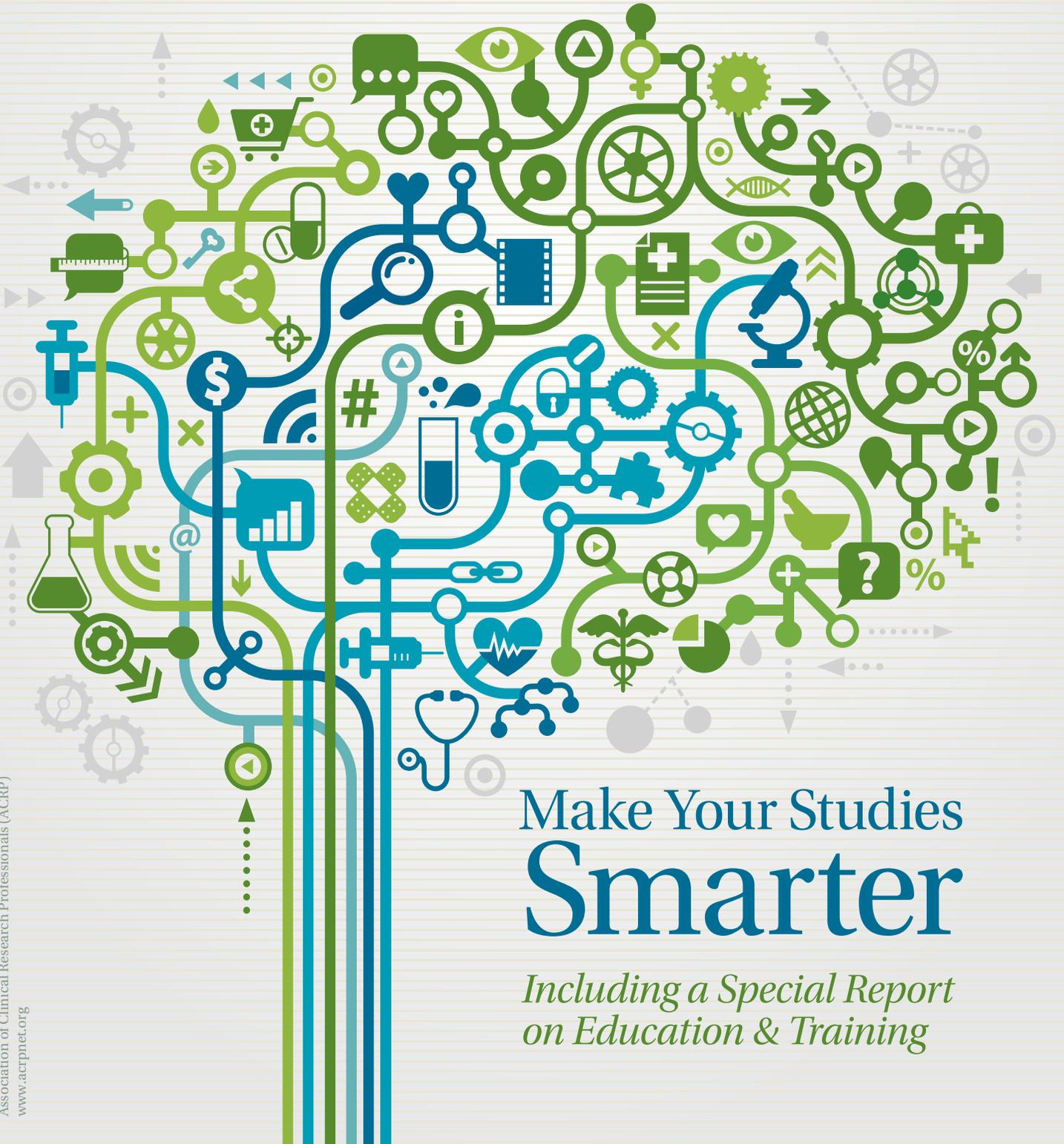


FEBRUARY 2017

Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

- 8 Quality Assurance Coordinators:
Ensuring Quality at the Site Level
- 11 Investigational Drug
Management: Five Things
Large Research Institutions
Should Consider
- 16 Is Bias Inherent in Reporting
Practices for Adverse Events?



Make Your Studies
Smarter

*Including a Special Report
on Education & Training*



With the final guideline now released, the clinical trial industry must prepare. The revisions are intended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated. As such, systematic analysis to ensure adherence to these proposed clinical trial standards is essential.

In response to the changes, Barnett has developed a series of web-based training courses that will assist teams in understanding and addressing the necessary changes. Specific offerings include:

10-Week Risk Management/Risk-Based Quality Management for Clinical Trials Certification Program

April 5 – June 7, 2017 • 1:00 PM - 3:00 PM Eastern
Wednesday Afternoons

Final ICH GCP E6 R2: Changes Impacting Clinical Investigators, Sites, and IND Holders (Sponsors-Investigators and Institutions)

April 13, 2017 • 9:00 AM - 11:00 AM Eastern

Final ICH GCP E6 R2: Sponsor Quality Management – Risk-Based/Risk Management Requirements and Approaches for Compliance

April 13, 2017 • 1:00 PM - 3:00 PM Eastern

Final ICH GCP E6 R2: Changes Impacting Sponsors/CROs

May 15, 2017 • 9:00 AM - 11:00 AM Eastern

Final ICH GCP E6 R2: Implementing Risk Management Approaches for Compliance

May 15, 2017 • 1:00 PM - 3:00 PM Eastern

EXPECT MORE. ACHIEVE MORE.



Make your next move count and grow in your career as a Covance Clinical Research Associate

It's time to discover your potential with a company that truly invests in you. As a Covance CRA, you will:

- ▶ Thrive in a supportive team environment
- ▶ Enter a role with a clear path for advancement
- ▶ Receive on-the-job training and mentoring
- ▶ Achieve a work/life balance with a flexible schedule

If you're looking for CRA experience, jump-start your career with the Monitoring Excellence Academy, an accelerated, on-the-job CRA training program built into your long-term Covance career path.

Explore CRA career opportunities at Covance.com/CRAcareers

Covance is committed to diversity in the workplace and is an equal opportunity employer (Minority/Female/Individual with Disability/Veteran). Your confidentiality and privacy are important to us.

COVANCE
SOLUTIONS MADE REAL®

→ CONTENTS

February 2017 • Volume 31, Issue 1 • ISSN 2334-1882

3

MANAGING EDITOR'S MESSAGE

Make Your Studies Smarter

Gary W. Cramer

EARN 3.0 CREDITS IN THIS ISSUE OF *CLINICAL RESEARCHER*

HS

Columns

5 EXECUTIVE DIRECTOR'S MESSAGE

6 CHAIR'S MESSAGE

25 WORKFORCE INNOVATION

28 PI CORNER

38 OPERATING ASSUMPTIONS

46 CAREERS—PASSING IT ON

Home Study

7 INTRODUCTION

8

Quality Assurance Coordinators: Ensuring Quality at the Site Level 

Bryan A. Moore, MA, CCRP;
Olga Pizov, RN, MSN, CCRP

11

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

Ji-Eun Kim, RPh, PhD;
Emmelyn Kim, MA, MPH, CCRA, CHRC

16

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

Robert Jeanfreau, MD

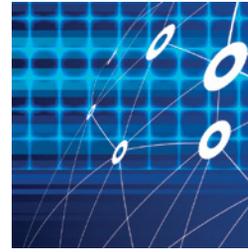
20 HOME STUDY TEST

Features



22

In Pursuit of Education and Training for Learning, for Listening, for Life



51

On the *CRbeat*



48

Introducing ACRP's Inaugural Class of Fellows

PEER REVIEWED



30

The New European Union Regulation for Clinical Trials

Yves Geysels, PhD;
Christopher A. Bamford, PhD;
Richard H. Corr



40

Accelerating Study Start-Up: The Key to Avoiding Trial Delays

Priya Temkar, MSc



Clinical Researcher is your platform.

