patient interaction
D. Eliminate the use of mobile technology

How Engaging Patients Will Change Clinical Trials for the Better

11. Patient advocates in the I-SPY2 trial provided scientific input, helped design recruitment materials, provided feedback on protocols, and even coauthored manuscripts. What disease did they have?

A. Non-Hodgkin's lymphoma
B. Idiopathic pulmonary fibrosis
C. Breast cancer
D. Major depressive disorder

12. What was the purpose of the OMERACT consortium, where patients were invited to attend conferences?

A. Raising awareness of rheumatoid arthritis
B. Developing and validating outcome measures
C. Lobbying for special access programs for new therapies
D. Conducting "citizen science" experiments

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

13. **Traditionally, when is the time patient involvement has been considered a priority?**
- **A.** When the trial is conducted in multiple countries
- **B.** When a trial fails to reach its recruitment targets
- **C.** When the trial is for a medical device
- **D.** When a trial is conducted using remote monitoring

14. **In a poll of 67 senior clinical trial executives at the 2014 Avoca Group Quality Consortium, what proportion had interviewed patients directly to optimize trial design?**
- **A.** 1%
- **B.** 7%
- **C.** 10%
- **D.** 44%

15. **In a survey of more than 1,600 members with chronic conditions on PatientsLikeMe, what proportion of members said they would help researchers improve the design of their trials?**
- **A.** 75%
- **B.** 82%
- **C.** 93%
- **D.** 99%

16. **In a survey of more than 1,600 members with chronic conditions on PatientsLikeMe, which of these factors was the least important to patients when considering whether to take part in a trial?**
- **A.** Possibility of placebo
- **B.** Doctor's recommendation
- **C.** Option to stay on treatment after trial
- **D.** Opportunity to improve own health

17. **What regulated reporting requirement is often perceived as a barrier to engaging with patients?**
- **A.** Insider trading
- **B.** Adverse event reporting
- **C.** Intellectual property violation
- **D.** Privacy laws

18. **Within a pharmaceutical company, where might expertise in engaging with patient groups reside?**
- **A.** Regulatory compliance
- **B.** Human resources
- **C.** Preclinical development
- **D.** Patient advocacy

19. **In the case study, which group of patients had the strongest negative reaction to an invasive test procedure?**
- **A.** Patients with severe symptoms from their disease
- **B.** Patients who had undergone the procedure before
- **C.** Patients who had not undergone the procedure before
- **D.** Patients with lower levels of education

20. **In the future, which group of stakeholders do the authors believe will become more involved in trial decisions?**
- **A.** Statisticians
- **B.** Scientists
- **C.** Clinicians
- **D.** Patients

Profit and the Patient Experience: Is There Room for Both?

21. **What type of planning does the author believe is necessary to achieve both a good patient experience and profitability?**
- **A.** General
- **B.** Specific
- **C.** Targeted
- **D.** Detailed

22. **The processes that are likely to have the most impact on increasing both the patient experience and profitability are related to which of the following?**
- **A.** Process management
- **B.** Financial management
- **C.** Time management
- **D.** Relationship management

23. **What type of criteria is vitally important to the success of a research site?**
- **A.** Comprehensiveness
- **B.** Financial
- **C.** Sponsor
- **D.** Study selection

24. **What criteria should the investigator use to select studies?**
- **A.** Studies that pay the most
- **B.** No criteria are required for most studies
- **C.** As many as the site staff can manage
- **D.** Criteria that best fit his or her practice

25. **Improper preparation can result in which of the following?**
- **A.** Increase time spent documenting and correcting mistakes
- **B.** Increase time spent creating new processes
- **C.** Decrease time spent with patients and caregivers
- **D.** Decrease times spent developing efficient processes

26. **What is one of the challenges in planning study budgets?**
- **A.** Fixed costs
- **B.** Varying costs
- **C.** Hidden costs
- **D.** Evaluation of costs

27. **In the author's example, a study with 20 patients will cost the investigator $500 to $700 for which of the following?**
- **A.** Patient stipends
- **B.** Medical records
- **C.** Staff salaries
- **D.** Establishing procedures

28. **The investigator can make better decisions on a patient's behalf when he or she has which of the following?**
- **A.** A fair budget
- **B.** Documented processes
- **C.** Timely patient reimbursement
- **D.** Complete records

29. **According to the author, patient satisfaction can result in which one of the following?**
- **A.** More compliance with study procedures
- **B.** Less compliance with study procedures
- **C.** Positive feelings about the investigator
- **D.** More likely to be eligible for a trial

30. **What are the three major topics discussed in this article?**
- **A.** Process, financial, relationship management
- **B.** Process, financial, study selection
- **C.** Availability, financial, personal touch
- **D.** Study selection, patient reimbursement, availability

Getting the fundamentals right is the foundation of any successful research study, and the core of those fundamentals is a winning CTMS solution. That's where CTMS for Investigators from Merge eClinical comes in. Feature-rich, scalable and secure, CTMS for Investigators streamlines the study management process and helps you organize and centralize your research.

CTMS
for Investigators

Be the best Site you can with these capabilities!

- Assess study feasibility and negotiate more profitable contracts
- Manage patient recruitment in order to become known as a "high enroller"
- Manage financials and profitability with comprehensive budgeting, revenue tracking and invoicing
- Ensure quick user adoption with tab-based navigation, user-customizable fields, and fewer clicks to enter, view and report data

To get started, please visit us online.
eClinicalOS.com/ctms

MERGE CTMS for Investigators is a solution of Merge Healthcare Inc. 866.387.4257 | eClinicalOS.com

Stuart Horowitz, PhD, MBA

[DOI: 10.14524/CR-15-4056]

NEW RULES: Use of a Single IRB for NIH-Sponsored Multicenter Research

The National Institutes of Health (NIH) is now considering a new policy on "Use of a Single Institutional Review Board (IRB) for Multi-Site Research."[1] The draft policy was first published on December 3, 2014, and the period open for public comments closed on January 29, 2015. While NIH is considering these comments, readers of *Clinical Researcher* might also consider the ramifications of the policy.

Background

For more than three decades, clinical research professionals in the biopharmaceutical and medical device industries have embraced central IRB review because of its consistency, effectiveness, and efficiencies. Biopharma encourages (but does not require) the use of a central IRB for review and oversight of research. Increasingly, however, biopharma companies are now mandating the use of a central IRB for sites participating in their clinical studies.

Central IRB review has been pivotal to the growth of clinical research in community settings where study sites often lack their own IRBs. Today, besides community sites, thousands of hospitals (including a third of all academic medical centers) also rely on central IRB review for biopharma research.

In contrast to biopharma-sponsored multicenter clinical trials (MCTs), most NIH-sponsored MCTs are reviewed by local IRBs, with a few notable exceptions. The National Cancer Institute (NCI) began contracting with central IRBs in 1999 for its extramural cooperative group oncology research in adults and children. Initially, NCI encouraged use of central IRBs, but did not require it. In 2014, however, NCI made reliance on its contracted central IRB a requirement of participating as a research site (with a few exceptions).

In addition, The National Institute of Neurological Disorders and Stroke has incorporated the use of a single IRB for its Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) and Network for Stroke Research (NIH StrokeNet). Based on NIH's experience with these central IRBs, not surprisingly it published a draft policy encouraging reliance on central IRB use for NIH-funded multicenter studies.

As Stated in the Draft Policy…

Purpose

The purpose of this Policy is to increase the use of single Institutional Review Boards (IRB) for multi-site studies funded by the National Institutes of Health (NIH). Its goal is to enhance and streamline the process of IRB review and reduce inefficiencies so that research can proceed efficiently without compromising ethical principles and protections.

Scope

NIH generally expects all domestic sites of multi-site NIH-funded studies to use a single IRB of record. The Policy applies to all domestic sites participating in NIH conducted or supported multi-site studies, whether supported through grants, contracts, or the NIH intramural program. While foreign sites in multi-site studies will not be expected to follow this Policy, they may elect to do so.

The draft policy goes on to say that the cost of such reviews will be paid by NIH as a direct cost of research, and that an awardee institution may have a review performed locally, but only at the institution's own expense.

Ethical Considerations

There are no regulatory impediments to the use of central IRB review for drugs and biologics. However, some people have expressed ethical concerns, believing that the local nature of a captive IRB (i.e., a locally convened committee comprising individuals captive of the investigators' institution and at least one local, unaffiliated member) is essential for ethical review.

IRB review and oversight is a cornerstone of ethical clinical research, and IRBs must use ethical principles in the context of local considerations in their decision making. IRBs also have a pivotal role after approval of research, and often work closely with investigators and others within an institution to assure that research volunteers provide valid informed consent. The concern often expressed over use of a single, central IRB is that a captive IRB can better fulfill its ethical obligations.

Perhaps, for single-site research, local IRB review may be most appropriate. Today, there are approximately 2,500 to 3,000 active captive IRBs in the U.S. (based on an analysis of Federalwide Assurances and IRB organizations).[2] Moreover, many IRBs were started when most studies were conducted at standalone sites by lone principal investigators.

The existence of all these captive IRBs does not mean they should re-review research already reviewed centrally; ethical concerns are not uniformly held, especially where MCTs are concerned. Further, both the draft NIH Policy and an editorial in *Nature* magazine[3] point out there is no evidence that redundant IRB review adds to human research protections. These sources also note there are compelling reasons to believe that independent IRB review of MCTs enhances human protections by eliminating institutional conflicts-of-interest and centralizing the collection of unanticipated problems.

In addition, one could argue that reliance on central review for MCTs provides the added "bandwidth" for captive IRBs to focus on local, single-center studies. A single IRB provides a clear path for communication between a single point of contact at the IRB and the sponsor. This is especially important regarding an IRB's concerns about a protocol for an MCT, in terms of enabling a single IRB to require protocol changes that protect research subjects at all sites.

A single IRB can also coordinate necessary site-level changes, such as not enrolling certain vulnerable populations at sites that lack the appropriate expertise, or requiring consideration for faith-based institutions in the process and form of informed consent. A qualified single IRB also has the context of all sites to find and manage compliance trends and safety issues across them.

There are no regulatory impediments to the use of central IRB review for drugs and biologics. However, some people have expressed ethical concerns.

Additional Considerations

The draft policy did not address the important matter of how to identify an appropriately qualified IRB. Any IRB functioning as a central IRB must have effective systems to manage these issues:

- **Local context**—This includes applicable law and local standards, institutional policies and resources, qualifications of the investigator and study staff, and community and subject considerations.
- **Effective and compliant information systems**—Although electronic IRB systems are prevalent at many local IRBs, most are not designed to support central IRB functions, such as the maintenance of separate records for each investigator conducting the same protocol at different sites.
- **Administration of review among multiple sites**—Processes need to be in place to support the unique needs of a central IRB. Continuing review cycles may be different or the same among sites. Research may need to be suspended at a single site or suspended at all sites, depending on the issue. Each institution may have unique needs, such as a requirement for specific consent language or legal terms.

NIH Has Yet to Decide

NIH is now reviewing all submitted comments regarding the draft policy and considering them. We can anticipate a response—and possibly a final policy—in the coming months.

Disclosure

For approximately the last 2.5 years, I have been (and remain) an executive with an independent IRB. Disclaimer: The views expressed here are my own.

References

1. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-026.html
2. www.hhs.gov/ohrp/assurances/index.html
3. Vol. 516, December 11, 2014. www.nature.com/polopoly_fs/1.16513!/menu/main/topColumns/topLeftColumn/pdf/516143b.pdf

Stuart Horowitz, PhD, MBA, (shorowitz@wcgclinical.com) is president for institutions and institutional services at WIRB-Copernicus Group.

Charting a Course *for the* Patient Centricity Movement

PEER REVIEWED

Kenneth A. Getz, MBA

[DOI: 10.14524/CR-14-0060]

It is widely known that product-centric innovation has been the preeminent drug development paradigm for more than the past 50 years. Under this paradigm, pharmaceutical and biotechnology companies have vied to innovate in an insular and secretive manner. Sponsors have largely sought to develop medical interventions internally, singularly focusing on performing great science to gather and analyze proprietary, competitively sensitive data. In this approach, patients are subjects; contract research organizations (CROs) and investigative sites are service providers; and healthcare payers and providers are consumers of newly launched products.

Patient-centric innovation, on the other hand, represents a fundamental and profound change to the product-centric paradigm. This movement began quietly in the broader healthcare arena, and has been building slowly since nearly a decade ago.

The number of new molecular and biologic entities in the R&D pipeline has been rising **7%** annually for two decades.

Further, patient centricity has picked up tremendous momentum and visibility since 2010. At that time, the President's Council of Advisors on Science and Technology recognized a significant change emerging, from which all healthcare and research would be "organized around the needs and specific characteristics of the patient."[1] That same year, the Patient-Centered Outcomes Research Institute was established under the Patient Protection and Affordable Care Act to engage patients and other stakeholders in improving patient care and outcomes through patient-centered comparative clinical effectiveness research.[2]

Today, patient-centric initiatives are being considered, piloted, and implemented at a furious pace across the clinical research enterprise. This article explores the promise of patient centricity and charts an aspirational course for this movement.

Addressing the Imperatives

Patient centricity addresses two critical operating imperatives:

1. **The need to optimize research and development (R&D) processes and practices; and**
2. **The need to achieve meaningful support from, and engagement with, the public, patients, and the broader healthcare community.**

The Need to Optimize R&D Processes and Practices

The R&D engine is innovating and generating substantial output, but the drug development enterprise is struggling to support it. R&D is highly productive; the number of new molecular and biologic entities in the R&D pipeline has been rising 7% annually for two decades, and now exceeds 10,000 active new molecular entities in the pipeline.[3] The total number of new drugs and

Despite ongoing efforts over the past five decades to improve drug development risk, the probability of successfully bringing a drug from discovery to commercialization is extremely low, and it's getting worse.

biologics approved by the U.S. Food and Drug Administration (FDA) has followed a consistent cycle of peak and trough years since the mid-1990s. The number of new molecular entities approved by regulatory agencies in the European Union and Japan have followed a similar pattern.[4]

Despite ongoing efforts over the past five decades to improve drug development risk, the probability of successfully bringing a drug from discovery to commercialization is extremely low, and it's getting worse. High levels of uncertainty and risk exist in clinical research, where, according to the Tufts Center for the Study of Drug Development (CSDD), only one out of every 10 drugs entering clinical testing will be approved by the FDA.[5] By comparison, 10 and 20 years ago, the overall success rates for drugs entering clinical testing were 16.4% and 19.1%, respectively.[5]

Clinical phase durations are no shorter today than they were in the early 1990s. Despite implementing a wide variety of new practices and technologies intended to accelerate clinical development cycle times, the opposite has occurred. The average total clinical phase duration is 6.8 years and has increased 15% during the past decade.

Longer clinical phase durations are mainly a function of the therapeutic classes that dominate research activity (e.g., oncology and central nervous system). Drugs targeting diseases in these therapeutic areas have longer average development cycle times.

Also, regulatory review and approval cycle times have changed little since the mid-1990s. The average time from submission of a new drug or biologic application to regulatory approval has been relatively consistent at 1.5 years.[3]

Meanwhile, the cost of R&D is extremely high and rising steadily. When all is accounted for, total spending worldwide on pharmaceutical R&D will exceed $140 billion (US$) in 2014, representing a 4.9% 10-year compound annual growth rate. Companies report that they anticipate limiting growth in R&D spending to 2% annually for the foreseeable future, to tie spending to expected increases in global industry revenue.[5]

When combined, high failure rates and long cycle times translate into high levels of capitalized investment required to develop a single successful drug. Tufts CSDD estimates that the average capitalized cost to bring a single drug through R&D and into the marketplace now exceeds $2.5 billion—more than double the estimated capitalized cost in 2008.[6]

Remarkable growth in protocol design complexity has been discussed in recent issues of *Clinical Researcher*. Scientific demands, study design practices, regulatory pressures, and evolving requirements from payers and providers have all contributed to a dramatic increase in the number of endpoints, procedures, eligibility criteria, and operating scope per protocol during the past decade.