Interested in writing a peer-reviewed article or guest column? You'll find our submissions guidelines at

acrpnet.org/submit

ACRP

■ FOR LEARNING ■ FOR LISTENING ■ FOR LIFE

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.

© Copyright 2017 Association of Clinical Research Professionals. All rights reserved. For permission to photocopy or use material published herein, contact www.copyright.com. For other information, write to editor@acrpnet.org.

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

Make Your Studies Smarter

➔ **MANAGING EDITOR'S MESSAGE**
Gary W. Cramer

[DOI: 10.14524/CR-17-4007]

“We can rebuild him. We have the technology. We can make him better than he was. Better, stronger, faster.”

—Oscar Goldman

The sentiment above, as intoned by actor Richard Anderson and burned into the minds of many viewers of TV's *“The Six Million Dollar Man”* series in the 1970s, is not too far off the mark of observations about the state of our enterprise that you may have heard or read from pundits representing various corners of the clinical research universe lo, this past decade or so.

From insights about integrating the latest technology into clinical trials, to adopting better study workflow processes, to strengthening patient recruitment pools, to making every step of clinical development operate faster, *faster*, *FASTER*, we may be forgiven for dreaming of suddenly having access to the endless budgetary resources of a super-secret government program to make it all come true. Hey, it worked out OK for Col. Steve Austin, the grievously injured hero (played by Lee Majors) of the aforementioned show, which saw him transformed from an ordinary test pilot into a crime-fighting cyborg.

However, aren't we forgetting something? Unless it goes without saying, what about, as we mix in all those other improvements, we also try to make our studies *smarter*? Gaining smarts was never part of the deal in saving poor rocket crash victim Col. Austin's life, but in the real world, in their own ways, and from their array of vantage points, I think it's something that the authors of the peer-reviewed articles in this issue could agree on as an important element in the evolution of clinical research.

Things to Think About Before You Hit the Ground Running

In “Quality Assurance Coordinators: Ensuring Quality at the Site Level,” authors Bryan A. Moore and Olga Pizov write that, whereas risk-based monitoring has become very popular in recent years, some have noted that the approach leaves room for improvement. They outline the potential for sites to employ onsite quality assurance coordinators as part of their clinical quality management plans, and make it sound like a smart move indeed for many sites to consider.

Next up, authors Ji-Eun Kim and Emmelyn Kim present practical strategies for enhancing overall investigational drug management for clinical trials

occurring at various research sites throughout large organizations in “Need Help With Investigational Drug Management? Five Things Large Research Institutions Should Consider.” Offering flexible training and education to personnel who are delegated to manage investigational drugs is just one of the facets of this topic into which they delve.

Closing out the Home Study articles for this issue, an opinion piece on “Is Bias Inherent in the Current Reporting Practices for Adverse Events?” from author Robert Jeanfreau elucidates how the term “adverse event” in and of itself bespeaks a certain prejudice, and goes on to show, among other things, the consequences of bias in the reporting of such events. Making studies smarter in this arena will take a groundswell of interest and collaboration between researchers, sponsors, and regulators, he writes.

This issue also brings us valuable ideas for study smartening regarding “The New European Union Regulation for Clinical Trials” from authors Yves Geysels, Christopher A. Bamford, and Richard H. Corr, and on “Accelerating Study Start-Up: The Key to Avoiding Trial Delays” from author Priya Temkar.

Taking the Leap

In *“The Six Million Dollar Man,”* the half-man/half-machine protagonist was famously often portrayed as running impossibly fast, leaping improbably high, and seeing incredibly distant objects with perfect ease. However, in the earliest episodes, it was shown that adjusting from his once-normal abilities to these and other cybernetically augmented ones did not come all at once, and surely not without some hiccups along the way.

Making your studies smarter by following the advice and inspirations to be gained from this issue's articles may similarly not be a “zero to 60 in five seconds flat” scenario. In reality, even as in science fiction, practice makes perfect. We look forward to hearing from you about your own experiences with improving your studies in these or any other ways that you would like to share by publishing your own articles in the pages of future issues of *Clinical Researcher*. Feel free to contact me whenever you want to take that leap.

Aren't we forgetting something? Unless it goes without saying, what about, as we mix in all those other improvements, we also try to make our studies *smarter*?



Gary W. Cramer (gcramer@acrpnnet.org) is managing editor for ACRP.

BY THE NUMBERS

This installment shines a light on recent reports about trends in the clinical research enterprise affecting both research sites and sponsors.

Turnover in the U.S. for clinical monitoring jobs at contract research organizations



remained high at **25.1%** in 2015, down slightly from **25.4%** in 2014, despite a **7%** spike in average salaries for professional positions in the same period.

(Source: HR+Survey Solutions/CRO Industry Global Compensation and Turnover Survey, www.hrssl.com)

Authors using a database to track the clinical and regulatory phase progression of more than 9,200 compounds between

1996 and 2014 found that nearly

90% of clinical trials ended in failure; however, the success rate of trials rose between 2012 and 2014 to **11.6%** from an all-time low of just **7.5%** between 2008 and 2011.

(Source: "Trends in Clinical Success Rates"/Nature.com, www.nature.com/articles/nrd.2016.85.epdf)



As of mid-December 2016, a cross-industry initiative to provide researchers with access to clinical trial data from **13** major pharmaceutical companies reported it had more than **3,200** trials available.

(Source: ClinicalStudyDataRequest.com/BusinessWire, www.businesswire.com/news/home/20161215005218/en/ClinicalStudyDataRequest.com-Expansion-Enables-Researchers-Access-Patient-Level-Data)

ACRP

■ FOR LEARNING ■ FOR LISTENING ■ FOR LIFE

EDITOR-IN-CHIEF

James Michael Causey

editor@acrpn.net

(703) 253-6274

MANAGING EDITOR

Gary W. Cramer

(703) 258-3504

EDITORIAL ADVISORY BOARD

CHAIR

Jerry Stein, PhD

Summer Creek Consulting LLC

VICE CHAIR

Paula Smailes, RN, MSN, CCRC, CCRP

The Ohio State University Wexner Medical Center

ASSOCIATION BOARD OF TRUSTEES LIAISON

Ernest Prentice, PhD

University of Nebraska Medical Center

TRAINING AND DEVELOPMENT COMMITTEE LIAISON

Suheila Abdul-Karrim, CCRA, CCRT

Freelancer

Victor Chen

The C and K Clinical Group

Fraser Gibson

Advantage Clinical

Gregory Hale, MD, CPI

All Children's Hospital

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

Roswell Park Cancer Institute

Stuart Horowitz, PhD, MBA

WIRB-Copernicus Group

Stefanie La Manna, PhD, ARNP, FNP-C

Nova Southeastern University

Jamie Meseke, MSM, CCRA

PPD, Inc.

Christina Nance

Baylor College of Medicine

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

Tufts University School of Medicine

Shirley Trainor-Thomas

GuideStar Clinical Trials Management

Heather Wright

Tampa Bay Clinical Research Center

ADVERTISING

Tammy B. Workman, CEM

Advertising & Exhibition Sales Manager

(703) 254-8112

tworkman@acrpn.net

For membership questions, contact ACRP at office@acrpn.net or (703) 254-8100

The Foundations of Fellowship and Lifelong Learning

→ EXECUTIVE DIRECTOR'S MESSAGE

Jim Kremidas

[DOI: 10.14524/CR-17-4004]

Education should be an active partner during the course of your entire career. Whether you're entering the profession or are already an established professional, you owe it to patients, the industry, and to yourself to keep your skillset sharp by learning and sharing your knowledge with others. This belief is at the core of ACRP's mission.



Jim Kremidas (jkremidas@acrpnnet.org) is the Executive Director of ACRP.

Announcing the ACRP Fellowship

"There's always something to learn no matter your level of experience," says 2017 ACRP Fellows inductee Barbara Grant Schliebe, MS, CCRA, CCRC, CCRP, FACRP, a clinical research monitor at the University of North Carolina at Chapel Hill. Fellowship is a mark of distinction; a recognition of leadership in, and contributions to, ACRP and the clinical research industry. It's another one of our initiatives designed to promote education even as we work together to demonstrate how it helps us to elevate our profession.

"We're all passionate about taking our profession to the next level," says Robert Greco, RPh, MPH, CCRA, FACRP, clinical trial head in Oncology Global Development at Novartis Pharmaceuticals Corp. and another member of the Fellows Class of 2017. We all agree education is an integral part of the effort.

By developing a Fellowship program and granting the FACRP designation, ACRP recognizes those who have made substantial contributions to the Association and the industry. It recognizes excellence and commitment to ACRP. I invite you to learn more about the program and our first seven fellows beginning on page 48 of this issue of *Clinical Researcher*.

Coming Up in Seattle

I'm also excited to talk about our many educational opportunities at the ACRP 2017 Meeting & Expo, coming to Seattle, Wash., in late April. In cooperation with Association members and other industry experts, we've worked to bring you a comprehensive program that gives you a snapshot of today's best practices, what to look for in the future, and the tools and training you'll need to thrive in tomorrow's environment.

We'll have nearly 100 sessions at the Meeting & Expo, each handpicked from many applications to present at the conference. I'd like to draw your attention to a few:

- Robert Romanchuk, Schulman IRB, on how to master your response to a U.S. Food and Drug Administration (FDA) Form 483

- Asha Nayak, Intel Corp., on how best to understand and leverage wearable devices to improve clinical trial data
- Amanda Alonso, Columbia University, on how to go paperless in a smart way that increases site efficiency and saves time and money
- Ryan Bailey, Rho, on putting patient-centric principles into practice

One of our Signature Series sessions explores the use of mobile technologies. It will be moderated by Virginia Nado of Roche/Genentech and other panelists from The Clinical Trials Transformation Initiative (CTTI), a public-private partnership founded by Duke University and the U.S. Food and Drug Administration. Other speakers include Linda Coleman, Director, Human Research Protection Program, Yale University; Phil Coran, Sr., Director, Quality and Regulatory Affairs, Medidata Solutions; and Matt Kirchoff, Clinical Research Operations Manager, International Research Pharmacy Operations, NIH/NIAID.

These and other sessions will provide you with the latest and most valuable information available to help you continue to grow as a clinical trial practitioner.

Finally, I hope you can join us for our first ACRP Podcast later this month. It will feature Ken Getz, director of sponsored programs and research associate professor at the Tufts Center for the Study of Drug Development, and David Vulcano, LCSW, MBA, CIP, RAC, AVP and responsible executive for clinical research at HCA (Hospital Corporation of America), giving us their insights on the state of clinical trials today and tomorrow. I'll also participate by outlining how ACRP is helping members thrive in today's challenging career landscape.

Join Us, Won't You?

The Fellows initiative, a wider array of conference sessions, and a new podcast series are just three of the ways we're working to help you advance your career. Have an idea for a Meeting & Expo session? Have a topic you'd like us to explore via podcast or webinar? Want to publish an article in *Clinical Researcher* or to be interviewed for the *CRbeat* e-newsletter? Please reach out to me directly at jkremidas@acrpnnet.org.

The Fellows initiative, a wider array of conference sessions, and a new podcast series are just three of the ways we're working to help you advance your career.

→ CHAIR'S MESSAGE

Jeff Kingsley, DO, MBA, CPI, FAAFP, FACRP

[DOI: 10.14524/CR-17-4003]

Value and Your Membership— In More Ways Than One

The word “value” can be used as a noun or a verb. It’s a noun when it expresses the worth or usefulness of something (e.g., your car has been of great value to me while my own was in the shop). It’s a verb when tied to an assessment of the value of something (e.g., the car was valued at \$25,000).

I believe ACRP can be called valuable in both senses of the word.

Looking at its value as a noun, I can categorically say it has been valuable to me on a professional and personal level. Professionally, it has helped me and my team at IACT Health to improve our service to patients and, I also believe, to the broader clinical trials industry. We’ve worked hard to define job roles and tie those to specific roles rather than simple tenure or general skills.

Personally, I’ve met many interesting people in our industry I likely would otherwise never have gotten to know thanks to ACRP. I feel like I recharge my battery, so to speak, every time I attend an ACRP Meeting & Expo or any other Association-related event. I learn about new best practices, new trends, and new challenges during what has got to be one of the most revolutionary periods in the history of clinical trials. Whether it’s new technologies, new regulations, or new patient expectations, it’s fair to say we’ve never seen our industry changing so quickly in so many different ways.

Beyond the Price Tag

I’d also like to think its value can be expressed using the word “value” as a verb. For example, while membership costs between \$60 and \$150, I believe its value goes well beyond that dollar figure. Whether it’s access to a strong suite of webinars on topics ranging from challenges in clinical research for precision medicine to updates on important new regulations, or the ability to ask and answer broad and specific questions via the ACRP Online Community, you gain the kind of information you need to advance your career and to do an even better job than you already do in your current role.

At the same time, ACRP gives us the opportunity to work together to elevate the professionalization of our field. For example, I think we should all be excited about our Association’s work to develop certifications and career paths based on clearly defined skills. This is your opportunity to contribute your ideas and opinions to help us shape our future.

My company is already leveraging some of these concepts in its job descriptions. It’s our hope to provide clear data points demonstrating the advantages of learning the right skills and match those to the right job. We’ve put together a four-step career ladder that clearly defines expectations and the value of certification, both in a professional and financial sense. We call our tiers Clinical Research Coordinator 1, Clinical Research Coordinator 2, Clinical Research Coordinator 3, and Senior CCRC. We also attach pay raises to successfully taking each step up that ladder.

Stay in Touch

I’m honored to be ACRP’s new Chair of the Association Board of Trustees. ACRP membership has given me so much over the past decade; I hope very much to be able to return some of that value to current and future members. Please reach out to me at jkingsley@iacthealth.com or +1 706-536-6619 if I can ever answer any questions or direct you toward an ACRP resource.

Working together, we can elevate clinical research to new heights.

ACRP gives us the opportunity to work together to elevate the professionalization of our field. For example, I think we should all be excited about our Association’s work to develop certifications and career paths based on clearly defined skills.



Jeff Kingsley, DO, MBA, CPI, FAAFP, FACRP, (jkingsley@iacthealth.com) is chief executive officer of IACT Health in Columbus, Ga., and Chair of the 2017 Association Board of Trustees for ACRP.