For the typical Phase III protocol conducted in 2012, study volunteers came from an average of 34 countries and 196 research centers, compared to 11 countries and 124 research centers 10 years ago. Moreover, in 2012, to qualify to participate in a typical Phase III protocol, each volunteer had to meet 50 eligibility criteria—up from an average of 31 inclusion and exclusion criteria 10 years ago.[7]

Achieving Meaningful Engagement of Patients and Their Support Network

A large and growing body of public and patient survey research shows that the vast majority of the general public is unfamiliar with, disconnected from, and wary of the clinical research enterprise. According to a global study from the Center for Information & Study on Clinical Research Participation, for example, six out of 10 people self-report that they have "No Knowledge" or "Very Little Knowledge" about clinical research and its role in advancing public health. Less than one in 20 Americans says that he or she knows where to find information about relevant clinical trials.[8]

A recent public poll conducted by the Kaiser Family Foundation found that the public has a strongly unfavorable view of research sponsors, with more than one-fourth of respondents saying that they don't trust pharmaceutical and biotechnology companies to offer reliable information about drug side effects and safety. Nearly half said they don't trust research sponsors to inform the public quickly when safety concerns about a drug are discovered.[9]

Healthcare providers and educators also remain largely outside the clinical research enterprise. Although doctors, nurses, and pharmacists are highly trusted sources for health-related information, less than one in six study volunteers report that they learned about clinical trials from their primary or specialty care physician or nurse, and half that rate learned about clinical trials from their pharmacist. Although minority patients demonstrate a high willingness to participate in clinical research, referral rates are even lower in these communities, in part due to the limited number of minority physicians participating in clinical research.[10]

Measuring the Fallout

Poor public, patient, and healthcare community awareness of, and virtually no connection to, clinical research contributes substantially to low levels of patient inquiry and randomization rates. Stringent eligibility criteria also make it difficult for patients to qualify to participate, and complicated protocols with demanding schedules of assessments greatly challenge volunteer retention rates.

Because of these trends, study conduct performance has been slipping. A recent Tufts CSDD study of several hundred global clinical trials found that sponsor companies must typically double the planned enrollment period to give investigative sites enough time to recruit study volunteers and complete a given clinical trial. Even when cycle times are extended, 39% of investigative sites, on average, in any multicenter global clinical trial will under-enroll, and 11% will fail to enroll a single patient.[11]

Of those study volunteers who have completed a clinical trial, the overwhelming majority (95%) report a willingness to consider participating in another trial. This positive statistic speaks to the research community's—particularly investigative site personnel's—integrity, compassion, and professionalism.

However, once their trial has ended, more than 90% of study volunteers report that they never received the study results, although nearly all wanted to know the results and what was learned from their participation.[8] The end-of-study experience leaves most study volunteers feeling forgotten and unappreciated by the clinical research enterprise.

Welcoming a Transformative Movement

The current R&D operating environment is inefficient, lengthy, risky, and costly. Further, failing to engage the public, patients, and their healthcare support networks has contributed greatly to these operating conditions. Patient centricity represents a compelling and potentially transformative new paradigm.

Patient centricity has been described loosely as a holistic and philosophically new approach to planning and executing pharmaceutical R&D. Patient-centric R&D seeks to engage patients and the healthcare community as partners in the R&D process. In this model, R&D innovation is an open process through which precompetitive information and drug development risk is shared among a broader community of external partners, including academic and basic research groups, co-development sponsors, development operations alliances, and patient advocacy groups.

The ultimate goal of patient centricity is to establish a partnership and engagement among patients and their healthcare support networks, and to engender in them a sense of connection and ownership in the success of efforts to develop new medical treatments.

As part of the patient centricity movement, clinical research professionals look to conduct not only great science, but also more feasible clinical trials that enhance study volunteer participation experiences and reduce the burden of participation. In this approach, CROs, investigative sites, healthcare providers, and payers each play important roles as R&D partners and supporters, helping to ensure that patient participation experiences are positive and that patient medical needs are met.

There are four core conceptual principles of patient centricity that guide clinical research enterprise planning and execution. Patient-centric clinical research is:

1. **RELEVANT:** Patient-centric research targets unmet medical needs identified in collaboration with patients and their healthcare support networks;
2. **PRACTICAL:** Patient-centric research agendas and clinical trial designs recognize and accommodate real-life patient and healthcare community needs and experiences;
3. **FEASIBLE:** Patient-centric clinical trials minimize the burden of patient participation and are supported by initiatives that improve convenience; and
4. **PARTICIPATORY:** Patient-centric research planning and execution amplify the patient's voice, receive support from the patient community, and give patients an opportunity to be actively involved and respected partners throughout the research process.

A large and growing body of public and patient survey research shows that the vast majority of the general public is unfamiliar with, disconnected from, and wary of the clinical research enterprise.

Recognizing the Trends

The past 24 months have brought a proliferation of initiatives touching all aspects of pharmaceutical R&D:

- Sponsor organizations are partnering with patient advocacy groups and forming precompetitive alliances to better understand unmet medical needs, to collaboratively set research agendas, to generate financial and community backing of R&D initiatives, and to solicit input into protocol designs to improve feasibility.
- Pharmaceutical and biotechnology companies are soliciting patient input on study designs through patient advisory boards, one-on-one interviews, crowdsourcing, and social media.
- Sponsors and CROs are piloting new approaches designed to make study participation more convenient. Telemedicine, home nursing networks, and direct-to-patient platforms, for example, are being used on select clinical trials to give patients the opportunity to participate in their own homes or in closer proximity to their residences and workplaces.
- Sponsors and CROs are establishing stronger relationships with a variety of healthcare delivery systems to leverage electronic health information. In doing so, companies hope to identify areas where medical interventions can be improved and better targeted, and to find and reach patients who might benefit by participating in clinical trials more rapidly and efficiently.
- Pharmaceutical companies and their contract research partners are piloting electronic informed consent forms and using wearable devices to improve the study volunteer experience, and to simplify and make easier the collection of outcomes data in real time.
- Sponsors and CROs are supporting more pragmatic clinical trial designs and trials conducted in real-world settings, instead of in the traditional, community-based, for-profit investigative site environment.
- A growing proportion of study endpoints are supported by protocol procedures collecting subjective, patient-reported outcomes. We can expect this trend to continue.
- Partnership under a patient-centric R&D model requires transparency and disclosure of clinical trial results to study volunteers and patient communities. A growing number of sponsors are now routinely disseminating clinical trial results, in lay language/nontechnical summaries, to volunteers at the completion of clinical studies.
- Patients and patient advocacy groups are playing far more active roles on committees to inform clinical research professionals and to serve patient communities. To name but a few examples: patients are participating on regulatory agency advisory committees; they are providing testimony at regulatory hearings; and they are serving on postmarketing surveillance committees.

Closing

In these early days, as yet, there is little to no information demonstrating tangible effects from the nascent patient-centric trends covered in this article. Over time, as more is learned, select initiatives will take hold, whereas others will not. Some patient-centric initiatives will deliver sufficient return on investment to affirm their becoming standard practice; some will be used as-needed; and others will prove too costly with limited to no measurable benefit.

At a minimum, the patient centricity movement is inspiring sponsor companies to challenge and transform outdated, legacy, product-centric R&D by improving patient engagement when it is essential to do so.

The ultimate goal of patient centricity is to establish a partnership and engagement among patients and their healthcare support networks, and to engender in them a sense of connection and ownership in the success of efforts to develop new medical treatments.

References

1. President's Council of Advisors on Science and Technology. Report to the President—Realizing the Full Potential of Health Information Technology to Improve Health Care for Americans: The Path Forward. December 2010, page 24. www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-health-it-report.pdf
2. Background about PCORI. www.pcori.org/content/why-pcori-was-created (Accessed on December 11, 2014)
3. Getz K, Kaitin K. Open innovation: the new face of pharmaceutical research and development. *Expert Rev Clin Pharmacol* 2012;5(5):481-3.
4. Dowden H, et al. Industry and regulatory performance in 2012: a year in review. *Clin Pharmacol Ther* 2013;94(3):359-66.
5. Kaitin K, DiMasi J. Pharmaceutical innovation in the 21st century. *Clin Pharmacol Ther* 2011;89(2):183-8.
6. DiMasi J. Tufts CSDD Briefing: Cost of Developing a New Drug. November 18, 2014. Tufts University School of Medicine. Boston, Mass.
7. Getz KA. Opportunities to optimize study design to drive development performance and efficiency. *Clin Res* 2014;28(2): 28-31.
8. Getz KA, New insights into study volunteer perceptions and experiences to inform patient-centric clinical trials. *Clin Res* 2014;28(2):17-21.
9. Kaitin K, Honig P. Reinventing bioinnovation. *Clin Pharmacol Ther* 2013;94(3):279-83.
10. Simmons D, Chappell J, Getz K, Hallinan Z. Are pharmacists a viable channel for education about clinical trial participation? *Drug Info J* 2011;45(4):443-53.
11. Lamberti MJ, Mathias A, Myles JE, Howe D, Getz K. Evaluating the impact of patient recruitment and retention practices. *Drug Info J* 2012;46(5):573-80.

Kenneth A. Getz, MBA, (kenneth.getz@tufts.edu) is the chair of the nonprofit Center for Information & Study on Clinical Research Participation and director of sponsored research and an associate professor at the Tufts Center for the Study of Drug Development, Tufts University School of Medicine. He is also the founder and owner of CenterWatch and a co-owner of the Metrics Champion Consortium.

Martin Robinson, PhD

[DOI: 10.14524/CR-15-4057]

How Competency Frameworks Can Help Protect Patients

The theme of this issue of *Clinical Researcher* is "Patient Centricity." In reality, all clinical research studies should consider the patient first. Patient protection is one of the two fundamental purposes of good clinical practice (GCP), as spelled out by the International Conference on Harmonization (ICH). The ICH GCP E6 (R1) guideline states that, "Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected."

Competence is a Rarely Used Word

All members of the clinical research team should be familiar with the principles of GCP and practical measures in place to protect human subjects, such as the process of informed consent, using a scientifically and ethically sound protocol, and having adequate safety reporting systems. However, a chain is only as strong as its weakest link.

Regulations and guidelines governing clinical research go into detail in describing the measures used to protect patients, but one area singularly lacking concerns the skills and abilities of the people whose job it is to uphold the purpose and principles of GCP, namely you and me. Regulations deal with the issue by requiring that, "Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task." (ICH GCP, Principle 2.8)

Regulations and guidelines governing clinical research go into detail in describing the measures used to protect patients, but one area singularly lacking concerns the skills and abilities of the people whose job it is to uphold the purpose and principles of GCP, namely you and me.

Martin Robinson, PhD, (mrobinson@iaocr.com) is principal director of IAOCR.

Education, training, and experience are important, but do not give the whole picture. Substandard training and narrow, poor quality experience can have negative effects on the ability of an individual. The key aspect of whether we can fulfill our role in clinical research is directly related to our competence (i.e., the possession of the required and observable skills, knowledge, and behaviors).

A search through clinical research regulations and guidelines for the word "competence" produces a scant return. The *Code of Federal Regulations* mentions it in 21 CFR in the context of institutional review board membership (56.107) and in using foreign data, relating it to the competence of investigators (314.106). The ICH GCP guideline mentions competence only once, for the documentation of a medical laboratory to perform the required tests.

Why is competence so important, and how can it affect patient safety, rights, and well-being? I can give you at least two real-life examples.

Potential Harm to Patients Through Incompetence

A clinical research associate (CRA) who was monitoring a study was so preoccupied with source data verification that she omitted to check and inventory the use of the study medication for 10 months. The result was that a patient not on the study was given the experimental medication, and this error was undetected for a considerable time.

Thankfully, the individual patient came to no discernible physical harm, although it is unclear what the mental impact was when the patient was informed of the error. The CRA had not appreciated the need to review regularly the dispensation and administration of the trial medications. By good fortune the mistake was not serially repeated to the jeopardy of patients' well-being on a larger scale.

Another example of lack of competence was evident when a friend of mine was almost enrolled into a clinical study without her knowledge. The situation occurred when she attended an extra clinic visit that she thought had been arranged as part of her normal treatment. It was only when she was presented with a consent form to sign, with no prior discussion or opportunity to ask questions, that she realized she was being invited to participate in a clinical trial.

On questioning the investigator and his team, my friend discovered that they seemed unaware that they had done anything wrong, justifying their actions (or lack of them) by saying that the study had been approved by an ethics committee.

In both cases, the rights and well-being of patients were put at serious risk through the incompetence of people involved in the conduct of a clinical trial. Having their competence assessed and then having the gaps in competence filled could have prevented both situations.

Using Competency Frameworks to Help Protect Patients

Competency frameworks come into their own in situations like these because they form a set of objective standards that can be used to benchmark performance. Starting with a job description or a detailed role summary, a set of competencies can be developed. The competencies are grouped typically in clusters to create a framework, and within each cluster, the competencies are described in terms of what the person in the job can observably demonstrate.

Competency frameworks are useful tools for the job holder and for line managers to assess performance objectively, and to implement measures to correct underperformance and reinforce good performance. The good news is that regulatory inspectors seem to ask more questions about how organizations measure the effectiveness of training in terms of competence, rather than merely asking to see documentation of attendance at training courses.

Patients in clinical trials deserve the best protection of their rights and well-being, and using competency frameworks is a vital instrument in this most sacred of principles of medical research.

Logistical Considerations for Integrating Patient-Reported Outcomes in Multiregional Clinical Trials

PEER REVIEWED | Ari Gnanasakthy, MSc, MBA | Carla DeMuro, MS

[DOI: 10.14524/CR-15-0003]

Patient-reported outcomes (PROs) are used increasingly in clinical trials for several purposes, including demonstrating efficacy as a primary endpoint and providing key data useful for product differentiation. Value propositions based on PROs, especially when included as nonprimary endpoints, provide data beyond the traditional efficacy and safety endpoints, and capture the patients' voice in drug development.

PRO is an umbrella term used to describe outcomes collected directly from the patient without interpretation by clinicians or others.[1–3] PRO data are collected via standardized questionnaires (also called instruments, scales, diaries, or checklists) designed to measure an explicit concept (construct) such as symptoms, activity limitations, and health status or health-related quality of life.

These PRO measures (PROMs) may include simple questions to measure the frequency (e.g., seizure rates in epilepsy) or severity (e.g., joint pain in arthritis) of a symptom.[4,5] More complex, multidimensional questionnaires are also used to measure health status in clinical trials. These include generic tools, such as the Short Form–36 (SF-36) Health Survey, which can be used across various disease areas, or symptom- and disease-specific measures that evaluate concepts important to patients experiencing the condition of interest.

A range of methodological issues must be considered to ensure the collection of high-quality data necessary for the various stakeholders for this information. Foremost, PROMs must be demonstrated to be both valid and reliable within the specific context of use.[6] In 2009, the U.S. Food and Drug Administration (FDA) formalized a set of evidentiary standards for using PROMs to support product label claims.[1]

Compared to other parameters captured in clinical trials, two aspects are unique to PRO data:

- PROs must be provided in the language most familiar to the patient. Therefore, appropriately translated and cross-culturally adapted PROMs must be used in clinical trials.[7]
- Unlike other assessments in typical clinical trials that can be queried at a later date, data from PROMs that capture how patients feel and function at specific times cannot be queried retrospectively.

The combination of these two aspects with the increased number of countries participating in clinical trials[8] has led to a need for special attention to the logistical issues of integrating PROMs into studies.

This manuscript highlights some of the key logistical challenges of integrating PROMs in multiregional clinical trials (MRCTs).

INTERNAL RESOURCE ALLOCATION

The resources required to integrate PROMs in clinical trials cannot be underestimated. When there are "off-the-shelf" existing PROMs fit for a purpose, typical activities require obtaining appropriately validated PROMs, ensuring the availability of appropriately cross-culturally adapted and translated PROMs, implementing the most appropriate data-capture methods, preparing training materials for study coordinators and patients, and compiling briefing books to seek scientific advice from regulatory authorities.

Including PROMs in study protocols also requires contributions from many functions, such as development, data management, biostatistics, regulatory, and outcomes research. Research teams must know the breadth of these activities and ensure adequate time and resources in the clinical development plan.

There are no standard timelines for obtaining correct versions of PROMs and accompanying documentation (such as scoring algorithms), permission/license from authors or agencies, or appropriate language versions for a particular clinical trial.

If an existing PROM does not fit the required purpose, developing a novel PROM is an extensive process that can span two or more years. A gap analysis early in a drug's development is essential to assess the need for new PROMs and to initiate activities to ensure timely integration in clinical trials.

Internal resources are often secured when the intended PRO objective is specified as critical to a strategic document, such as the target product profile. Once integrated in the target product profile, one can be assured there is agreement among all functions and management that the PRO objective is essential to satisfying the product's regulatory needs, commercial needs, or both.

Agreement would be delineated when the PRO is the primary endpoint, but it may not when the PRO is a nonprimary endpoint, unless internal processes are in place to seek timely agreement. Lack of commitment from all parties often translates into suboptimal data, missed opportunities, and possibly additional cost.