HOME
STUDY

HS

Make Your Studies Smarter

HOME STUDY TEST

Earn 3.0 Continuing Education Credits

This test expires on February 28, 2018

(original release date: 2/1/2017)

ACRP EDITORIAL ADVISORY BOARD

Jerry Stein, PhD (Chair)
Ernest Prentice, PhD (ABoT Liaison)
Suheila Abdul-Karrim, CCRA, CCRT
Victor Chen
Fraser Gibson, CCRA, CCRP
Gregory Hale, MD, CPI
Julie M. Haney, RN, BS, MSL, CCRC
Stuart Horowitz, PhD, MBA
Stefanie La Manna, PhD, ARNP, FNP-C
Jamie Meseke, MSM, CCRA
Christina Nance, PhD, CPI
Grannum Sant, MD, BCh, BAO (Hons.),
MA, FRCS, FACS
Paula Smailes, RN, MSN, CCRC, CCRP
(Vice Chair)
Shirley Trainor-Thomas, MHSA
Heather Wright, BS, BA:
Nothing to Disclose

ACRP STAFF/ VOLUNTEERS

Gary W. Cramer
Jan Kiszko, MD
Jo Northcutt
Deepti Patki, MS, CCRC
Barbara van der Schalie
Christine Streaker
Nothing to Disclose
Karen Bachman:
Alcon speaker's bureau
James Michael Causey:
Contributor, AssurX blog

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

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

ACRP DISCLOSURE STATEMENT

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

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

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.

ACRP 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-2017-HMS-002)



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 11147-2017-HMS-002)



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.

Quality Assurance Coordinators: Ensuring Quality at the Site Level

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

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

[DOI: 10.14524/CR-16-0025]

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

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

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

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

In addition to quality issues, remote monitoring may even increase costs for sites by increasing the

amount of time that study coordinators have to prepare for and deal with monitoring activities.⁵ Remote monitoring may increase the cost of study coordinators for a typical study by more than three times the cost seen with traditional monitoring.⁵ This increased time burden for coordinators may come from file transfer activities and repeated requests for documents.

Looking Beyond the Challenges to the QAC Solution

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

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

LEARNING OBJECTIVE

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

DISCLOSURES

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

In essence, the RBM approach focuses on maximizing efficiency and effectiveness in monitoring in an attempt to save resources (e.g., time and money). Some have claimed that, in certain situations, RBM can reduce costs over traditional monitoring approaches by 20% or more.

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

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

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

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

QACs in Action

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

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

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

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

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

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

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

Eyes on the Prize

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

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

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

• **Improved work flow:** QACs focus efforts on process improvement activities, which can translate into greater efficiency, effectiveness, and compliance for the entire site.

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

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

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

References

1. U.S. Food and Drug Administration. 2013. Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring. www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf
2. Causey JM. 2015. Risk-based monitoring: hope or hype? *Clin Res* 29(5):59–62.
3. Underwood T. 2016. The rise of risk based monitoring of clinical trials. *Quanticate CRO Blog*. www.quanticate.com/blog/the-rise-of-risk-based-monitoring-in-clinical-trials
4. QuintilesIMS™. Risk-based monitoring. www.quintiles.com/services/riskbased-monitoring
5. Kassin M, Goldfarb NM. 2016. The cost to sites of remote monitoring. *J Clin Res Best Pract* 12(10).
6. National Institute of Allergy and Infectious Diseases/Division of Microbiology and Infectious Diseases. 2016. Policy on DMID Clinical Quality Management (Version 6.0). <https://www.niaid.nih.gov/sites/default/files/qualitymgmtplan.pdf>

Bryan A. Moore, MA, CCRP, (bmoore31@jhmi.edu) is a senior compliance monitor with Johns Hopkins University School of Medicine in Baltimore, Md.

Olga Pizov, RN, MSN, CCRP, (OPizov@clinicalrm.com) is a senior quality assurance specialist with ClinicalRM in Hinckley, Ohio.

Need Help With Investigational Drug Management?

Five Things Large Research Institutions Should Consider

PEER REVIEWED

Ji-Eun Kim, RPh, PhD | Emmelyn Kim, MA, MPH, CCRA, CHRC

[DOI: 10.14524/CR-16-0024]

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

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

1 Develop a Centralized Review of Drug Management in Research

Appropriate investigational drug management and drug accountability are key components in clinical research compliance. Both the U.S. Food and Drug Administration's (FDA's) *Code of Federal Regulations* (CFR) and the tenets of Good Clinical Practice (GCP) from the International Conference

on Harmonization specify regulatory requirements and industry standards for investigators and their delegated individuals.^{1,2} A centralized review system should be considered to evaluate the management of investigational drugs across a large organization.

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

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

HS

LEARNING OBJECTIVE

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

DISCLOSURES

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

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

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

2 Provide a Risk-Based Framework

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

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

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

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

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

3 Get Involved Early by Providing Support

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

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

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

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

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

before DEA and state inspections occur at the site. Such details should optimally be discussed during the study feasibility stage, as coordinated efforts among facilities, pharmacy, security, safety, compliance, and legal department may be needed and fulfillment of the requirements may impact the study budget due to increased costs for DEA registration, state licensure, security set up, etc.

4 Ensure Reviews are Meaningful While Setting Expectations

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

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

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

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

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

aseptic preparations, as applicable to each investigational drug. If the site does not have adequate resources and procedures, the research team should utilize pharmacy services.

- Delegation:** PIs must consider staff expertise and qualifications when delegating drug handling and administration. For example, if licensed individuals must carry out delegated tasks, such as drug preparation, dispensation and administration, the PI must have their licenses and any pertinent training records on file. When opting to manage an investigational drug at the site, the PI must assess the need for unblinded personnel delegated to handle an open-labeled drug and placebo for a double-blinded study. Lastly, the PI must ensure that unblinded and blinded personnel perform their tasks as delegated to maintain study blinding.

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

5 Offer Flexible Training and Education

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

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

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

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

Conclusion

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

A key component for a centralized review process is to get involved early by assessing regulatory requirements as a whole for the study; this will allow sites to set strategic priorities to reduce

potential delays and avoid other implementation issues. However, reviews should be made meaningful by asking standard key questions regarding management of the investigational drug throughout the life cycle of the study.

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

References

1. International Conference on Harmonization. 1996. *Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance*. www.fda.gov/downloads/Drugs/.../Guidances/ucm073122.pdf
2. U.S. Food and Drug Administration. 1987. Investigational New Drug Application. *Code of Federal Regulations* Title 21, Part 312. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=312

Ji-Eun Kim, RPh, PhD, (jkim31@northwell.edu) is a research pharmacist with the Office of Research Compliance for Northwell Health in New Hyde Park, N.Y.

Emmelyn Kim, MA, MPH, CCRA, CHRC, (ekim@northwell.edu) is director of research compliance with Northwell Health.

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

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

PEER REVIEWED | Robert Jeanfreau, MD

[DOI: 10.14524/CR-16-0012]

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

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

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

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

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

The Scientific Method in Clinical Research

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

HS

LEARNING OBJECTIVE

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

DISCLOSURES

Robert Jeanfreau, MD:
Nothing to disclose

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

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

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

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

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

Applying What We Know

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

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

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

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

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

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

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

Standing the Test of Time

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

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

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

Clearly, establishing the validity of clinical trials by ensuring that they are free from as much bias as possible is the major focus of evidence-based

medicine. To this end, the authoritative *Cochrane Handbook for Systematic Reviews of Interventions* provides guidelines for evaluating the quality of clinical research and identifies six subclasses of bias: selection, performance, detection, attrition, reporting, and miscellaneous.⁵

Consequences of Bias in the Reporting of Adverse Events

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

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

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

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

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

Working Toward Bias Elimination

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

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

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

References

1. Simpson JA, Weiner ESC. 1989. *The Oxford English Dictionary*. Oxford: Clarendon Press.
2. Bhatt A. 2010. Evolution of clinical research: a history before and beyond James Lind. *Persp Clin Res* 1(1):6–10. www.picronline.org/downloadpdf.asp?issn=2229-3485;year=2010;volume=1;issue=1;spage=6;epage=10;aulast=Bhatt;type=2
3. U.S. Food and Drug Administration. Statement of FDA Mission. www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/budgetreports/ucm298331.pdf
4. Penn State Eberly College of Science. STAT 509—Design and Analysis of Clinical Trials. Lesson 4: bias and random error. <https://onlinecourses.science.psu.edu/stat509/node/26>
5. Higgins JPT, Green S. 2008. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, England: Wiley-Blackwell.
6. U.S. Food and Drug Administration. Postmarketing Surveillance Programs. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm

Robert Jeanfreau, MD, (robertjeanfreau@medpharmics.com) is an internist affiliated with multiple hospitals and serves as the president and medical director of Medpharmics in Metairie, La.

Make Your Studies Smarter

OPEN BOOK TEST

This test expires on February 28, 2018

(original release date: 2/1/2017)

Quality Assurance Coordinators: Ensuring Quality at the Site Level

1. Risk-based monitoring (RBM) approaches attempt to:
 - A. Decrease the number of data points
 - B. Save resources
 - C. Increase risk
 - D. Shorten monitoring plans
 2. Some have claimed that RBM can reduce costs over traditional monitoring approaches by at least:
 - A. 10%
 - B. 20%
 - C. 25%
 - D. 30%
 3. One way to enact safeguards and increase quality is for sites to:
 - A. Conduct new clinical trials
 - B. Increase study team members' salaries
 - C. Employ onsite quality assurance coordinators (QACs)
 - D. Ignore RBM plans
 4. QACs may perform function like:
 1. Source data verification
 2. Pharmacy and lab audits
 3. Obtaining informed consent
 4. Staff training
 - A. 1, 2, and 3 only
 - B. 1, 2, and 4 only
 - C. 1, 3, and 4 only
 - D. 2, 3, and 4 only
 5. Incorporating the QAC role will assist sites in the delivery of accurate clinical data, and encourage the focus on subject safety during the conduct of a clinical trial by:
 1. Developing quality assurance and quality control procedures
 2. Focusing on process improvement
 3. Having the QAC be part of the study team
 4. Relying on an RBM approach
 - A. 1, 2, and 3 only
 - B. 1, 2, and 4 only
 - C. 1, 3, and 4 only
 - D. 2, 3, and 4 only
 6. The QAC may perform the following:
 1. Provide real-time monitoring of study data
 2. Conduct study procedures
 3. Conduct a dry run prior to study initiation
 4. Ensure written procedures are in place that reflect study activity
 - A. 1, 2, and 3 only
 - B. 1, 2, and 4 only
 - C. 1, 3, and 4 only
 - D. 2, 3, and 4 only
 7. The QAC responsibilities are defined by:
 - A. The protocol
 - B. U.S. Food and Drug Administration (FDA) regulations
 - C. A clinical quality management plan
 - D. An RBM plan
 8. Quality management plans:
 1. Take into account potential risks specific to each study
 2. Include quality assurance activities
 3. Include quality control activities
 4. May not be amended after the initiation of the study
 - A. 1, 2, and 3 only
 - B. 1, 2, and 4 only
 - C. 1, 3, and 4 only
 - D. 2, 3, and 4 only
 9. QACs may have direct access to:
 1. FDA systems
 2. Institutional review board systems
 3. U.S. Department of Health and Human Services systems
 4. Electronic medical records
 - A. 1 and 3 only
 - B. 1 and 4 only
 - C. 2 and 3 only
 - D. 2 and 4 only
 10. Benefits of the QAC role include:
 1. Real-time monitoring
 2. Greater access to data and information
 3. Increase in study budget
 4. Better compliance with regulations
 - A. 1, 2, and 3 only
 - B. 1, 2, and 4 only
 - C. 1, 3, and 4 only
 - D. 2, 3, and 4 only
- ### Need Help With Investigational Drug Management? Five Things Large Research Institutions Should Consider
11. Based on the article, which of the following scenarios presents the greatest challenge for investigational drug management?
 - A. A central investigational pharmacy providing services for a single hospital campus
 - B. Many outpatient clinics situated separately from hospital facilities, spread out across multiple regions, and individually providing investigational drugs to research participants
 - C. Research drug trials primarily occurring in one geographical location
 - D. A large organization that provides investigational drug management services through a central investigational pharmacy
 12. At what level should a centralized review of investigational drug management optimally be embedded?
 - A. Local institutional review board (IRB)
 - B. External IRB
 - C. Central IRB
 - D. Institution-specific research approval process
 13. A centralized review of investigational drug management will be able to:
 - A. Resolve operational issues at each research site
 - B. Comprehensively review all studies and sites handling investigational drugs and capture relevant data
 - C. Bypass IRB approval
 - D. Increase subject enrollment
 14. Which of the following should be considered when a principal investigator (PI) opts to manage investigational drugs at his or her own practice?
 - A. Convenience for the research team
 - B. The experience of the research team with investigational drug handling
 - C. The PI's academic rank
 - D. The size of the practice and its office space
 15. Which of the following will decentralized institutions have a greater need to provide?
 - A. Centralized investigational pharmacy services
 - B. Outsourced research staff
 - C. Guidance documents, tools, and training based on ongoing reviews and audits
 - D. Single IRB review