PROTOCOL DETAILS

The study protocol describes the plan for conducting the clinical study and explains the purpose and function of the study and how to carry it out. It should include pertinent information, such as PRO objectives, assessment rationale, assessment schedule, modality of data capture, and analyses.

Study teams may fail to realize that many PROMs have distinct versions designated for various disease severity levels, with different recall periods, or for subpopulations, such as pediatrics. For example, there are two versions of the Asthma Quality-of-Life Questionnaire—an original published in 1991 and a standardized version, both available in self-administered versions, interviewer-assisted versions, and versions specific to children.

The protocol should include PROM names and corresponding versions or citations to assist in obtaining the correct PROM, and accompanying documents, such as scoring guides. Failure to do so may result in scoring of data intended for a PROM version that is incorrect for the study. Wherever possible, citations relating to validation, cultural adaptation, and analyses should also be included in the protocol.

Unique procedures should also be specified when data are expected from "special" populations (e.g., caregivers of elderly patients, parents of young children, or patients with movement disorders).

OBTAINING APPROPRIATE PROMS

Identifying appropriate PROMs depends on regulatory, commercial, and market access needs. This process is beyond the scope of this manuscript, but is covered elsewhere.[6,9]

Once a PROM has been identified for use, the following three criteria must be met before the PROM is integrated in a clinical study:

- The PROM must be the latest version available, although there may be exceptions if the drug development program requires maintaining consistency between studies. Details of versions and any requirements for specific PROMs are available from relevant websites (e.g., PROQoLID.org), publications, or the developers of the PROMs.
- All necessary validated language versions should be available at the time of submissions to institutional review boards/independent ethics committees (IRBs/IECs). These groups require the PROMs in local languages, so all required language versions of the questionnaires must be available at submission.
- Appropriate permission to use the measure must be granted, where applicable, and all relevant contractual matters between the developer (or the agent of the developer) and the sponsoring company must be signed off and archived.

There are no standard timelines for obtaining correct versions of PROMs and accompanying documentation (such as scoring algorithms), permission/license from authors or agencies, or appropriate language versions for a particular clinical trial. Therefore, study teams must account for these complexities during the planning stage—when writing the clinical development plan and target product profile—if PROMs are needed in a clinical trial.

The efficiency of integrating all necessary language versions of PROMs in an MRCT in a timely fashion depends on seamless interaction between the sponsoring company, the translation vendor, the ePRO vendor, and the PROM developer.

Data collection for PROMs requires special consideration, not only because patients are involved, but because the quality of data depends on the training and the predefined responsibilities of the study coordinator, investigator, and field monitor.

Study teams are advised to start activities, especially those relating to the acquisition and translation of the PROMs, well in advance (often months before the study starts), so they can be ready for submission to the relevant IRBs/IECs.

Members of study teams may be tempted to change various aspects of an existing PROM to suit their study. However, any changes to wording, sequence, response options, instructions, and administration method may invalidate a PROM. Permission must be obtained from the authors of the PROM (or translation) and documented before any changes are made. Changes may also warrant validation studies. These issues are important when a PROM developed for paper administration is considered for electronic data capture (ePRO).[10–12]

LANGUAGE VERSIONS

New translations of PROMs are often required for MRCTs. PROM translations, also called cultural adaptations, must adhere to strict methodology and may take six to nine months to develop.[7]

The PROM translations required for a specific clinical trial are governed not only by the official languages of the country, but also by the languages spoken by minority populations in that country. Knowledge of ethnic mix and the locations of study centers may also help identify language versions required.

Companies that provide translation services should also provide certificates of translation. Certificates for existing translations can be obtained from the authors of the instruments. Even if translations are available, the corresponding certificate of translations must also be available in time for IRB/IEC submissions.

An increasing number of IRBs and IECs now require certificates of translation and finalized patient-facing screenshots for PRO instruments (if ePRO is used) before studies are approved. IRBs and IECs are usually forgiving if certificates of validation are not available for instruments developed many years ago, but have been widely used and accepted. If certificates of translations are not available, study teams may consider retranslation.

RESOURCE MANAGEMENT

The efficiency of integrating all necessary language versions of PROMs in an MRCT in a timely fashion depends on seamless interaction between the sponsoring company, the translation vendor, the ePRO vendor, and the PROM developer. Since a typical study may include multiple PROMs, the roles, responsibilities, and lines of communication should be defined as early as possible following the completion of necessary legal obligations between all parties.

INVESTIGATOR MEETINGS

Investigator meetings and site initiation meetings are key opportunities to provide information and training materials for PROMs. A presentation should cover topics such as the purpose of the PROMs, the number of questions in each PROM, and the details of the response scales. A list of recommended topics is given in the sidebar.

Written instructions, such as training manuals or case report form completion guidelines, are strongly recommended, and archiving prerecorded trainings (e.g., on DVD) at the site may help refresh training or train new staff for longer trials. Documentation of this training should be included in the PRO evidence dossiers submitted to the regulatory agencies.

PREPARING THE SITE

Preparing the study sites is the key to successful study execution. Because field monitors are the main contacts in the participating sites, both the field monitors and clinical site staff must be informed and trained on the objectives, requirements, and methods of PRO data collection. The following actions are crucial:

- The center has received approval for IRB requirements.
- Appropriate steps have been taken to ensure study coordinators and investigators are trained for their duties and responsibilities before, during, and after data-collection activities.
- The site staff know that PROMs are integral to the study and not separate from the protocol. A person dedicated to the trial (e.g., study coordinator) should be designated as the person responsible for the administration of the PROM, and he/she should have the interpersonal skills necessary to assist patients without influencing their responses. Influencing patients' responses by interpreting the questions or by suggesting responses may introduce bias and invalidate the study results.
- Whenever PROMs are included as part of a trial design—especially in diseases relating to mental disorders or serious conditions such as cancer—patients may have a heightened expectation of access to support services. In disease areas where this may be a concern, study coordinators should identify a short list of social services, mental health, counseling, or pastoral resources

available to address patients' emotional needs. Study staff may also have the name and contact number for someone to call in case a patient becomes upset. For protocols using PROMs with especially sensitive questions, some IRBs require researchers to state how psychosocial distress will be identified and addressed.

- The site must agree on resources and guidelines for storage, protection, and access restriction of source documentation.

SITE TRAINING

The field monitor must be the key interface between the trial's sponsor and the site's staff during a trial. Although initial site training may be done at the investigator meetings, most interaction will occur between the field monitor, site coordinators, and investigators. Therefore, field monitors' acceptance of the importance of PRO assessments is crucial to ensuring that the correct message is transmitted to participating sites.

Data collection for PROMs requires special consideration, not only because patients are involved, but because the quality of data depends on the training and the predefined responsibilities of the study coordinator, investigator, and field monitor.

The training of study coordinators is essential for improving data quality, minimizing inconsistencies, and satisfying regulatory guidance.[1] Training considerations must include the possibility of inexperienced study staff administrating questionnaires and the burden on both staff and patients of administrating multiple questionnaires. Documentation of site and patient training is part of a PRO evidence dossier submission to support label claims, so care should be taken in documenting this training.

Field monitor and site personnel training should not be confined to investigator meetings or site initiation visits. Ongoing dialogue should be encouraged among site coordinators and field monitors, who may communicate issues or concerns directly to the study trial leader. Further actions to be considered are provided in the sidebar.

CONCLUSION

PROs are increasingly used in clinical trials to demonstrate efficacy and differentiate products. Unlike traditional efficacy and safety endpoints, a PRO strategy faces unique logistical challenges when implementing it at the study level.

The key to successful implementation of PROMs in MRCTs is anticipating the logistical considerations early in the process and having clearly defined roles and responsibilities for sponsors, PROM authors, translation companies, and ePRO companies.

Recommended Topics for Investigator Meetings When Using PROs

- ☑ Purpose of inclusion of each PROM
- ☑ Number of questions and time required to complete each PROM
- ☑ Details of response scales
- ☑ Dimensions covered (e.g., physical functioning, social functioning, etc.)
- ☑ Recall period related to the questions or dimensions
- ☑ Assessment schedule of each PROM by way of a schematic diagram of the study design highlighting the visits and order in which the PROMs will be administered
- ☑ Language versions of PROM for each participating country
- ☑ Aspects related to how the required materials (e.g., PROMs, ePRO devices, training materials, storage of devices) will be distributed to the study centers
- ☑ Ways of dealing with patients with special needs, such as visual impairment or movement disorders
- ☑ Responsibilities of the study coordinator and investigator before, during, and after the PROMs are completed

Recommendations for Study Site Training When PROs are Included

- ☑ All sites and field monitors should participate in training at the investigator meeting. Sites should communicate any changes in site coordinators to allow for communication of training materials to new personnel.
- ☑ A specific section of clinical trial newsletters should address any PRO-related issues.
- ☑ Positive feedback should be given to sites to encourage compliance and keep their focus on the PRO section of the protocol.
- ☑ A regular question-and-answer letter may be circulated by the study teams to site field monitors to ensure resolution of questions that arise.
- ☑ Site field monitors should address their questions directly to study leaders to ensure consistency of solutions.
- ☑ A feedback questionnaire may be collected from site coordinators and patients to obtain their comments on the PRO assessment process.
- ☑ Webinars or training modules should be offered to centers that join the study late.

References

1. U.S. Food and Drug Administration. 2009. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
2. Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, Rothman M. PRO Harmonization Group. Incorporating the patient's perspective into drug development and communication: an Ad Hoc Task Force report on the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. *Value Health* 2003;5:522–31.
3. Doward LC, McKenna SP. Defining patient-reported outcomes. *Value Health* 2004;September–October, 7 Suppl 1:S4–8.
4. Elger CE, Stefan H, Mann A, Narurkar M, Sun Y, Perdomo CA. 24-week multicenter, randomized, double-blind, parallel-group, dose-ranging study of rufinamide in adults and adolescents with inadequately controlled partial seizures. *Epi Res (Amsterdam)* 2010;88:255–63.
5. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;149:177–93.
6. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, Ring L. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1—eliciting concepts for a new PRO instrument. *Value Health* 2011;14(8):967–77.
7. Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M, et al. Multinational trials—recommendations on the translations required, approaches to using the same language in different countries, and the approaches to support pooling the data. The ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force Report. *Value Health* 2009;12:430–40.
8. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. *Nature Rev Drug Disc* 2008;12(7):13–4.
9. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, Ring L. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 2—assessing respondent understanding. *Value Health* 2011:978–88.
10. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, Lenderking WR, Cella D, Basch E. Recommendations on evidence needed to support equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health* 2009;June:419–29.
11. Stone AA, Shiffman S, Schwartz JE, et al. Patient non-compliance with paper diaries. *BMJ* 2002;324:1193–1194
12. Tiplady B. Electronic patient diaries and questionnaires—ePRO now delivering on promise? *Patient* 2010;3:179–183

Ari Gnanasakthy, MSc, MBA, (gnanasakthy@rti.org) is head, Patient-Reported Outcomes, RTI Health Solutions, Research Triangle Park, N.C.

Carla DeMuro, MS, is head, Patient-Reported Outcomes, RTI Health Solutions, Research Triangle Park, N.C.

Margo Michaels, MPH

[DOI: 10.14524/CR-15-4059]

How Can Recruitment and Retention be "Patient-Centered"?

Most of us have seen the definition of patient-centered care, but seldom do we think how it applies to our processes and procedures to ensure an individual's informed decision making about clinical trial participation.

Over its 10 years of activity, the Education Network to Advance Cancer Clinical Trials (ENACCT) developed a list of core principles related to operationalizing patient-centered clinical trials at the site level. However, these principles must be operationalized in the real world by improving the skills and behaviors of research team members and organizational systems at sites.

As you review these principles, you will see their inherent challenges; few sites can claim to deliver each of them in a consistent manner. The key is to improve staff skills at a steady pace while moving the overall site along toward one day achieving these principles through the combined effort.

ACRP will soon offer new courses related to the professional skills and processes needed for this important work; stay tuned for more information later in 2015.

For more information on topics related to this column, please visit the ACRP Clinical Trials Recruitment Interest Group online at www.acrpnet.org/Interest-Groups/Clinical-Trials-Recruitment-.aspx.

Margo Michaels, MPH, (margomichaels@hc-aa.com) was the founder of the Education Network to Advance Cancer Clinical Trials (ENACCT), and now is a consultant developing patient-centered accrual programs.

> Patient-centered care is "healthcare that establishes a partnership among practitioners, patients, and their families (when appropriate) to ensure that
>
> • decisions respect patients' wants, needs, and preferences and
>
> • patients have the education and support they need to make decisions and participate in their own care."
>
> —Institute of Medicine, *Crossing the Quality Chasm*, 2001

The Seven Principles for Operationalizing Patient-Centered Clinical Trials at the Site Level

Principle	What it Means	Example
1. Trials are normalized throughout the institution through effective patient communication by all staff/providers	Ensuring that clinical research is not an afterthought, but is integrated in patient care and organizational culture	Providing training for all staff to encourage patient inquiry
2. 100% of patients beginning new treatment will be effectively prescreened for trial eligibility	Ensuring that all patients are screened for trial eligibility and that all eligible patients are offered trial participation	All patients beginning treatment are prescreened for initial eligibility criteria and the resulting "flag" is acted upon
3. 100% of those (who appear) eligible will be offered trial participation		
4. Clinical trials selected for local implementation will more appropriately meet the needs of local patients	Ensuring that the site only opens trials that meet the needs of people seeking care in the catchment area	If 50% of cancer cases in a site's area are stage 3 colon cancer, 50% of the site's trials should be for stage 3 colon cancer patients
5. All interested will have their information, knowledge, and behavior needs met throughout the consent process	Ensuring informed decision making through addressing communication and educational needs Ensuring comprehension throughout consent process	Implementing "Teach Back" for all staff consenting patients
6. All enrolled participants will receive adequate support to ensure their compliance and retention throughout the trial	Promoting the importance of keeping appointments, treatment adherence, patient safety, and connection to the study	Anticipating potential access barriers before they occur
7. Trials are normalized in the community to increase referrals and inquiry	Enhancing external relationships to optimize understanding of trials and change behaviors for the better	Developing community advocate training program

Factors Influencing Patient Participation in Clinical Trials in India

PEER REVIEWED | Jeroze Dalal, PhD

[DOI: 10.14524/CR-14-0047]

Patient recruitment in clinical trials is recognized as the leading bottleneck[1] in drug development. The multifarious and difficult forces affecting patient enrollment—such as protocol complexity, low disease incidence, competitive recruitment, patient concerns about side effects, unfavorable media portrayal of clinical research—have no quick and easy solutions. The major consequences are delayed trials that drain drug developers' research and development budgets.

Trial sponsors can play a prominent role in the recruitment process by creating patient awareness and developing collaborative working relationships with all stakeholders, including investigators and their staff.

There are several motivators for patients to enroll in trials. In a national poll carried out in the United States, the majority of respondents believed that the opportunity to improve their health is an important deciding factor to participate in a trial.[2] Where there are no current treatments available, the option of receiving the latest treatment as part of a clinical trial can be an exciting opportunity. Further, patients' demographic characteristics, such as age, gender, socioeconomic status, disease stage, and overall health and performance status may also affect enrollment.[3,4]

Patients who express greater trust in their doctor seem more likely to participate in randomized clinical trials.[5] Treatment by a specialist with close monitoring of health, especially in life-altering diseases such as cancer, is also related to accrual in clinical trials.[6]

Existing literature offers limited information on the motivations and attitudes of Indian patients; hence, it seemed important to gain an understanding of patients' perspectives regarding trial participation.

Research Methodology

The goal of a questionnaire-based study was to determine the factors influencing participation of patients in clinical trials in India. To understand patients' attitudes toward trial participation, the questionnaire obtained answers to the following questions:

- Why patients participate in clinical trials
- Reasons for nonparticipation in clinical trials
- Willingness to participate
- Does disease category of the patient affect participation

The questionnaire captured patient demographic details such as gender, age, educational qualification, previous trial participation, consultation with physician/family members before participation, patient's feelings about the importance of clinical research, and willingness to participate.

A sample of patients across six Indian cities from outpatient departments of government and private hospitals were approached to include an equitable mix of ethnicity and socioeconomic status, with cancer, neuropsychiatric diseases, and diabetes as the targeted specialties. The study included patients who had previously participated in research, patients who had declined to participate, and those who had never been approached to participate. Terminally ill cancer patients, those with severe neuropsychiatry problems, and minors were excluded.

An informed consent was obtained from the participants before administration of the questionnaire through face-to-face interviews.