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

- 16.** Poorly designed protocols without specific instructions or plans for investigational drug handling and management will likely lead to:
- Expedited IRB approval
 - Accelerated study initiation
 - Compliance with regulatory requirements
 - Inconsistent investigational drug management
- 17.** For investigator-initiated studies, who is responsible for ensuring the quality of investigational drugs?
- The local IRB
 - The PI
 - A central reviewer
 - The U.S. Food and Drug Administration
- 18.** What is the function of a centralized reviewer with expertise in investigational drug management during the institutional approval review process?
- Identify the necessary resources and procedures for investigational drug management to promote compliance with regulatory requirements and to facilitate research
 - Write investigational drug handling procedures for individual sites
 - Develop the study budget
 - Purchase resources for drug management
- 19.** If a central research location receives and distributes an investigational product to multiple sites within a large organization, which of the following must be established in addition to other drug handling procedures?
- Drug randomization
 - Drug administration
 - Subject enrollment
 - Drug transport and tracking
- 20.** Which of the following formats will provide a more flexible and efficient approach for training and education within a large organization?
- Face-to-face lectures
 - On-the-job training
 - Web-based courses
 - Individualized coaching
- 21.** An adverse event is:
- Any side effect directly attributable to a drug or device
 - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
 - Any negative symptom identified by a subject during the course of a clinical trial
 - Any negative symptom or lab abnormality identified as a result of the drug under investigation
- 22.** The scientific method is:
- Ultimately flawed, as evidenced by Heisenberg's principle of uncertainty
 - Not utilized in human research because it would place human subjects at unacceptable risk
 - A process of testing, under controlled conditions, the validity of a hypothesis as determined by the evaluation of measurements obtained during testing
 - Only utilized in the laboratory setting where every possible variable can be controlled
- 23.** The first double-blind, controlled study in humans:
- Yielded the first and only effective treatment for the common cold
 - Was conducted on prisoners without their consent
 - Was the streptomycin trial in 1946
 - Was the patulin study in 1943
- 24.** Efforts to ensure the safety of human subjects in clinical trials:
- Begin before a drug or device is first used by or on a volunteer study participant
 - Are likely to be fully characterized only as Phase III studies are conducted
 - Are of concern only when the U.S. Food and Drug Administration (FDA) is more interested in a product's safety vs. its efficacy
 - Begin through the conduct of unofficial studies by researchers who are independent of the product's manufacturer
- 25.** The FDA's mission is to:
- Protect the public health by assuring the quality of food and effectiveness of investigational drugs only
 - Protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation
 - Protect the public health by assuring the safety of medical devices only in response to consumer complaints
 - Protect the public health by preventing foreign food and medical products from being used in the U.S.
- 26.** Error, as defined in the scientific method:
- Will always invalidate the conclusions of a study
 - Is readily detectable
 - Is the difference between the true value of a measurement and the recorded value
 - Can always be uncovered by careful statistical analysis
- 27.** Systematic error is:
- An unintentional error due to chance
 - Always intentional
 - Due to faulty systems
 - Also known as bias
- 28.** The publication that provides guidelines for evaluating the quality of clinical research is:
- Cochrane Handbook for Systematic Reviews of Interventions
 - Code of Federal Regulations
 - Guidelines for Good Clinical Practice
 - Cochrane Guide to Reputable Research
- 29.** "Positive" adverse events are:
- Only discovered in Phase IV studies
 - Tracked through patient registries
 - The reason postmarketing surveillance is conducted
 - Subjective in nature
- 30.** Possible benefits of identifying "positive" adverse events include:
- A greater understanding of a drug's mechanism of action
 - Identification of other possible uses for the drug under investigation
 - Fostering a sense of objectivity that is a hallmark of all scientific endeavors
 - Simplification of warning labels for prescription drugs
 - 1, 2, and 3 only
 - 1, 2, and 4 only
 - 1, 3, and 4 only
 - 2, 3, and 4 only

In Pursuit of Education and Training for Learning, for Listening, for Life

Education fuels personal and professional growth. Whether you are at the beginning of your career, already established, or even taking your first glances at retirement, now is always the right time to explore classes, webinars, and other events from which you can learn about today's best ideas and tomorrow's most likely trends.

Clinical Researcher reached out to Association of Clinical Research Professionals (ACRP) members for feedback on how education has helped them perform their jobs better and avoid the tedium that can morph into burnout. As can be gleaned from their input below, the benefits of continuing education mentioned by our interviewees touched on a wide range of topics with "evergreen" importance to career establishment and growth.

"I find education and constant training are effective in helping all staff involved in the research process to stay sharp and focused on requirements to perform job functions," says Karen Dziadziola, RN, CCRC, a clinical research manager with Carolina Clinical Trials, LLC.

"I think that the advancement of our careers is a positive effect of ongoing training, but the bigger picture is our responsibility as professionals to continuously improve the field," says Samkeliso Beusterien, MS, CCRP, CCRA, with the University of Michigan Health System.

Marty Osbourn, RN, ADN, CCRC, research director for Kentucky Pediatric/Adult Research, has managed a clinical research site within a private practice for 25 years. She sees the value of training from another perspective. "I am consistently faced with the dilemma of the level of education of a potential employee when I hire," she says. "Over the years, I have learned that there are so many aspects to conducting clinical trials, and the level of education required for those aspects vary."

What follows are edited interviews with these and two more ACRP members who have remained active in education for their entire careers.



Linda Schumacher, RN, BSN, CCRC:

I am a research nurse in a rural area of Missouri working in oncology. When you are based in a rural area, it is very hard to keep yourself updated. There are no local professional organizations to reach out to or network with. My institution depends on me to know what to do to meet the current needs of the department, no matter what that might be (administration, coordination, regulations, Good Clinical Practice, etc.). I am a member of the Chicagoland Chapter of ACRP. I traveled to Chicago to attend the prep course for my certification, and then traveled to Kansas City to take the test. I read or at least skim all the [ACRP] blogs to try to keep up on what is happening and what other sites are running into or having problems with, to make sure I would know what to do in those situations (you don't know what you don't know). I am fortunate to work for an institution that works hard to put our patients first in all things, and will go that extra mile to meet their needs and the needs of its employees. I am looking forward to new learning and networking opportunities at the ACRP Meeting & Expo this year in Seattle.

The advancement of our careers is a positive effect of ongoing training, but the bigger picture is our responsibility as professionals to continuously improve the field.



Marty Osbourn, RN, ADN, CCRC:

Education requirements depend on the role. For my research nurse positions, absolutely, I believe that education is essential. I require my research nurses to be a registered nurse (RN) or licensed practical nurse (LPN). I haven't really seen significant difference between an RN or LPN, but have definitely seen the difference in the practical abilities of a nurse versus staff who are not a trained nurse conducting study procedures. I believe that a nursing background is very beneficial in determining eligibility for studies, assessing patients for adverse events, reviewing medical histories, collecting vital signs, and conducting other more specific assessments or procedures. It goes without saying all of these procedures are performed with the oversight of the principal investigator (PI) or a physician sub-investigator.

A qualified, competent research nurse is an asset to the investigators. Collecting the data, after all, is an important aspect of any clinical trial, second only to patient safety, of course. After working with many different level of personnel through my career, I have trained and managed more than 40 full-time staff members, with varying levels of education. I consistently have recognized that a nursing degree (or a similar medical degree, such as a medical assistant) is important for the staff member performing the study procedures and collecting data. I am also more confident that a research nurse will always meet the regulatory expectations of being a medically qualified staff member to perform specific medical procedures that are not required to be completed by a physician or nurse practitioner. This, in turn, will prevent questions by sponsors or regulatory agencies about the qualifications of staff. Preventing questions by providing quality data by qualified staff is one of my overall goals from a site perspective.



Lee Truax-Bellows, FNP, CCRA, RQAP-GCP, TIACR, president and CEO of Norwich Clinical Research Associates:

I started as a monitor and without continuing my education, I never would have been able to move beyond that role. One of the things that I love about clinical research is that there are so many different opportunities within it. You need the related education in order to be able to move around within the industry itself. That's the primary reason I encourage people, unless they want to remain a monitor or in whatever level they entered at. Usually, I [attend educational events] specific to the role I'm seeking. When we started working with medical devices, I started taking medical device courses. When I wanted to become a project manager, I went out there and started taking medical device courses, and the same with regulatory consulting. Some of it was self-education through reading blogs and attending courses and webinars. Being able to move around in the industry can help you to avoid burnout, too.

Training also gives you the skillset to mentor someone. I recently had someone [who had visited] the ACRP website come to me and ask if I could mentor them in several ways, and I agreed to do so. I do a lot of that. The nice thing about mentoring is, if you don't know [something], it forces you to look it up! I learn a lot about differences between clinical labs and Good Laboratory Practice labs just by researching to help mentor someone. It helps you keep up to speed. It's one of the reasons I like the blogs—they help to keep you current on the latest questions, what people's thoughts are, and where the industry is currently going. It needs to be done on a continuous basis.