The summary statistics in the study were the number of observations and the mean and standard deviations in the age of participants and their underlying diseases, among others. After all data queries were resolved, categorical values were summarized using frequencies and percentages and a chi-square test was performed. The data were entered in a database designed in Statistical Package for Social Sciences Version 21 (SPSS) and reviewed and validated using edit check programming facility.

Results

In total, 308 patients between the ages of 23 and 81 were approached for this study, of which 303 responded; 63% were patients of oncology, 18.8% of diabetes, and 18.2% of neuropsychiatry.

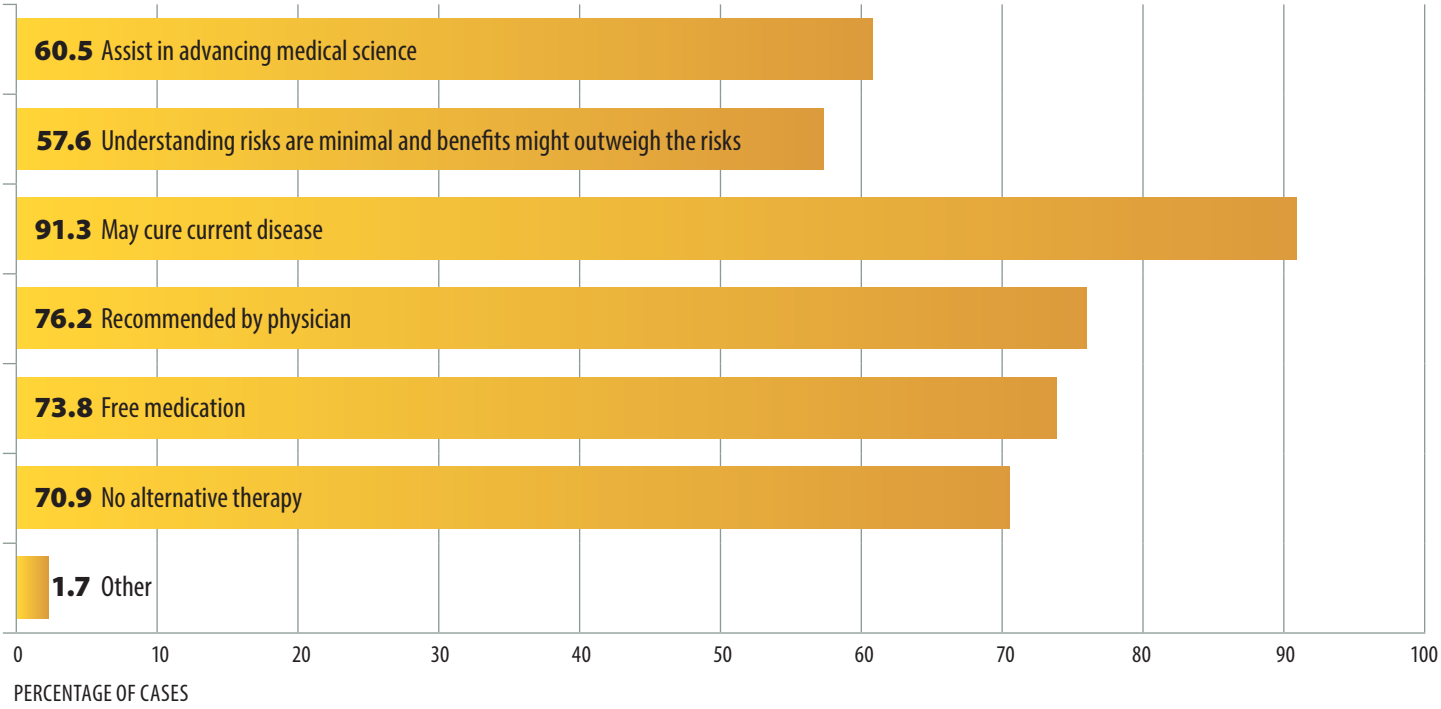
Why Patients Participate in Clinical Trials

To understand the reasons for trial participation, pre-set options were provided for the patients to rate in order of importance, with a rating of 1 being critical on a scale of 1 to 7. The options offered were:

- assist in advancement of medical science,
- understanding that the risks are minimal and benefits might outweigh the risks,
- may cure the current disease,
- recommended by my physician,
- do not have to pay for medication and other investigations,
- no other alternative therapy available, and
- other.

The results are shown in Figure 1.

FIGURE 1: Reasons for Patient Participation in Clinical Trials



Reasons for Nonparticipation in Clinical Trials

Among 303 patients who responded, 131 (43.2%) had not participated in past clinical trials. Interestingly, 53% of this group stated they were not aware of the option to participate in clinical trials. Further, 16%, though given the option to participate in trials, had failed the eligibility criteria as per the protocol, and the remaining 31% reported they had no option to participate since their physicians were not conducting trials.

The respondents also indicated reasons for declining trial participation. The overall perceived disadvantages of participation in this study were low, with only 3% of patients citing the risk of experimental drugs and the amount and frequency of blood to be drawn.

Willingness to Participate

If offered the chance to participate in future trials, 226 patients (74.6%) indicated they would be willing. Among those who had participated in clinical trials in the past, an overwhelming 87% expressed willingness to participate in future trials, which may indicate that past participants felt they had benefited from trial participation. In response to another question, this group indicated they believed that they were treated with "dignity and respect." On the other hand, only 59% of trial-naïve patients would enroll in trials. The difference was statistically significant ($p < 0.001$) (see Table 1).

TABLE 1: Patients' Willingness to Participate in Future Trials

Previous Participation in Trials	Willingness to Participate in Future Clinical Trials		Total (N)
	Yes	No	
Participated	149 (87%)	23 (13%)	172 (100%)
Not Participated	77 (59%)	54 (41%)	131 (100%)

Does Disease Category Affect Participation?

Among the patients enrolled in this study, 91% from the diabetes group showed willingness to participate in future trials, followed by 73% of cancer patients, and 64% of those with neuropsychiatry problems (see Table 2). The differences between the oncology and diabetes ($p = 0.004$) and neuropsychiatry and diabetes ($p = 0.0005$) groups were statistically significant, but no significant difference was noted between oncology and neuropsychiatry ($p = 0.189$) (see Table 3).

TABLE 2: Willingness to Participate by Disease Category of Patients

Disease Category	Willingness to Participate in Future Clinical Trials		Total (N)
	Yes	No	
Oncology	139 (73%)	52 (27%)	191
Neuropsychiatry	35 (64%)	20 (36%)	55
Diabetes	52 (91%)	5 (9%)	57

The overall perceived disadvantages of participation in this study were low, with only

3%

of patients citing the risk of experimental drugs and the amount and frequency of blood to be drawn.

Discussion

The results showed that a majority (91.4%) of patients would participate in a clinical trial because they believed that the investigational drug "may cure the disease," indicating some hope of therapeutic response, whereas some were motivated because they were recommended by their physicians, and others were inclined to participate in a trial due to availability of free medication and other investigations.

Nearly 71% of patients were motivated because no alternative therapy was available. For a patient whose illness has progressed on standard therapy and for whom no other established therapy is available, a small chance of therapeutic benefit could be a justification for study entry, as the drug under testing may be the patient's last resort to be cured of the illness.[7-9]

The doctor-patient relationship is a complex one and, culturally, Indian patients depend significantly on the recommendation of their physicians, as seen in this study. Similar results were observed in another study in which patients who placed greater trust in their doctors were more likely to enroll in a clinical trial (65% of those who trusted a family physician highly, and 54% of those who trusted a hospital physician highly).[5,10]

Poverty can be a significant factor influencing trial participation in developing countries. A majority of the economically disadvantaged population in India depends on free or subsidized treatment from government healthcare centers and dispensaries, since not all can afford health insurance. To reduce the possibility of coercion of poor underprivileged patients to join clinical trials, government institutions should be selected in addition to private or semi-private hospitals. As this study did not compare economic status, the effect of economic background of participants in clinical trials should be explored further.

"The desire to help advance related research and potentially help future patients" was quoted by 60.5% patients. Past studies have shown similar results where research participants are often altruistic and enroll in clinical trials mainly hoping the trial will have some underlying therapeutic benefit for them and future patients.[11] Although it remains unknown and speculative what role altruism plays in motivating Indian patients, the present study suggests that altruism may not be the sole motivating factor; self-interest is more important.

Past participants had a higher acceptance rate than trial-naïve participants (87% vs. 59%), since they may have benefited from trial participation and believed that they were treated with "dignity and respect." The reasons given by the respondents were clear improvement in signs and symptoms since participating in a trial, or their condition was "in control" for those with diabetes. Another possible explanation is that patients felt they were "giving something back," helping others by participating.

According to some respondents, patients seemed to receive more individual attention because of trial participation. The clinician was perceived to give more time and to be available to have detailed discussions with them. Patients felt comfortable and more cared for, since there was close monitoring of their condition, with several tests being conducted at regular intervals and several follow-up visits being conducted thereafter, as required by the protocol. The results are reiterated among U.S. respondents, where 82% who had participated in a clinical study said they would participate again.[2,12]

The patients in the diabetes group showed the greatest willingness to participate in future trials, followed by cancer patients, and then those with neuropsychiatry problems, although a majority was in favor in each group. The reason for high participation in the diabetes group may be because diabetes is a chronic disease and the risk with diabetes medications is low. Also, effective collaboration among multiple health providers may be associated with better quality of care, and patient-doctor collaborations may affect diabetes outcomes.

Since diabetes care is self-care, patients manage their own disease by taking medications, dieting, exercising, or engaging in other forms of health-related behavior. With this comfort level, such patients are highly likely to favor trial participation. Reassurance provided by regular clinical examinations and the personal nature of clinical care in diabetes studies has also been a motivator.[13]

Meanwhile, there could be many reasons the rate of participation in cancer trials is much lower than expected. The primary concern is that the mortality rate is high, chances of survival are strongly related to the stage of the disease, early diagnosis is difficult to achieve, and treatment can be complex because it involves several specialties, including surgery, radiotherapy, and chemotherapy, with their primary and side effects.

Other factors that may restrict the number of cancer participants include difficulty in understanding complex protocols, lengthy consent forms, and poor compliance. Cytotoxic drugs—the commonly accepted and tested treatment for most cancers—are highly toxic.

TABLE 3: Willingness to Participate by Therapeutic Area—Statistical Significance

Therapeutic Area	Oncology	Neuropsychiatry	Diabetes
Oncology	—	Not significant	$p = 0.004$
Neuropsychiatry	Not significant	—	$p = 0.0005$
Diabetes	$p = 0.004$	$p = 0.0005$	—

Some cancer patients may decline to participate because of negative perceptions that the treatments are experimental, and therefore inferior to accepted regimens. Likewise, if a physician does not believe that a trial is better than current treatments, then he or she is not likely to recommend participation to the patient.

Finally, the observation that fewer neuropsychiatry patients were agreeable to participation could result from their underlying psychiatric illness. Such patients take time to develop insight into their illness and accept the diagnosis. If the patient has not accepted the diagnosis, he or she is unlikely to enter future trials. For example, patients suffering from schizophrenia may be paranoid, and therefore suspicious when offered a "different" or a "special" treatment. Anxiety is a common feature in many psychiatric conditions, which also could negatively influence a patient's willingness to participate in a trial.

Other Points to Consider

Family support is another critical element of early engagement in outpatient treatment. Many psychiatry and cancer patients may still depend on the resources of their families for housing, money, and transportation. Family members (or caregivers) may work full time or on daily wages, and may not be able to take time off from work to bring patients to study appointments. This could be a significant barrier to enrollment in studies; therefore, both the patients' and families' acceptance of the diagnosis and treatment are critical to participation in research studies.

Past research has shown that patients were less likely to participate in research if someone important to them was against it.[14] In patriarchal or hierarchical societies, male members of the family could positively or negatively influence participation of a female patient in a trial.[15] This highlights that strategies to improve recruitment must address barriers with both patients and their immediate families.

The doctor-patient relationship is a complex one and, culturally, Indian patients depend significantly on the recommendation of their physicians, as seen in this study.

More than half of the patients surveyed understood that risks of participation are minimal and benefits may outweigh the risks. However, different studies have shown different results regarding patients' knowledge and understanding of clinical trials and their inclination to enroll in trials.

Llewellyn-Thomas et al.[15] observed that patients who demonstrated greater knowledge about the trial were less willing to participate in it. This is contradictory to previous research, which suggests that poor understanding of the need for clinical trials and of the manner in which trials are conducted is a significant barrier to participation.[5] Also, Ellis et al.[16] suggested that breast cancer patients with a better understanding of issues about clinical trials have more favorable attitudes toward randomized clinical trials, and are therefore more willing to consider participation. Physicians should spend enough time in discussing drug profiles and anticipated benefits and risks of trial participation during the informed consent discussion and on an ongoing basis.

Further, although consent forms inform patients not to expect to receive a therapeutic benefit, a large proportion of patients continue to perceive health benefits with study participation. Suhadev and colleagues[7] also concluded that potential participants were more likely to participate if they were convinced that the clinical trial would benefit them in terms of good health and protection from or prevention of some disease.

Conclusion

The key motivators to enrollment include the opportunity for treatment, perceived benefits of personal attention, recommendation by one's treating physician, a desire to assist with research and/or to feel connected with the study, and the chance to avail oneself of free medication. Indeed, many Indian patients may participate in trials due to the perceived health benefits associated with participating in them. Similar results have been reported among the U.S. population in the Will & Why Survey[12] in June 2001 and in a Research!America national poll on clinical research in May 2013.[2]

Insight into patients' points of view on trial participation is critical in planning recruitment strategies for clinical studies. So is an understanding of the perceptions of investigators, since they play a significant role in influencing patients' decisions to participate. Patient participation can also be greatly influenced by the underlying disease condition, by experiences from previous participation, and by the recommendation of the treating physician.

Further, the attention provided to patients by investigators and their teams has a positive impact on patients' willingness to participate in research. This study also concluded that patients enrolled in diabetes trials were more willing to participate in future trials than cancer or neuropsychiatric patients.

In summary, a carefully planned design, implementation, and follow-through of sound recruitment strategies may contribute to the success of clinical trials from initiation to close-out.

References

1. *The Bottleneck in Patient Recruitment.* www.isrreports.com/free-resources/the-bottleneck-in-patient-recruitment-2/
2. Zogby Analytics for Research!America (2013). *National Poll: Clinical Research.* www.researchamerica.org/2013clinicaltrialspoll
3. Howard J, DeMets D. BHAT research group. How informed is informed consent? *The BHAT experience. Controlled Clinical Trials* 1981;2:287-303.
4. Mettlin C, Cummings M, Walsh D. Risk factors and behavioral correlates of willingness to participate in cancer preventive trials. *Nutrition Cancer* 1985;7:189-98.
5. Ellis PM, Buttow PN, Simes RJ, Tattersall MH, Dunn SM, MacLeod C. Doctors' participation in breast cancer clinical trials: does it influence their recommendations for standard therapy in breast cancer? *Breast* 1999;8:182-7.
6. Slevin M, Mossman J, Bowling A, Leonard R, Steward W, Harper P, et al. Volunteers or victims: patients' views of randomized clinical trials. *Br J Cancer* 1995;710:1270-4.
7. Suhadev M, Nyamathi AM, Swaninathan S, Venkatesan P, Sakthivale MR, et al. A pilot study on willingness to participate in future preventive HIV vaccine trials. *Indian J Med Res* 2006;124:631-40.
8. Nugrat ZA, Craig W, Campbell NC, Bissett JD, Cassidy J, Nicolson MC. Patient motivations surrounding participation in phase I and phase II clinical trials of cancer chemotherapy. *Br J Cancer* 2005;92:1001-5.
9. Cheng JD, Hitt J, Koczwara B, Shulman KA, Brunette CB, Gaskin DJ, et al. Impact of quality of life on patient expectations regarding phase 1 clinical trials. *J Clin Oncol* 2000;18:421-8.
10. Zullino D, Conus P, Borgeat F, Bonsack C. Readiness to participate in psychiatric research. *Can J Psychiatry* 2003;48:480-4.
11. Patel MX, Doku V, Tennakoon T. Challenges in recruitment of research participants. *Adv Psychiat Treat* 2003;9:229-38.
12. *The Will & Why Survey: Examining America's Motivation to Participate in Clinical Studies.* http://shop.bbkworldwide.com/products/white-paper-examining-americas-motivation-to-participate-in-clinical-studies
13. Lawton J, Fox A, Fox C, Kinmonth L. Participating in the United Kingdom Prospective Diabetes Study (UKPDS): a qualitative study of patients' experiences. *Br J Gen Pract* 2003;53:394-8.
14. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomized controlled trials: a systematic review. *J Clin Epidemiol* 1999;52:1143-56.
15. Llewellyn-Thomas HA, Thiel EC, Sem FW, Woermke DE. Presenting clinical trial information: a comparison of methods. *Patient Educ Couns* 1995;25:97-107.
16. Ellis PM, Butow PN, Tettersall HN, Dunn SM, Houssami N. Randomized clinical trials in oncology: understanding and attitudes predict willingness to participate. *J Clin Oncol* 2001;19(15):3554-61.