I am consistently faced with the dilemma of the level of education of a potential employee when I hire.



Samkeliso Beusterien, MS, CCRP, CCRA:

I believe that ongoing training is essential in our profession. I earned a Master of Science degree in Clinical Research Administration from Eastern Michigan University in 2011. I currently work as a clinical research associate (CRA) in an emergency medicine clinical trials network at the University of Michigan. Because I am fortunate enough to work at a large academic institution, I have regular access to educational opportunities on campus, such as seminars, webinars, and workshops. We have a Clinical and Translational Science Award-funded Michigan Institute for Clinical & Health Research here at U of M. I regularly read their study coordinator newsletter for updates in the clinical research enterprise, as well as other available resources for training research staff. I also participate in ongoing education activities in order to maintain my certifications through ACRP and SoCRA, and rely on many resources to meet the requirements. Even the ACRP Online Community forum is a form of ongoing education—I find that I always learn something from the various topics that come up from others within the profession.

Here are two recent examples of how ongoing education helped me in tangible ways:

- We are incorporating risk-based monitoring into the monitoring plan for one of our trials. To prepare, I completed the ACRP eLearning course on “Risk-Based Monitoring: The Essentials for CRAs.” I also found the ACRP Online Conference Library replay of a presentation from a recent Meeting & Expo on “Remote Monitoring: How Far Can We Go?” very helpful. These educational resources helped me to think about my role in implementing a successful risk-based monitoring plan, and even my strategy and goals when I go out on a site visit.
- Ensuring that study teams have the appropriate regulatory and protocol training is a big part of what we do during our trials. In an effort to provide additional educational opportunities within our network (which includes hundreds of study coordinators in hospitals across the country), we have applied for accreditation

of our ongoing study coordinator education within the university. I read the June 2014 issue of *Clinical Researcher* and watched several relevant sessions on the ACRP Online Conference Library to prepare. From there, I used the Joint Task Force for Clinical Trial Competency document to build our application. It helped me immensely to define the competency domains we were trying to improve with our training. I’m really pleased to see the work that ACRP is doing toward standardized competence requirements, which I think increases the overall credibility and professionalism of the clinical trial workforce. I’m also very pleased to see the different training and education resources that ACRP provides for research professionals to that end.



Karen Dziadziola, RN, CCRC:

When I started as a clinical research coordinator (CRC), I had only bedside hospital experience as a diploma-educated RN. As I was becoming disenchanted with bedside nursing care, my nurse manager recommended I try clinical research, and so my career began. I absolutely had no idea what clinical research consisted of; I had only participated by doing non-standard of care procedures for these “studies” in the cardiac unit in which I worked.

The hospital in which I was employed at the time sent me to a weekend course on basic clinical research. This was an excellent way to learn the ropes and start getting my feet wet. This course in no way gave me the complete education needed to perform my job, but I was lucky enough to work side by side with a coordinator who was extremely organized and experienced. Having the basic course and experienced staff to work with gave me the knowledge and confidence to become the experienced coordinator I am today. I was able to obtain and maintain my CCRC status since 2009, and I feel this certification is one that lets sponsors and contract research organizations know this site takes clinical research seriously [and stays current on developments in the field].

I find education and constant training are effective in helping all staff involved in the research process to stay sharp and focused on requirements to perform job functions.

→ WORKFORCE INNOVATION

Terri Hinkley, RN, BScN, MBA, CCRC, FACRP

Let's Focus on Competency, Not Tenure

I'd like to begin my inaugural *Clinical Researcher* column by wishing you all a very happy 2017! Personally, I'm very eager to see what 2017 brings, as we have some exciting and innovative initiatives planned for the year.

In my new role at ACRP, I'm focused on initiatives, products, and services intended to further develop the clinical research workforce. For those of you who know me, you know this is my passion and what I care most about. For those of you who don't know me, I hope you will see, over the ensuing months and years, that professionalization of the clinical research profession is what drives me forward every day. I am committed to this profession and to everyone who practices in it, and I look forward to working with you and on your behalf to move the needle in clinical research education, training, and professional development. To that end, I wanted first to provide you all with an update on ACRP's efforts to map the competencies required of clinical trial monitors.

Concerning Competency

As you may recall, ACRP released a position paper in September 2015 calling for the end of the arbitrary practice of requiring two years of monitoring experience for entry-level monitors, a practice which pretty much eliminated the monitor/clinical research associate (CRA) pipeline and resulted in an acute shortage of trained and qualified CRAs. ACRP believed, and still does today, that by focusing on competency rather than tenure, we can identify, educate, train, and prepare the future clinical research workforce.

Competence is defined as the knowledge, skills, and attributes (or attitudes) required to competently perform a task or role. In recent years, many industries and educational institutions have begun to zero in on knowledge *application* vs. knowledge *acquisition*, and have increasingly focused on competencies as a more reliable predictor of performance. Further, data from medical education programs have indicated that patient safety is enhanced by emphasizing competencies.¹

Given the increased focus on competence, and the Joint Task Force for Clinical Trial Competency Framework, ACRP identified an opportunity for the industry to reconsider how it approaches workforce planning and development.

Initially, ACRP planned to work with the task force to map the entry-level competencies required of study monitors. However, after some robust discussion, the task force members determined that exercise would be incomplete, and that to do their job well, felt it was necessary to map the competencies required over the life cycle of a CRA. Therefore, they determined that they would map not only the entry-level competencies, but the intermediate, experienced, and lead CRA competencies as well.

I'm excited to say that the CRA Competency Task Force, after a one-year effort, has completed the work of mapping the competencies of CRAs using the Joint Task Force for Clinical Trial Competency Framework as the foundation. The task force also considered other competency frameworks from participating task force organizations, academic institutions, and other entities, like the International Academy of Clinical Research, a for-profit training and accreditation provider in the U.K.

ACRP has recently released the competencies for public comment; you can access them by searching for "monitoring competencies" on the ACRP website. The competencies will be available for public comment until March 5, 2017. Once we've considered the feedback received during the public review period, we will disseminate and publicize the final competencies.

Following the dissemination of the CRA competencies, ACRP will quickly shift gears and begin working on the competencies required of site staff. **Stay tuned, you won't believe what we have planned for 2017...you spoke, we listened!**

I look forward to working with you and on your behalf to move the needle in clinical research education, training, and professional development.

Reference

1. Steinhäuser J, Chenot J-F, Roos M, Ledig T, Joos S. 2013. Competence-based curriculum development for general practice in Germany: a stepwise peer-based approach instead of reinventing the wheel. *BMC Research Notes* 6:314–21.



Terri Hinkley, RN, BScN, MBA, CCRC, FACRP, (thinkley@acrpnet.org) is the ACRP Workforce Innovation Officer, and had earlier served as Deputy Executive Director.

ACRP 2017 MEETING & EXPO

SEATTLE, WASHINGTON — APRIL 28 – MAY 2



Innovation. Implementation. Collaboration.

See the future of clinical research at the ACRP Meeting & Expo. Learn from the influencers, innovators, and regulators driving change in clinical trial operations. You and your team will gain practical strategies to manage change, streamline operations, and minimize risk. Position yourself for success at the premier education and networking event for clinical research professionals.

Who's Attending?

2,000+ Clinical Research Professionals, Including Trial Coordinators, Monitors, Investigators, Project and Site Managers, Patient Recruiters, and More

100+ Expert Speakers from Sponsors, CROs, Sites, Regulatory Agencies, and More

100+ Exhibiting Companies and Organizations

Why Should You?