Jeroze Dalal, PhD, (jeroze.j.dalal@gsk.com) is head of clinical operations for India and Pakistan at GlaxoSmithKline Pharmaceuticals, Ltd.

Beth D. Harper, MBA

[DOI: 10.14524/CR-15-4054]

Interview with Debra Ayer, MSN, MBA, RN, CCRP

This month we showcase the career of Debra Ayer, a long-time nurse and clinical researcher whose career has spanned more than 30 years.

Q: How did you first become interested in clinical research, and can you describe the path you took to get involved in this field?

A: My nursing career pathway initially started with medical/surgical nursing and critical care nursing. I fell in love with being a dialysis nurse, which afforded me many opportunities over 25 years, including being the director of nursing, in both acute and chronic areas and then as an administrator.

My main office was at a large Miami dialysis unit affiliated with the local Jackson Health System and the University of Miami. Working closely with the university's nephrologists and psychologists, I quickly became involved in their research efforts and helped in presenting poster boards at nephrology conferences.

Each sponsor has added training and required that more members of the clinical research team be trained and maintain documentation of that training.

Q: Can you tell us more about the different roles you've held?

A: I have always had management roles that involved both hands-on patient care and administrative responsibilities, and teaching opportunities. While I was working as a dialysis administrator, I was completing my MSN and MBA in healthcare administration. I was offered a position as a research program manager, and became involved in overseeing nephrology clinical trials. Tied to this, I became certified by the Society of Clinical Research Associates as a CCRP.

Following this position, I became the manager of cardiovascular and cancer research, then the research integrity coordinator at Broward Health Medical Center in Ft. Lauderdale. Through this role, I have helped to grow the program and develop research policies and processes.

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

A: As I love to learn and network, I joined ACRP several years ago. I love attending our local chapter meetings and have attended national meetings. I have benefited from the ACRP webinar trainings. ACRP really supports the researcher in opportunities for learning and sharing.

Q: Since your career has spanned many years, what is the most significant change (or top changes) you have seen? How has this affected the industry, either positively or negatively?

A: Over the last 10 years in clinical research, I think some of the most significant changes include the intensity of how the investigator and team are trained and all of the requirements that surround the training. Each sponsor has added training and required that more members of the clinical research team be trained and maintain documentation of that training. All of this affects the time it takes to open a trial. Also, with the current emphasis on risk-based monitoring, sites must mirror the monitoring requirements of each sponsor and assume an increase of site-level quality and responsibility.

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

A: I believe educating one's self and maintaining a professional approach to one's career is most important. At our hospital site, there were few site-level opportunities for education for the researcher; so I created a quarterly one-hour seminar in my role as research integrity coordinator with the institutional review board (IRB) coordinator. We offer this seminar to researchers following an IRB meeting.

Looking for a pathway to your professional development as a CRC, CRA, or PI? You can find your pathway at www.acrpnet.org/MainMenuCategory/Education/Find-Your-Pathway.aspx

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

A: First, seek opportunities for education that will help you understand the roles and responsibilities of each member of the research team—for example, by attending role-based training for study coordinators and monitors, and by taking investigator and IRB training. Second, try to network and share your ideas with colleagues in the research arenas. Third, ensure that you belong to an organization like ACRP, which can offer you a great deal of support, many educational opportunities, and the chance to build a network of friends and colleagues.

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

A: I have been involved in many areas of nursing; however, research has been one of the most rewarding and interesting parts of my professional career. I am so excited when one of the drugs or devices we were involved with in clinical trials goes to market. I would also encourage anyone interested in research to attend a university now offering programs in clinical research.

Debra, thank you for your contributions to the clinical research team. You practice what you preach by continuously pursuing educational advancement for yourself and promoting educational opportunities for your staff and colleagues.

Beth D. Harper, MBA, (bharper@clinicalperformancepartners.com) is the president of Clinical Performance Partners, Inc.

Current Status and Future of Cannabis Research

PEER REVIEWED | Ethan B. Russo, MD
Alice P. Mead, JD, LLM | Dustin Sulak, DO
[DOI:10.14524/CR-15-0004]

Although cannabis is primarily viewed by the public as a recreational drug or agent of abuse, its medical application spans recorded history.[1,2] Evolution has yielded a cannabis plant that produces a family of some 100 chemicals called phytocannabinoids ("plant cannabinoids"), many of which have distinct and valuable therapeutic effects.[3,4]

Cannabis is a versatile herb that can produce a variety of medicinal preparations with distinct pharmacologic properties, depending on the content of cannabinoids and other phytochemicals, many of which possess synergistic effects.[4] The best known plant cannabinoid is tetrahydrocannabinol (THC), the primary psychoactive agent in cannabis, responsible for the preponderance of the cannabis "high"; however, it is also a powerful analgesic,[5] muscle relaxant,[6] and antinausea agent,[7] among myriad other effects. Coming to greater recognition is its analogue sister, cannabidiol (CBD), which distinguishes itself by its lack of intoxication and its ability to complement the pain relief, antiemetic, anticonvulsant,[8] and other benefits of THC, while modulating and attenuating its associated side effects (anxiety, tachycardia, et al.).[4,9–13]

Cannabis is a versatile herb that can produce a variety of medicinal preparations with distinct pharmacologic properties.

To gain regulatory approval of a cannabis-based product, pursuing the dietary supplement/botanical path—as opposed to the pharmaceutical one—may be an option for certain preparations. Dietary supplements rarely contain substances with abuse potential, and manufacturers and vendors of such products can make only "structure and function" claims (e.g., "promotes heart health"), rather than medical claims. Therefore, it is probably unlikely that cannabis preparations with a notable amount of THC could be treated as dietary supplements. However, nonpsychoactive cannabinoids, such as CBD could be descheduled (i.e., removed from the federal Controlled Substances Act [CSA]) and developed and marketed as botanical supplements.

Cannabis exerts its effects through a variety of receptor and nonreceptor mechanisms. All vertebrates tested to date harbor an endogenous cannabinoid system (ECS),[14] a regulator of physiological homeostasis whose function has been summarized as "relax, eat, sleep, forget, and protect."[15] The ECS has three components: endocannabinoids, biosynthetic and catabolic enzymes, and two cannabinoid receptors—CB1, the "psychoactive" neuromodulator that is the most abundant G-protein coupled receptor in the brain, and CB2, a nonpsychoactive immunomodulatory and anti-inflammatory receptor most abundant in the periphery.[14,16]

Although various surveys support the idea that the American public already accepts the medical utility of cannabis and is acting upon that belief in ever higher numbers, the U.S. Food and Drug Administration (FDA) requires more rigorous proof. Additionally, a survey of Colorado family physicians found that; "Despite a high prevalence of use in Colorado, most family physicians are not convinced of marijuana's health benefits and believe its use carries risks. Nearly all agreed on the need for further medical education about medical marijuana."[17]

If cannabis-based medicines are to overcome prejudice and gain greater trust from physicians, their production must be standardized and their contents proven safe and efficacious in randomized clinical trials (RCTs) that follow accepted scientific method and are the *sine qua non* of regulatory bodies such as the FDA[18] However, botanical cannabis is highly inconsistent and variable in its chemical composition.

Procedures for standardization of plant-based medicines have been formally presented in the U.S., providing an FDA blueprint for their regulatory approval in the "Guidance for Industry: Botanical Drug Products."[19] Meanwhile, although cannabis smoking may not be epidemiologically linked to lung cancer,[20] it is responsible for chronic cough, sputum, and cytological changes,[21,22] which render smoked cannabis an impossible candidate for approval as a prescription product in most jurisdictions.

Anecdotal claims for efficacy of crude cannabis hold no sway for the FDA.[18] There is a relative paucity of published RCT data for inhaled cannabis: the existing trials for pain total only three patient-years of data, whereas the corresponding figure for nabiximols (Sativex®, GW Pharmaceuticals), a standardized oromucosal extract spray combining THC, CBD, and other cannabis components, exceeds 6,000 patient-years of data in published studies of pain, or a two thousand-fold difference.[5] The latter is also approved in 26 countries for treatment of spasticity in multiple sclerosis, and is currently completing clinical trials for opioid-resistant cancer pain in the U.S. and elsewhere.[23–25] This agent has fulfilled criteria of safety and consistency, and has not been abused or diverted to any degree in more than 30,000 patient-years of recorded usage.

Regulatory Challenges and Solutions

The FDA has responsibility for assessing human research and evaluating data from clinical studies. Such research is initiated by an individual researcher in an investigator-initiated trial (IIT) or by a pharmaceutical company. In both situations, an Investigational New Drug (IND) application containing one or more protocols must be presented to, and allowed by, the FDA.[26]

For industry-sponsored programs, the FDA requires a range of nonclinical/preclinical studies and then clinical trials to demonstrate that the product meets the FDA's exacting standards of quality, safety, and efficacy in a particular patient population.

The FDA has clarified that it will allow both IITs and RCT development programs with cannabis or cannabis-derived products. Examples of such IITs have been completed and published.[27,28] An industry-sponsored development program is also progressing with a cannabis-derived product.[29] Finally, FDA has promulgated "expanded access" regulations in the *Code of Federal Regulations* in 21 CFR sections 312.310, 312.315, and 312.320, allowing seriously ill patients who lack conventional treatment options and clinical trial opportunities to be treated with an investigational product on a compassionate access basis. More than 300 children

The FDA has clarified that it will allow both IITs and RCT development programs with cannabis or cannabis-derived products.

with various types of medication-resistant epilepsies have been allowed by FDA to receive treatment with a cannabis-derived (but purified) CBD product under such expanded access programs.[30]

Studies involving herbal cannabis must obtain the material from the National Institute on Drug Abuse (NIDA), which is the sole federally lawful source of research-grade cannabis. NIDA has contracted with the University of Mississippi to grow cannabis (of various cannabinoid ratios and potencies) for research.[31,32]

FDA has approved at least two products based on botanical extracts; however, FDA has not previously approved any raw botanical/herbal material as a prescription medicine. Such material would face regulatory challenges, such as achieving adequate purity, displaying batch-to-batch standardization, and identifying an appropriate method of delivery (i.e., one that would supply a precise and reproducible dose without the production of toxic by-products).

Cannabis, THC, and products containing botanically or synthetically derived cannabinoids found in the cannabis plant are classified under Schedule I of the federal CSA. The CSA contains five schedules corresponding to a substance's abuse potential and medical usefulness.

Schedule I and II substances are subject to strict security, recordkeeping, and other measures. Substances in Schedule I have "no currently accepted medical use in the U.S." and a high potential for abuse. Substances in Schedule II also have a high potential for abuse, but have an "accepted medical use," a phrase given specific meaning by the federal Drug Enforcement Administration (DEA) and upheld by federal courts:

1. The drug's chemistry must be known and reproducible;
2. There must be adequate safety studies;
3. There must be adequate and well-controlled studies proving efficacy;
4. The drug must be accepted by qualified experts; and
5. The scientific evidence must be widely available.[33]

If FDA approves a cannabis-derived product, such approval constitutes "accepted medical use," and that product will then be moved to a less stringent schedule. Although a substance and a product containing that substance are in the same schedule, "differential" scheduling is possible. For example, Marinol, a product comprising synthetic THC in sesame oil, is classified in Schedule III, whereas other forms of THC remain in Schedule I.[34] This may serve as precedent if a cannabis-derived product is FDA approved and rescheduled, although cannabis may remain in Schedule I.

Cannabis's (and THC's) Schedule I status means there are additional hurdles to overcome to conduct research in the U.S. As provided in 21 CFR section 1301.13, a physician who holds a DEA registration (license) to prescribe controlled substances in Schedules II–V may conduct research within those schedules as a "coincident activity" to his or her existing registration, with no further approval from the DEA.

However, to conduct research with a Schedule I substance, an investigator must secure a Schedule I research registration from DEA (which is substance- and protocol-specific), and (often) a Schedule I research license from the state-controlled drugs agency. These additional steps can add three to six months to the time required before an investigator can begin the research project.

A specific medical product cannot be prescribed by physicians and dispensed by pharmacists unless the FDA has approved that product (the "compounding pharmacy" exception is very limited). Therefore, even if cannabis were moved to Schedule II, physicians could not automatically prescribe it directly to patients. Although the NIDA single-source supply is the only domestic source, cannabis-derived products may be manufactured in Europe or elsewhere, and the finished product may be imported into the U.S. for research or ultimately for commercial distribution following FDA approval.[35]

Current Status of Clinical Cannabinoid Medicine

Due to the obstacles involved in human clinical research using cannabis, widespread use in the clinical setting has preceded well-established data on dosage, delivery systems, safety, and efficacy. In states that have legalized medical cannabis, about 0.77% of the population use cannabis with the recommendation of a medical provider.[36]

Although various surveys support the idea that the American public already accepts the medical utility of cannabis and is acting upon that belief in ever higher numbers, the U.S. Food and Drug Administration (FDA) requires more rigorous proof.

Cannabinoids are considered nonlethal and have a wide range of effective and tolerated dosages. Many patients use medical cannabis in a harm-reduction paradigm to decrease or discontinue the use of prescribed and illicit substances.[37] Also, the growing number of medical providers accepting cannabis as a viable treatment option[38] may attest to observed or suspected clinical efficacy. Meanwhile, observational studies can inform the emerging clinical practice of cannabinoid medicine, while guiding the development of clinical experimental design.[39]

One of this article's authors has observed clinical responses in his patient population in oral doses beginning as low as 0.1 mg cannabinoids/kg body weight/day, whereas some find optimal benefits at doses as high as 25 mg/kg/day. This wide dosing range is complicated by a biphasic dose-response curve, where lower doses may exhibit greater efficacy and tolerability than higher doses, as seen in a clinical trial of nabiximols for poorly controlled chronic pain in opioid-treated cancer patients.[24]

Another clinical trial of inhaled cannabis for neuropathic pain found low-potency (3.5% THC) and high-potency (7% THC) cannabis to have equivalent analgesic properties.[27] Biphasic dose-response effects may be due to subjects' sensitization to cannabinoids at lower doses and tolerance building at higher doses. This hypothesis is supported by preclinical studies in which administration of exogenous cannabinoids both upregulate endocannabinoid system function at acute and lower doses via increased endocannabinoid production,[40] cannabinoid receptor expression,[41] and cannabinoid receptor affinity,[42] and downregulate endocannabinoid system function upon persistent agonism via membrane receptor endosome internalization.[43]

Bidirectional effects are often related to dosage,[44,45] with high doses of cannabinoids potentially causing symptoms usually ameliorated by lower dosages. The mindset of the cannabis user and setting in which the cannabis use takes place also influence bidirectional effects; anxious subjects tend to become less anxious and more euphoric, nonanxious individuals tend to become somewhat more anxious,[46] and stressful environments can precipitate adverse emotional responses.[47]

Polymorphisms have been associated with variable responses to cannabis, including protective effects on development of cannabis dependence in adolescents,[48] intensity of withdrawal and craving during cannabis abstinence,[49] and white matter volume deficits and cognitive impairments in schizophrenic heavy cannabis users.[50]

Cannabis use history also complicates clinical response, with cannabis-naïve patients demonstrating more frequent adverse effects[51] and regular users demonstrating less psychotomimetic, perceptual altering, amnestic, and endocrine effects.[52]

Another factor to note is that physicians often lack training in using botanical medicines, and endocannabinoid physiology is still absent from most medical school curricula. Many legal cannabis patients receive permission to use cannabis from their physician, but must rely on formula selection and dosing instructions provided by cannabis growers or dispensary staff with little training or experience.

Properly interpreting observational data on medical cannabis patients requires an understanding of the chemical composition and potency of the cannabis preparations used, and of the pharmacokinetics of the delivery system employed. Laboratories offering third-party chemical analysis of herbal cannabis preparations under industry-published standards[53] can be found in most states that allow the use of medical cannabis.[54]

Due to the obstacles involved in human clinical research using cannabis, widespread use in the clinical setting has preceded well-established data on dosage, delivery systems, safety, and efficacy.

Conclusion

The endocannabinoid system regulates physiologic homeostasis and is an exciting target for disease management and health promotion. Cannabis-based preparations are poised to become an accepted option in mainstream medicine, with broad support from preclinical models, patient testimonials, and more recently, human clinical trials.

However, numerous regulatory, botanical, and pharmacologic factors challenge the collection and interpretation of clinical data on the efficacy of cannabinoid therapies. The understanding of an individual's optimal dosing and delivery method of cannabinoids for various ailments is still emerging, and must be guided by both observational and experimental data.

Clinical researchers can overcome the challenges inherent in cannabinoid therapeutics and help elucidate solutions for a wide variety of prevalent health challenges.

Acknowledgments

The authors would like to express sincere thanks to Tyler Strause, Brendon Strause, and Linda Strause, PhD, for their excellent support and review in preparing this article.

Studies involving herbal cannabis must obtain the material from the National Institute on Drug Abuse (NIDA), which is the sole federally lawful source of research-grade cannabis.

References

1. Russo E. History of cannabis and its preparations in saga, science and sobriquet. *Chem Biodiversity* 2007;4(8):2624-48.
2. Russo E. The pharmacological history of cannabis. In Pertwee R, ed. *Handbook of Cannabinoids*. Oxford, UK: Oxford University Press, 2014.
3. Izzo A, et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* 2009;30(10):515-27. [doi: S0165-6147(09)00128-X [pii] 10.1016/j.tips.2009.07.006]
4. Russo E. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol* 2011;163 (7):1344-64. [doi:10.1111/j.1476-5381.2011.01238.x]
5. Russo E, Hohmann A. Role of cannabinoids in pain management. In Deer T, Gordin V, eds. *Comprehensive Treatment of Chronic Pain by Medical, Interventional and Behavioral Approaches*. New York: Springer, 2013, pp181-197.
6. Novotna A, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011;18(9):1122-31.
7. Duran M, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 2011;70(5):656-63.
8. Devinsky O, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia* 2014;55(6):791-802.
9. Russo E, Guy G. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66(2): 234-46.
10. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol* no. 2008;153(2):199-215.
11. Morgan C, Curran H. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry* 2008;192(4):306-7.
12. Morgan C, et al. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacol* 2010;35(9):1879-85.
13. Morgan C, et al. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. *Br J Psychiatry 20*10;197(4):285-90.
14. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 2006;58(3):389-462.
15. Di Marzo V, et al. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci* 1998;21(12):521-8.
16. Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Prog Lipid Res* 2011.
17. Kondrad E, Reid A. Colorado family physicians' attitudes toward medical marijuana. *J Am Bd Fam Med* 52-60.
18. Russo E. The solution to the medicinal cannabis problem. In Schatman ME, ed. *Ethical Issues in Chronic Pain Management*. Boca Raton, Fla.: Taylor & Francis, 2006, pp 165-94.
19. Center for Drug Evaluation and Research (CDER), Office of Training and Communications, Division of Drug Information (HFD-240). Guidance for Industry—Botanical Drug Products. www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm070491.pdf
20. Hashibe M, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2006;15(10):1829-34.
21. Tashkin D. Effects of marijuana smoking on the lung. *Ann Am Thorac Soc* 2013;10 (3):239-47.
22. Tashkin D. Smoked marijuana as a cause of lung injury. *Monaldi Arch Chest Dis* 2005;63(2):93-100.
23. Johnson J, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-79.
24. Johnson J, et al. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage* 2012.
25. Portenoy R, et al. Nabiximols for opioid-treated cancer patients with poorly controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain* 2012;13(5):438-49.
26. U.S. Food and Drug Administration (FDA). Guidance for Industry: Investigations New Drug Applications (INDs)—Determining Whether Human Research Studies Can be Conducted Without an IND. September 2013. www.fda.gov/downloads/Drugs/Guidances/UCM229175.pdf
27. Abrams D, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 2003;139(4):258-66.
28. Wilsey B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9(6):506-21.
29. GW Pharmaceuticals. GW Pharmaceuticals commences Phase 2/3 clinical trial of epidiolex as a potential treatment for epilepsy in Dravet syndrome. October 30, 2014. www.gwpharm.com/
30. Throckmorton D. Mixed Signals: The Administration's Policy on Marijuana—Part Four—the Health Effects and Science. Before the Subcommittee on Government Operations Committee on Oversight and Government Reform, U.S. House of Representatives, June 20, 2014. http://oversight.house.gov/hearing/mixed-signals-administrations-policy-marijuana-part-four-health-effects-science/
31. FDA. FDA and marijuana.2014. www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm
32. FDA. FDA and marijuana: questions and answers. 2014. www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm
33. Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131 (D.C.Cir. 1994).
34. Department of Justice (DOJ), Drug Enforcement Administration. Schedules of Controlled Substances: Rescheduling of the Food and Drug Administration Approved Product Containing Synthetic Dronabinol [(-)- Δ9-(trans)-Tetrahydrocannabinol] in Sesame Oil and Encapsulated in Soft Gelatin Capsules from Schedule II to Schedule III. 64 *Fed. Reg.* 35928 (July 2, 1999).

35. DOJ, Drug Enforcement Administration. Importer of Controlled Substances; Notice of Registration; Catalent CTS, LLC, 78 *Fed. Reg.* 69131 (November 18, 2013).
36. ProCon.org, Number of Legal Medical Marijuana Patients (as of October 27, 2014). http://medicalmarijuana.procon.org/view.resource.php?resourceID=005889. Accessed January 7, 2015.
37. Reiman A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduction J* 2009;6(1):35.
38. Adler J, Colbert J. Medicinal use of marijuana—polling results. *N Eng J Med* 2013;368(22):866-8.
39. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312(7040):1215-8.
40. Burstein S, Hunter S. Stimulation of anandamide biosynthesis in N-18TG2 neuroblastoma cells by δ9-tetrahydrocannabinol (THC). *Biochem Pharmacol* 1995;49(6):855-8.
41. Cichewicz D, Haller V, Welch S. Changes in opioid and cannabinoid receptor protein following short-term combination treatment with Δ9-tetrahydrocannabinol and morphine. *J Pharmacol Exper Ther* 2001;297(1):121-7.
42. Oviedo A, Glowa J, Herkenham M. Chronic cannabinoid administration alters cannabinoid receptor binding in rat brain: a quantitative autoradiographic study. *Brain Res*1993;616(1):293-302.
43. Hsieh C, et al. Internalization and recycling of the CB1 cannabinoid receptor. *J Neurochem* 1999;73(2)493-501.
44. Leweke F, Koethe D. Cannabis and psychiatric disorders: it is not only addiction. *Addiction Biol* 2008;13(2):264-75.
45. Hollister L. Health aspects of cannabis. *Pharmacol Rev* 1986;38(1):1-20.
46. Abel E. Changes in anxiety feelings following marihuana smoking. *Br J Addiction Alc Other Drugs* 1971;66(3):185-7.
47. Gregg J, et al. Emotional response to intravenous delta9tetrahydro cannabinol during oral surgery. *J Oral Surg* 1976;34(4):301-13.
48. Hopfer C, et al. Cannabis receptor haplotype associated with fewer cannabis dependence symptoms in adolescents. *Am J Med Genet Part B: Neuropsych Genet* 2006;141(8):895-901.
49. Haughey H, et al. Marijuana withdrawal and craving: influence of the cannabinoid receptor 1 (CNR1) and fatty acid amide hydrolase (FAAH) genes. *Addiction* 2008;103(10):1678-86.
50. Ho B, et al. Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. *Schizophrenia Res* 2011;128(1):66-75.
51. Hall W, Pacula R. *Cannabis Use and dependence: Public Health and Public Policy.* Cambridge University Press, 2003.
52. D'Souza D, et al. Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacol* 2008;33(10):2505-16.
53. American Herbal Pharmacopeia. Cannabis inflorescence. In Upton R, Dayu RH, Craker L, ElSohly M, Romm A, Russo E, Sexton M, eds. *Standards of Identity, Analysis, and Quality Control.* Scott's Valley, Calif., 2013.
54. Halford B. Chemists analyze cannabis for safety and potency. *Chem Eng News* 2013;91(49):32-3.

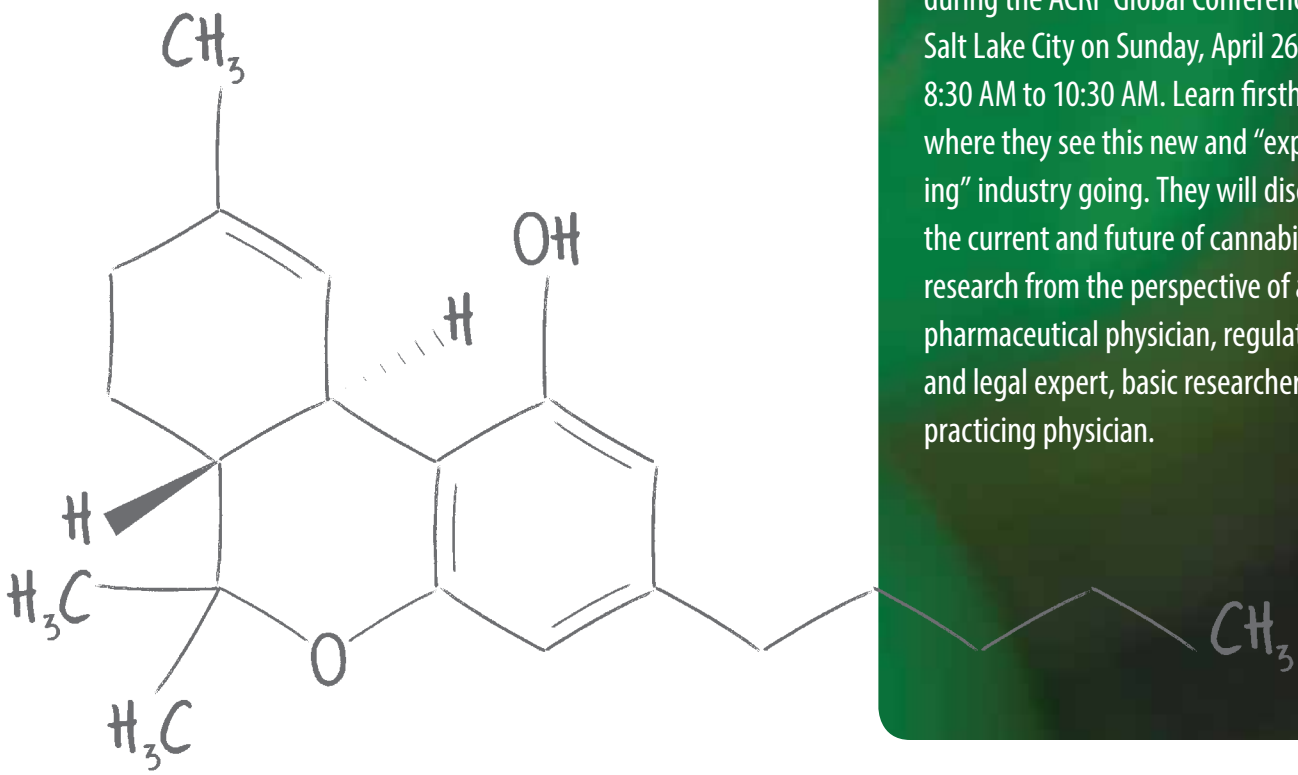
Ethan B. Russo, MD, (erusso@phytecs.com) is medical director of PHYTECS and past president of the International Cannabinoid Research Society.

Alice P. Mead, JD, LLM, is vice president, U.S. Professional Relations, GW Pharmaceuticals.

Dustin Sulak, DO, (drsulak@gmail.com) is founder and medical director of Integr8 Health, Falmouth, Maine.

Clear the Mud: Current and Future of Cannabis Research.

The authors of this article will be joined by Sean McAllister, PhD, to speak at a two-hour session presented during the ACRP Global Conference in Salt Lake City on Sunday, April 26 from 8:30 AM to 10:30 AM. Learn firsthand where they see this new and "exploding" industry going. They will discuss the current and future of cannabis research from the perspective of a pharmaceutical physician, regulatory and legal expert, basic researcher, and practicing physician.



KELLY® scientific resources

land the job you deserve

As the world's leading scientific and clinical research staffing provider, Kelly® offers opportunities to work on today's most challenging, research-intensive, and relevant projects. You'll get access to some of the world's highest-regarded scientific organizations—in pharmaceutical, medical device, biotechnology, clinical research, site management, and academia.

Our connections can lead you to innovative scientific pursuits you'll be proud to help advance. We work with 97 of the *Fortune* 100™ companies, and we found opportunities for more than 11,000 scientific professionals last year.

Talk to us about opportunities in:

- Clinical research (in-house and field-based)
- Data management
- U.S. and international regulatory affairs
- Biostatistics and analysis
- Drug safety
- Medical writing
- Project management
- GCP audit and quality assurance
- Clinical operations and support
- Project life cycle

"Working with Kelly has allowed me to engage in multiple clinical research projects for a variety of pharmaceutical and biotechnology companies. I often refer colleagues to Kelly, due to the exceptional experiences I have had with projects and my recruiter."

—Tasha K., BSN, RN, Safety Scientist, Medical Writer

Stop by **Booth 710** at the ACRP Global Conference to talk to a representative and to drop off your résumé.
Or, email your résumé to **scientific@kellyservices.com** today.

kellyservices.us/sciencecareers

Assessing a Site's Ability to Coordinate a Multicenter Study: *A Project Manager's Perspective*

PEER REVIEWED
Dionne Bobb, MPH, MS, CCRC
[DOI: 10.14524/CR-14-0025]

The coordinating center (or lead site) is responsible for the overall conduct of a clinical study, inclusive of management of external sites and all study data. The coordinating center described in this article is also enrolling patients in the multicenter study at hand.

The leadership of the coordinating center of a multicenter study has important responsibilities, including being answerable to the project's funding source and for the conduct of the other institutions participating in the project. Thus, the site must assess its ability to properly manage all the details involved before nominating or declaring itself to be the coordinating site for a multicenter study. Simultaneously, the coordinating center should review the study's objective(s) and confirm that they are in agreement with the study objectives.

This article summarizes the steps involved in assessing a center's ability to be the coordinating site for a multicenter study. In addition, it suggests items that the site must review as part of this process, which include, but are not limited to:

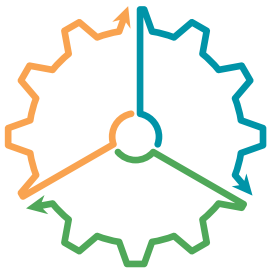
- determining the time that can be dedicated to managing the sites;
- understanding the skillset needed to manage external sites;
- determining if any gaps must be filled on the lead team; and
- deciding which sites are the best fit for the project, given its scientific and recruitment goals.

The *Code of Federal Regulations* (e.g., CFR Title 21 and CFR 42 Subchapter D, 45)[1] and the International Conference on Harmonization's guideline for Good Clinical Practice (ICH GCP)[2] are some of the resources a coordinating center can use to determine the responsibilities associated with study management and assess its capacity to do the necessary work. The overall assessment will involve a minor time commitment; however, appropriate management will enable the study teams at all sites to concentrate on reaching the study's scientific goals.

ADMINISTRATIVE CAPACITY AND SITE MANAGEMENT

A large component of any research study is its administration. Therefore, when a multicenter study is coordinated by a site (as opposed to a pharmaceutical company or a contract research organization) the site must weigh its ability to absorb the administrative needs involved in coordinating the study. As part of this process, the site should determine if the existing staff have the time (person hours) to perform the tasks associated with the project and with managing other sites.

A range of responsibilities is included with the coordination and management of a multicenter study. Some of the important areas requiring close management, with a brief description of the general responsibilities, follow.



Regulatory and Document Management

The key component of regulatory management ensures that all of the needed documentation is in place to conduct the study. This includes, but is not limited to, ensuring all paperwork has been filed with and approved by the study's sponsor and all applicable institutional review boards (IRBs) and regulatory agencies (U.S. Food and Drug Administration [FDA], European Medicines Agency, Medicines and Healthcare Products Regulatory Agency, etc.). Educational training must be completed (ICH GCP Sections 4 and 5). In addition, the standard operating procedures and protocol must be updated to reflect changes in the conduct of the study or scope of work; the updates must be sent to all study sites, and all study-related documents must be filed in the study's master regulatory file.

Cost Analysis and Financial Management

The coordinating center should perform a cost analysis to determine if it (and its parent institution) can absorb the cost of coordinating a multicenter study, and to give external sites a sense of what costs may be incurred as a result of participating in the study. Even a study involving only data collection may need to budget for investigator and coordinator time and IRB fees.

The coordinating site manages the finances of the study. Before the study begins, all the contracts must be in place (ICH GCP 5.9). Once the study begins, the coordinating center must ensure that the funds are distributed under the contract terms as any agreed-upon milestones are achieved. The coordinating center can decide if sites must send an invoice or if funds are paid upon confirmation of a clean dataset. Regardless, this must be done in a timely manner, since most sites need the funds to offset the costs associated with their research operations.

Study Communication

The FDA requires study sites be kept informed of any changes related to the study drug (21 CFR 312.55). Even if a project is not under the FDA's authority, it is best practice to keep sites informed about the overall progress of the study. The information must be transmitted to the sites in a timely manner, particularly when documents require regulatory review and/or approval. It is therefore important to assess what communication method best fits a project.

This assessment stage must consider:

- Which team members will communicate information?
- What resources are available at the lead site for communication? (e.g., video-conferencing capabilities, high-speed Internet)
- The communication culture beyond the coordinating site's institution

Understanding the communication culture of all sites on a study will help to ensure optimal transfer of information. For example, at the coordinating site, all individuals may have access to mobile devices throughout the workday; however, sites in remote areas may not have such capabilities. This limitation would be an important factor in determining the communication style for the project.

Recruitment

Managing recruitment for a multicenter study is a challenging process that includes selecting the proper sites (see the "Selecting Sites to Meet Recruitment Goals" section of this article) and ensuring that sites are enrolling patients who meet the inclusion criteria and sending the needed data (see "Data Management" below). As part of this process, the coordinating center should keep sites informed about overall patient enrollment, the sites' individual levels of progress, and confirmation that a site's enrollment is in line with expectations.

If there are recruitment challenges at individual sites, the coordinating center should meet with staff at the underperforming site to discuss possible ways to increase recruitment (e.g., adding additional investigators or advertising for patients, if applicable). If all efforts fail, the coordinating center may need to close the site and recruit new sites to help reach the overall enrollment goal.

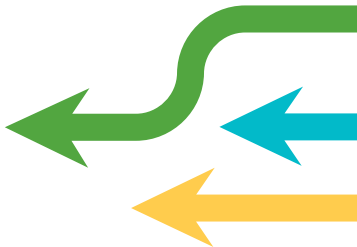
Data Management

Clean and complete study data will help the study team to determine if the study proved its hypothesis. As part of the study preparation process, the coordinating site should determine how it will verify that the data collected are correct. To verify the data, sites may perform routine onsite monitoring (ICH GCP 5.18). However, if onsite monitoring is not feasible due to personnel or budgetary constraints, the coordinating center may ask that de-identified copies of the source documents be sent for comparison.

In addition, the lead site should evaluate if it can protect the data in a manner to ensure participant privacy and if its staff members have the appropriate data management software and statistical skillset for handling the data. For example, if the study calls for collection of qualitative data, the project needs a statistical team able to analyze that data, as well as the quantitative data.

The tasks discussed in each area can be assigned to one team member or several, depending on the number of sites and the complexity of

The site must assess its ability to properly manage all the details involved before nominating or declaring itself to be the coordinating site for a multicenter study.



the protocol and budget structure. More complicated studies will require management in additional areas.

To determine if the existing staff can absorb the administrative needs associated with the study, a list of the responsibilities associated with each management area should be created and the number of hours associated with completing each task should be estimated. Assessing person hours should be a simple approximation, and should not take too much additional time. The reason for this is twofold: First, everyone's skill level varies, so an approximation will suffice. Second, once the study begins, the time it takes for the tasks will vary based on a variety of factors, including learning curve and competing and shifting priorities. Thus, minor adjustments will be made to the estimated number of person hours during the study.

SKILL SET AND INFRASTRUCTURE ASSESSMENT

Two areas that are integral to the success of a study are the lead team's skillset and the institution's infrastructure. These will vary from study to study, but a simple analysis can determine if the project has what is needed.

Site leaders should create two assignment tables: a study assignment table and a project assignment table. The study table should contain every item that must be completed for the scientific aspect of the research study (see Table 1). The project table should contain all of the items needed to support the conduct of the study. These are typically administrative and/or technical in nature (see Table 2).

Once the two tables are completed, site leaders may assign roles to the existing staff and institutional teams/departments. Wherever there is a gap (due to the lack of existing skillset or infrastructure), the lead site should determine if it is feasible to train someone for the needed role, if it is necessary to outsource it, or if an inability to fulfill this task means that the study cannot be conducted at this site.

Deciding to outsource any aspect of the project has varying implications; the coordinating center may not have to find someone to perform the assignment, but it will have to manage the vendor/team/consultant assigned the role. Therefore, outsourcing will also involve a time commitment to ensure that the vendor is meeting milestones, responding to site and sponsor needs, and being paid in a timely manner.

TABLE 1: Sample Study Table*

Protocol Tasks	Task Assigned to an In-House Team	Task Outsourced	Person/Team Completing the Task
Screening	√		Study Coordinator 1 and 2/ Investigator(s)
Advertisement for study patients		√	Media Center for Patient Advertisement
Recruitment		√	Center for Patient Recruitment
Consenting	√		Principal Investigator; Study Coordinator 1 and 2
Pre-study assessment	√		Study Coordinator 1 and 2
Intra-study assessments	√		Study Coordinator 1 and 2
Study follow-up visits	√		Study Coordinator 1 and 2
Adverse event reporting	√		Regulatory Coordinator
Discharging the patient from the study	√		Principal Investigator

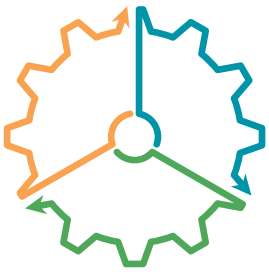
**This is a sample study table of a fictional study. A real study would detail each assessment.*

TABLE 2: Sample Project Table*

Financial and Contractual Management*	Task Assigned to an In-House Team	Task Outsourced	Person/Team Completing the Task
Develop budget	√		Financial Manager 1
Negotiate budget	√		Financial Manager 1
Review and negotiate contract language		√	Contract Review Company
Sign contract	√		Principal Investigator
Manage budget	√		Financial Manager 1
Review and approve invoices	√		Study Coordinator 1
Pay external sites	√		Finance Payment Coordinator
Track expenditures	√		Study Coordinator 1
Financial progress reports		√	Progress Report Company

** Only one of the four major project areas is highlighted in this table.*

The coordinating center should perform a cost analysis to determine if it (and its parent institution) can absorb the cost of coordinating a multicenter study, and to give external sites a sense of what costs may be incurred as a result of participating in the study.



SELECTING SITES TO MEET RECRUITMENT GOALS

Selecting a site to be part of a multicenter project is an intricate process. According to ICH GCP, several factors must be evaluated before an investigator and his/her site may participate in a study. For example, when selecting a site, one must consider its demonstrated ability to recruit subjects who meet the project's recruitment goals and its available resources for supporting the project (ICH GCP 4.2.1, 4.2.2, 4.2.3).

One method of selection is to send a survey to potential sites. Various websites allow users to create free surveys, though a fee may be required to analyze the data and easily compare results across sites.

The survey questions will be determined by the study design and, to some extent, the population of the study participants. The following generic questions should be included:

- How many studies are ongoing at the site?
- Does the site have any competing studies that may affect its ability to recruit?
- How many full-time and part-time coordinators will be assigned to this project?
- Are coordinators already hired? If not, will they be hired in time for study startup?
- If only one coordinator is on site, is there anyone who can assist if he/she is unavailable?
- Does the site provide GCP/human subjects protection training for the clinical research team?
- How many subjects at the site are expected to meet the study inclusion criteria every week?
- What percentage of the eligible participants is likely to participate in this study?
- Would participants expect compensation for participation?

Another consideration is that many communities are increasingly diverse, particularly regarding language. If project leaders anticipate enrolling many non–English-speaking participants, the survey should ask questions that will assess a site's ability to recruit study participants in a manner that enables them to actively engage in the full research experience. Important questions to ask are:

- Are there members of the study team who speak language X?
- If not, how will team members communicate with the study participants?

At some sites, non-study team members will be used for this purpose. However, if a potential site's communication plan for non–English-speaking participants involves the use of non-study team members, then the coordinating center should determine:

- How quickly can the individual be available for translation and explanation?
- How much time can the person devote to the project?
- Will the individual be given an overview of the study prior to translating?
- Does the translator have a positive or negative bias toward the study?

Engaging in this process is one step in determining which centers would be eligible for the study.

DATA STORAGE

GCP dictates that study records be kept for at least two years after a product is granted its last marketing approval in an ICH region, or until there are no pending marketing applications in an ICH region (ICH GCP 4.9.5). The sponsor may require the records be kept longer than the ICH or other regulator recommendation. The coordinating center should ensure that the sites have the resources needed to maintain the documents for the recommended timeframe by assessing well in advance what should be done with any study data (case report forms, etc.) after the study is complete.

Onsite options for storage may be limited. For example, if the coordinating center needs a site to store 10 surveys of one page each for a year, it may not be much of a problem; however, storing 2,000 surveys of 20 pages each for 10 years may be more of an issue. Various onsite and offsite storage options may be available, including the chance that a sponsor will provide funding for offsite storage or for document scanning.

CONCLUSION

Although it may seem that being the coordinating center is an exciting undertaking, it should be done only if leadership at the lead site firmly believes in taking on the responsibilities of—and the metrics support for—this role. The ultimate success of the study itself will depend on many factors beyond the scope of this article.

The process proposed here aims to help sites evaluate what would be required of a site interested in coordinating a multicenter study. Conducting this evaluation beforehand should enable the site to determine the management requirements before initiation of the study, thus decreasing the chance of administrative issues hindering the progress of the project once it has begun.

References

1. *Code of Federal Regulations*. Accessed July 1, 2014. www.ecfr.gov
2. International Conference on Harmonization. ICH GCP (E6). http://ichgcp.net/

Dionne Bobb, MPH, MS, CCRC, (dabee002@gmail.com) is an independent consultant who has worked in a variety of roles, including as a research coordinator and data manager, and most recently as a project manager on multicenter studies.

Jeff Kingsley, DO, MBA, MS, CPI, FAAFP

[DOI: 10.14524/CR-15-4061]

Placing the Patient **Front and Center**

In a March 2000 *Family Practice Management* article from Peter Teichman,[1] I first found a system to substantiate what I felt in my heart to be the ideal physician-patient relationship. The article was titled "Documentation Tips for Reducing Malpractice Risk," but its stated goal was a secondary gain in my eyes compared to the primary benefit of a patient-centric medical practice paradigm with placement of the patient at the forefront of his or her care.

My job is not to coerce or cajole my patients, or to tell them what to do. My job is to teach and guide them in the best way I can.

Physicians are familiar with the typical progress note style called "SOAP"—Subjective, Objective, Assessment, Plan; however, the gist of the Teichman manuscript is to change SOAP to SOOOAAP—Subjective, Objective, Opinion, Options, Advice, Agreed Plan. Awesome! Short though it may be, I never forgot this article, and I encourage you to look it up yourself.

When the deadline for submitting a column for this issue of *Clinical Researcher* arrived with a theme of patient centricity in research, I knew instantly that I would write about SOOOAAP.

I am not a god. I'm a doctor. I have no right to tell my patients what to do, but I am highly educated and have far more knowledge of the human body and its pathophysiology compared to most of my patients. So how can I reconcile these two facts? Simple. I can be a teacher. My job is to teach my patients and guide them. My job is not to coerce or cajole my patients, or to tell them what to do. My job is to teach and guide them in the best way I can.

The thrust of the *Family Practice Management* article was about reducing malpractice risk, but as applied to the clinical research enterprise, its lessons are more important to the processes of gaining truly informed consent and delivering ongoing care.

How to Use SOOOAAP

Subjective: "I'm sick as a dog. I have a fever and muscle aches. It just started yesterday."

Objective: Fever 102.0 F (38.9 C), ill appearance, rapid antigen test (RAT) + influenza A.

Opinion: "In my opinion, you have the flu. Your symptoms are consistent with my examination and the RAT test. However, there can be false positives with that test. So this could still be a different viral illness."

Options: "You have no other health problems. In my opinion, you have three options. First, I have a research trial looking at new therapies to treat influenza. [This is a lengthier discussion than I can summarize here.] Second, I can prescribe a medication that is already on the market, such as oseltamivir, which should shorten the duration of your illness. Or third, you can do nothing, and this should run its course on its own."

Advice: "My advice is to try and treat your infection within a trial or to prescribe an already approved drug. The compound we're studying is showing really promising results so far, but I can't tell you that it works. That's the point of research. However, I'll be watching you far more closely inside a research trial than outside one. We'll be doing daily blood work, physical exams, and viral titers to keep a close watch on how you are doing. Additionally, if at any time, you seem to be doing worse or to be intolerant to this drug, we can stop the trial immediately and treat you outside the trial. [Again, this is a lengthier discussion than I can summarize here.]"

Agreed Plan: "Mr. Smith has agreed to enroll in the XXX research protocol. I first discussed the protocol with him in depth. He was then given the informed consent form to read at his leisure. Once all questions were answered to his satisfaction, he signed the form—prior to any study procedures being performed. As agreed, we will proceed as per protocol. However, as agreed, if at any time, this course of action seems not in his best interest, we will immediately perform an early termination visit and treat him outside this research protocol."

Conclusion

So what does "patient-centric research" mean? It means focusing on the needs, values, and role of the patient. It also means that our patients come first—before our enrollment numbers and before our research protocols.

Our patients are autonomous, wonderful people, and our job is to teach and guide, not to dictate. Always be patient centric in your approach to clinical trials and daily clinical practice.

Reference

1. Teichman P. Documentation tips for reducing malpractice risk. *Fam Pract Manag* 2000;7(3):29-33. www.aafp.org/fpm/2000/0300/p29.html

Jeff Kingsley, DO, MBA, MS, CPI, FAAFP, (jeffkingsley@serrg.com) is chief executive officer of the Southeast Regional Research Group in Savannah, Ga., and is treasurer of the ACRP Board of Trustees.

ACRP 2015 GLOBAL CONFERENCE & EXHIBITION

SALT LAKE CITY, UTAH
APRIL 25–28, 2015

www.acrp2015.org

The Association of Clinical Research Professionals thanks the following partners* for their generous sponsorship of the ACRP 2015 Global Conference & Exhibition.

GOLD SPONSORS

imarc UNIVERSITY
CLINICAL RESEARCH EDUCATION

SILVER SPONSORS

BARNETT EDUCATIONAL SERVICES

CenterWatch

INTEGREVIEW IRB

GLOBAL MESM MEDICAL EQUIPMENT SOLUTIONS

PAREXEL
YOUR JOURNEY. OUR MISSION.™

SPG CRN

MEDIA PARTNERS

Clinical Researcher
The Authority in Ethical, Responsible Clinical Research

Life Science Leader

*as of March 9, 2015

BRONZE SPONSORS

Advanced Clinical

CLINIPACE WORLDWIDE

COMPASS IRB

Complion Regulatory eSystem

DOCS Resourcing Excellence

inc Research

DrugDev do more trials

HealthCarePoint

inVentiv Health

MERGE

Novella CLINICAL RESOURCING
A Quintiles Company

PRAclinical

PHOENIX Software International

Rho

SCRS Our Voice. Our Community. Society for Clinical Research Sites

SynteractHCR

TCR

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY

ITEM & EVENT SPONSORS

BARNETT EDUCATIONAL SERVICES

CISCRP THE CENTER FOR INFORMATION & STUDY ON CLINICAL RESEARCH PARTICIPATION

Complion Regulatory eSystem

DOCS Resourcing Excellence

Drexel UNIVERSITY ONLINE

FOMAT MEDICAL RESEARCH

FXM RESEARCH

imarc UNIVERSITY CLINICAL RESEARCH EDUCATION

inc Research

inVentiv Health

JBR JEANBROWN RESEARCH

JLR JLEWIS RESEARCH

MERGE

GLOBAL MESM MEDICAL EQUIPMENT SOLUTIONS

PAREXEL YOUR JOURNEY. OUR MISSION.™

SynteractHCR

TEUTEBERG INCORPORATED
Online & Social Media Marketing for Patient Recruiting

UNIVERSITY OF UTAH SCHOOL OF MEDICINE
Clinical Trials Office

Brent Ibata, PhD, JD, MPH, RAC, CCRC, CHRC

[DOI: 10.14524/CR-15-4060]

Personalized/Precision Medicine, Pharmacy Compounding, Laboratory Developed Tests, and *In Vitro* Companion Diagnostic Devices

In his 2015 State of the Union speech, the President of the United States announced a new clinical research initiative:

> Twenty-first century businesses will rely on American science and technology, research, and development. I want the country that eliminated polio and mapped the human genome to lead a new era of medicine—one that delivers the right treatment at the right time. In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable. So tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes, and to give all of us access to the personalized information we need to keep ourselves and our families healthier.

If funded, the Precision Medicine Initiative would provide $215 million to support clinical research with five broad objectives:

- more and better treatments for cancer;
- a voluntary national research cohort of one million research volunteers;
- regulatory modernization;
- public-private partnerships; and
- a commitment to protecting patient privacy.

In the last four years, the U.S. Food and Drug Administration (FDA) has released guidance for industry signaling the agency's intent to exercise greater regulatory oversight over activities that will be central to a future with personalized/precision medicine. These include guidance documents for pharmacies that compound customized human drug products, laboratories that develop tests, and *in vitro* diagnostic (IVD) devices (see Table 1).

TABLE 1: Precision Medicine–Related FDA Guidance

Title	Date
Guidance for Industry and FDA Staff—*In Vitro* Diagnostic (IVD) Device Studies—Frequently Asked Questions	**June 25, 2010**
In Vitro Companion Diagnostic Devices—Guidance for Industry and Food and Drug Administration Staff	**August 6, 2014**
Guidance—Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act	**July 2014**
Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories—Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)	**October 3, 2014**
Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories—FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)	**October 3, 2014**

In Vitro Companion Diagnostic Devices

In its 2014 guidance titled "*In Vitro* Companion Diagnostic Devices," the FDA defines such a device as an IVD "that provides information that is essential for the safe and effective use of a corresponding therapeutic product," and provides examples of when an IVD companion device could be "essential":

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

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**.

- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

In the 2014 guidance, the FDA describes its thinking on IVD companion devices in clinical trials:

> IVD companion diagnostic devices used to make treatment decisions in clinical trials of a therapeutic product generally will be considered investigational devices, unless employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) [in the *Code of Federal Regulations*] because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices.

Pharmacy Compounding of Personalized Medications

In *Thompson v. Western States Med. Ctr.,* 535 U.S. 357 (2002), the U.S. Supreme Court held as unconstitutional the application of the Federal Food, Drug, and Cosmetic Act (FDCA) that restricted a pharmacists ability to speak to personalized uses of compounded medications. Writing for the majority, Justice Sandra Day O'Connor wrote:

> Forbidding the advertisement of compounded drugs would affect pharmacists other than those interested in producing drugs on a large scale. It would prevent pharmacists with no interest in mass-producing medications, but who serve clienteles with special medical needs, from telling the doctors treating those clients about the alternative drugs available through compounding. For example, a pharmacist serving a children's hospital where many patients are unable to swallow pills would be prevented from telling the children's doctors about a new development in compounding that allowed a drug that was previously available only in pill form to be administered another way.

In response to the Supreme Court ruling in *Thompson V. Western States Med. Ctr.*, the FDA issued a 2014 guidance titled "Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act," describing compounded drug products exempt from the good manufacturing practices (501(a)(2)(B)), labeling (502(f)(1)), and new drug application (505) sections of the FDCA. Among the criteria for exemption are the requirements that the compounded drug is: 1) compounded for a specific patient; 2) compounded by a licensed pharmacist or physician; 3) compounded in compliance with the *United States Pharmacopoeia* (USP) chapters on compounding using bulk drug substances that comply with USP or National Formulary standards, or by a component of an FDA-approved drug manufactured in compliance with applicable sections of the FDCA.

Laboratory Developed Tests

In its draft guidance laying out the "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" the FDA defines an LDT as "an IVD that is intended for clinical use and designed and manufactured and used within a single laboratory" that is "a facility with a single [Clinical Laboratory Improvement Amendments] certificate as described in 42 CFR 493.43(a)-(b)."[1]

In the draft Framework guidance, the FDA describes the need for increased regulatory oversight of LDTs:

"[T]echnological advances have increased the use of diagnostic devices in guiding critical management decisions for high-risk diseases and conditions, particularly in the context of **personalized medicine.**" [emphasis added]

Conclusion

Personalized/precision medicine will require a different approach to regulatory oversight and participation of clinical research professionals to gather the evidence to guide future use of drugs and devices targeting the person, and not just the diagnosis. New *in vitro* diagnostic devices and laboratory developed tests will be needed to guide the appropriate patient-specific compounding of drugs and programming of devices.

Personalized/precision medicine will require a different approach to regulatory oversight and participation of clinical research professionals to gather the evidence to guide future use of drugs and devices targeting the person, and not just the diagnosis.

Reference

1. Centers for Medicare & Medicaid Services. Clinical Laboratory Improvement Amendments (CLIA). www.cms.gov/clia

Brent Ibata, PhD, JD, MPH, RAC, CCRC, CHRC, (ibataba@gmail.com) is the director of operations at the Sentara Cardiovascular Research Institute, teaches for the online Masters of Clinical Research Administration Program through the University of Liverpool and Master of Science in Regulatory Affairs at Northeastern University, is on the faculty of Eastern Virginia Medical School, and is vice chair of the ACRP Board of Trustees.

ARTICLE SUBMISSION GUIDELINES

Clinical Researcher welcomes submissions on topics that are relevant to clinical research professionals globally. Writing an article for *Clinical Researcher* is an excellent way to boost your professional development, gain recognition, share important information about the latest developments in clinical research with fellow professionals around the world, and help ACRP maintain its role as the leading voice and information resource for clinical research professionals everywhere.

The Peer Review Process

The Editorial Advisory Board (EAB) reviews all articles for relevancy, accuracy, organization, objectivity, and integrity. Your article will be reviewed by two or more EAB members in a completely confidential, doubleblind process; that is, you will not know who your reviewers are and they will not know who you are. The time frame is usually two weeks, but depends on a number of variables, including the availability of reviewers who have the expertise to review the topic and the current production schedule. The EAB considers all submissions seriously and makes every effort to review articles fairly and provide detailed, constructive feedback as needed. For a comprehensive explanation of the process, including what reviewers look for and authorship criteria, see www.acrpnet.org/MainMenuCategory/Resources/Clinical-Researcher/Submit-an-Article.aspx.

If accepted for publication, articles are published in the next available issue, although some submissions may be held for use in an issue that presents many articles on the same theme. Note, however, that the EAB will review **any** article on **any** clinical research topic **any** time it is submitted.

Submission Requirements

- Preferred article length: up to 2,500 words, accompanied by an abstract of up to 150 words.
- Submissions must be originals and submitted exclusively to *Clinical Researcher.* Authors of accepted articles must sign a copyright release, granting ACRP all rights to future publication and distribution in print and electronic forms.
- Articles may be based on research, data, new developments, or informational topics. Review articles may be considered, but contact the Editor prior to your submission for guidance.
- ACRP reserves the right to edit the content of the article.
- Submissions must not be commercial or in any way convey self-interest or promotion.
- EAB reviewers may ask the writer to revise the article according to their recommendations.
- Insert reference numbers manually within the text. **Do not use automatic footnoting and referencing.** Reference all sources at the end of the article. *Clinical Researcher* uses a modified University of Chicago Press reference style. Basically, each reference must list all authors, publication year, article title, and full name of journal with volume, issue, and page numbers. If the citation is published on the Internet, provide full URL pathway for readers to access it.
- Figures and tables are allowed, but those from previously published material must be submitted with a letter from the author or publisher granting permission to publish in *Clinical Researcher.* Any fees associated with reprinting must be paid by the author prior to publication of the article in *Clinical Researcher.*
- Electronic images should be high-resolution files (at least 300 to 600 dpi) with captions.

Clinical Researcher uses the PeerTrack submission and peer review system. Prospective authors should log in or register (if new to the site) at **www.edmgr.com/clinresearcher**, follow the instructions to the required contact information, upload articles in Microsoft Word (12 point Times Roman, double spaced), and **make certain that there is no author information inside the article file(s)**. The system will assign an article number and convert the file to a blinded PDF, which the author must approve before it is ready for peer review. Direct any questions to **editor@acrpnet.org**.

Check out the Editorial Calendar for 2015, at www. acrpnet.org/MainMenuCategory/Resources/Clinical-Researcher/Editorial-Calendar.aspx

Ask 8 of the world's top 10 pharma companies about our sourcing expertise and call us in the morning.

Myoderm knows what's at stake for our clients, so we scour the world for the comparators they need for clinical trials. Our ability to locate restricted and hard-to-find drugs is unmatched. And so are our services, including our ability to handle both one-time shipments and the ongoing management and delivery of drugs and supplies to local trial sites. That's why eight of world's top 10 pharma companies place their trust in us. You will, too.

MYODERM
The Optimal Source

myoderm.com

TRAINING OPPORTUNITIES

eLEARNING COURSES

Building Quality Management Systems for Sites and Sponsors: Root Cause and CAPA

The Drug Development Process: Improving Trial Feasibility and Exploring Your Growth Potential

GCP for the Experienced CRA: Improving Monitoring Efficiency and Effectiveness

GCP for the Experienced CRC: Partnering with Your Investigator to Reduce Risk and Avoid Common Inspection Findings

GCP for the Experienced Investigator: Reducing Risks and Avoiding Common Inspection Findings

Key Skills for Ensuring Quality Control through Risk-Based Decision Making

Mastering the Event Reporting Cycle: Understanding Your Impact on Patient Safety

Risk-Based Monitoring: The Essentials for CRAs

Risk-Based Monitoring: The Essentials for CRCs

Risk-Based Monitoring: The Essentials for Investigators

Theory to Practice: Operationalize Your Clinical Study Protocol

NEW IN 2015

Site Quality Management Tools: SOPs, Metrics, and Training

ICH Gap Analysis Tool

GCP Test-Out Challenge

Form FDA 1572: Get it Right the First Time

Understanding Clinical Trial Protocols: Key Considerations for Effective Development and Feasibility Review

LIVE WEBINARS

APRIL 1, 2015
An Approach to Quality Management in an Academic Setting to Increase Effectiveness and Efficiency
Connie Catha and Stephanie Gaudreau

APRIL 15, 2015
Lessons Learned from Audits: A Case Study
Soumya J. Niranjan

MAY 6, 2015
Using Gamification to Incentivize Sites
Niki Kutac

MAY 13, 2015
Coverage Analysis, Budgeting, and Pre-Award Practices Limiting Fiscal Risk in Clinical Research
Tina Noonan and Erika Stevens

JUNE 3, 2015
Patient Navigators in Cancer Clinical Trials
Lucy Gansauer and Margo Michaels

WEBINAR REPLAYS

FDA/EMA Inspection Lessons Learned: Ineligible Subject Enrollment
Glenda Guest
ORIGINAL AIR DATE: DECEMBER 18, 2014

An Effective Corrective and Preventive Action Program (CAPA)
Susan Leister
ORIGINAL AIR DATE: DECEMBER 10, 2014

Recruiting and Retaining Geriatric Patients: Strategies for Success
Sandra Mutolo
ORIGINAL AIR DATE: NOVEMBER 20, 2014

Addressing the Shortage: How to Develop and Retain Highly Qualified CRAs to Close the Talent Gap
Laurie Halloran
ORIGINAL AIR DATE: NOVEMBER 5, 2014

Site Visibility: How to Increase Visibility in Your Community to Attract More Potential Trial Subjects
Julie Carrico
ORIGINAL AIR DATE: OCTOBER 22, 2014

Improving Communication Skills to Address the Barriers of Informed Consent
Stephanie Christopher
ORIGINAL AIR DATE: OCTOBER 10, 2014

Standardizing Principal Investigator (PI) Delegation Records to Balance Site Operations and Regulatory Requirements
Nadine Nemunaitis and Staci Horvath
ORIGINAL AIR DATE: OCTOBER 1, 2014

Using Clinical and Operational Data to Determine Optimal Onsite Monitoring Visit Frequency
Marcus Thornton
ORIGINAL AIR DATE: SEPTEMBER 25, 2014

Posting Study Results to Public Trial Registries/ Data Banks—Made Easy
Robin Smith
ORIGINAL AIR DATE: SEPTEMBER 10, 2014

CRAs as Site Recruitment Managers: Yes or No?
Beth Harper, Gretchen Goller, and Nikki Christison
ORIGINAL AIR DATE: SEPTEMBER 3, 2014

Fraud Enforcement in Clinical Research Under the False Claims Act
Shauna Itri
ORIGINAL AIR DATE: AUGUST 28, 2014

Quality Risk Management for Sites: Why Should Sponsors Have All the Fun?
Sandra "SAM" Sather
ORIGINAL AIR DATE: AUGUST 27, 2014

Setting Your Sites Up for Success: Industry Trends and Best Practices for Sponsors and CROs
Beth Harper
ORIGINAL AIR DATE: AUGUST 20, 2014

Vulnerability: What the Regulations Don't Say
Bob Romanchuk
ORIGINAL AIR DATE: JULY 30, 2014

FDA/EMA Inspection Lessons Learned: Protocol Deviations—Why They Occur and How to Handle Them
Lee Truax-Bellows
ORIGINAL AIR DATE: JULY 16, 2014

Best Practices in Managing Outsourced Clinical Trials
Laurie Halloran and Tina Forrister
ORIGINAL AIR DATE: JULY 9, 2014

Updating Your Patient Recruitment Strategy: The Importance of Implementing Social Media and Online Campaigns
Wade Strzinek
ORIGINAL AIR DATE: JUNE 25, 2014

FXM RESEARCH

IT'S NOT JUST CLINICAL RESEARCH!

IT'S CLINICAL RESEARCH EXCELLENCE... SUSTAINED!

Founded in the year 2000, **FXM Research** is a privately owned and operated Clinical Research Site that conducts phase II, III, and IV clinical research trials specializing in Dermatology. Throughout the years, our ability to deliver aggressive, time bound enrollment goals, while providing trustworthy data to Pharmaceutical companies and CROs, has earned **FXM Research** a great deal of notoriety and fame within the Dermatology research industry.

Today, FXM Research's success is widely regarded throughout our four operating branches: **FXM Research Corp.**, based in Miami, Florida and home of our headquarters, **FXM Research Miramar**, located in the city of Miramar, Florida and **FXM Research International**, including two branches in Belize City, Central America.

OUR MISSION

At the core of our business and operating systems, **FXM Research** mission is to support pharmaceutical companies and CROs with introducing new and approved FDA medications successfully into the marketplace. We perform this efficiently and effectively by providing the highest quality service in a timely fashion and at the lowest possible cost.

- We specialize in conducting phase II, III, and IV Dermatology Clinical Trials.
- Our primary concerns are subject safety and adherence to the protocol.
- Turnover time for Regulatory Documents, budgets, and contracts is usually 24 to 48 hours.

OUR SUCCESS

- We offer experienced, trained, and bilingual personnel (English and Spanish), who interact with our subjects, sponsors, and CROs as a cohesive team.
- Our Principal Investigators are Board Certified Dermatologists and Certified Clinical Research Investigators with many years of extensive experience. They are located onsite and are available full-time.
- Most subjects are recruited from the office of our PI's private practice, and/or FXM Research's extensive clinical database. We draw heavily from a Spanish speaking population, a group often under-represented in clinical trials. We also have continuing extensive experience with a pediatric population.
- We do whatever is necessary to accommodate our subjects' school and/or work schedule, which maximizes compliance and retention.
- We are confident that we can surpass sponsors expectations relating to cost, subject enrollment/retention, and the quality of our work.

TO CONTACT US

Francisco Moncada, R.N., B.S.N., C.C.R.C., President & Director of Clinical Research
Email: info@fxmresearch.com • www.fxmresearch.com

FXM Research Corp.
Hector Wiltz, M.D., C.C.T.I.
(305) 220-5222 Office
(305) 220-5779 Fax

FXM Research Miramar
Francisco Flores, MD
(954) 430-1097 Office
(954) 430-5502 Fax

FXM Research International – Belize, Central America
Julitta Bradley, MD & Ines Mendez-Moguel, MD
(305) 220-5222 Office
(305) 220-5779 Fax

Higher Standards, Experienced Consultants!

Call us today and see what makes us unique!

Clinical Research Consulting, Inc

HIGHER STANDARDS • EXPERIENCED CONSULTANTS

101 Federal Street · Suite 1900 · Boston, MA 02110-1821
phone (508) 865-8907 · **fax** (508) 865-8908 · **web** www.eclinicalresearchconsulting.com