100+ Educational Sessions Uniquely Tailored to Professionals Conducting Clinical Trials

Networking Opportunities for Peer-to-Peer Exchange and Engagement

Ability to Earn Continuing Education Units

On-Demand Access to All ACRP 2017 Sessions through the Online Conference Library for 2 Years

What's New for ACRP 2017?

- More Advanced-Level Content for Experienced Professionals
- Educational Sessions for a Broader Spectrum of Professionals
- Greater Emphasis on Practical Application to Improve Trial Operations
- "Master Series" Helping Put Theories into Practice
- Educational Content Aligned with Core Competencies for Clinical Research Professionals

Program Highlights*

FRIDAY, APRIL 28 - PRECONFERENCE WORKSHOPS

Hands Across the Water: A Comparison of Clinical Trials in the EU and U.S.
Practicing Good Science Through Ethical Study Design
GCP Auditing: Apply Your New Skills at Work
Tools to Help Clinical Sites Optimize Performance and Maintain GCP Compliance
Fine-Tune Your Vulnerability Radar: Protecting the Vulnerable
Unlocking the Value of Ethics Using Educational Games

SATURDAY, APRIL 29

Mastering Your Response to the Dreaded FDA Form 483
Wearables and Big Data: The New Gold Standard for Clinical Trials
The Seismic Shift in the Monitoring Paradigm: From Quality Control to Quality Assurance
eConsent: Preparing for Paperless Consent
Going Paperless: A Smart Way to Increase Site Efficiency and Save Resources
The 2016 Medical Device Directive: What It Means to You

SUNDAY, APRIL 30

Investigator Attrition: Strategies to Turn the Tide
The ICH GCP E6 R2 Revisions: Impact on the PI and Site
Bring Your Own Device: Is it Right for Your Clinical Research Enterprise?
Forging a New Path to Professionalism: GCP vs. Core Competency-Based Training
Maximizing the ROI of Your Clinical Trial Management System
Melding Consumer Big Data with Medical Big Data: The Regulatory and Ethical Implications

MONDAY, MAY 1

Beyond Audit Survival: The Busy Professional's Guide to Audit Preparation
Trends, Strategies, and Tools for Achieving Informed Consent
Build a Better Site Budget to Ensure Trial Success
Putting Patient-Centric Principles into Practice
2017 Update: U.S. Healthcare Regulatory Changes and their Impact on Clinical Research

TUESDAY, MAY 2

Medical Cannabis: A Substitute for Prescription Opioid Use?
The Power and Reach of Social Media in Clinical Trials
Optimize Workflow and Resource Allocation Using LEAN-R
Returning Research Test Results: Know Your Ethical and Legal Obligations

* Subject to Change

HOTEL & TRAVEL

Book your room through ACRP to make sure you get the lowest guaranteed rates on your stay in Seattle. Plus, you can save 10% on your flight by flying Delta.

ATTENDEE ROI TOOLKIT

Use the attendee ROI toolkit to gain employer support for your trip to ACRP 2017. Show the return on investment you and your organization will enjoy.

GROUP DISCOUNTS

Save \$100 on your registration with special discounts for groups of three or more colleagues from the same organization.

CONFERENCE.ACRPNET.ORG

Visit us online to register or learn more about the ACRP 2017 Meeting & Expo.



■ FOR LEARNING ■ FOR LISTENING ■ FOR LIFE

Reducing Clinical Trial Time and Cost by Increasing Knowledge



Trainning has long been a topic of serious consideration in our industry, and I am delighted that professionalism has more recently emerged as an added facet in conversations about the value and goals of training in clinical research settings. With the high demand for research professionals at all levels of clinical research operations, we have concerned ourselves with how to quickly and effectively train novices to perform complex, highly regulated jobs. This deserves ongoing attention, of course, but I think we have missed a critical area of training that would be beneficial for many individuals to have: business training.

They are trained to do the job, but not how to think through the *business* of what they do. Understanding the bigger picture represents a major difference between a trade and a profession.

As an industry, we routinely publish articles that lead with statistics regarding the tremendous costs caused by trial delays in start-up and execution. Now, imagine if new employees were trained not only *how* to do their jobs, but *why* each task matters for the company and the industry and how to do each task efficiently.

This type of training likely occurs at managerial levels, but not among new hires who could still make use of a basic understanding of financial and project management principles and applications. I contend this type of training would change people's behaviors. In turn, those collective changes in perspective and behaviors would alleviate some of the financial pains in our industry.

Furthermore, training new clinical research coordinators (CRCs), clinical research associates (CRAs), data managers, lab specialists—you name it—in basic principles of business would have a long-term effect; it would foster professionalism in the industry. To some extent right now, most of these jobs receive training like one would in a trade school. That is, they are trained to do the job, but not how to think through the *business* of what they do. Understanding the bigger picture represents a major difference between a trade and a profession.

What Can We Solve if We Put Our Minds Together?

Suppose we took one significant problem area and “solved” it as an industry. Elsewhere in this issue, Priya Temkar makes a strong case for the need to decrease time in startup. What would be the financial impact for all of us—from drug developers to patients—if we accomplished this?

Let me give you a startling piece of data: 95% of the time spent performing a typical process is just time spent waiting.¹ That means that, whatever amount of time it takes to complete the process, only about 5% of that time is spent on the actual work.

This insight comes from a book on Lean Six Sigma, which is a business improvement methodology aimed at eliminating waste—wasted time, wasted steps in processes, and wasted activity doing re-work. In a different publication, Dawn Pope² presented two case studies from our industry and found that using Lean Six Sigma principles had a remarkable impact on efficiency, with very little cost. Pfizer decreased its contract times with academic medical centers by more than 50%, and Copernicus IRB decreased submission times by 20% (and did so with fewer errors).



I am not advocating for Lean Six Sigma, per se; I am advocating for teaching people how to think not just about their jobs, but about business as a whole.

Every person employed in the clinical trial enterprise engages in processes where there is a tremendous amount of waste. Recently, I saw two CRCs take an hour apiece responding to issues on monitoring visit follow-up letters that never should have been in the letters. (As examples, there were lists of documentation noted as missing but actually in the regulatory binders, and accountability records that were noted as pending issues only because the CRA had not found the time to review those records in nearly nine months.)

Nearly one hour per CRC was thus not spent recruiting patients or entering data for the sponsor. It was time, in other words, that did not help the trial at all, but simply protected the principal investigator from future repercussions that can be caused by an inaccurate monitoring letter if a Food and Drug Administration representative happened to visit the site.

I assume there is also a project manager above each CRA who has to review such lengthy follow-up letters, which reflect poor time management more

than poor quality. I further assume there is a quality professional at the larger contract research organizations who is analyzing data from those letters and considering site quality metrics. Our own site's quality people read each letter, advise the CRCs, and follow-up on the responses given to the CRAs' letters. In all, then, each follow-up letter that contains misinformation is a cause of several hours of unnecessary work.

Imagine, then, if new CRAs were trained to understand the consequences of a poor letter, just as new CRCs need to be trained on the consequences of poor data entry. Now imagine this effect multiplied by thousands of CRAs and CRCs.

When it All Comes Down to it...

It is as simple as giving people the *why*. There are certain actions that mean little to the person doing them, but translate to great waste for the trial. By adding business training to job training, we foster professionalism through doing nothing more than explaining *why* each task is important and *how* to complete those tasks efficiently.

References

1. George ML. 2003. *Lean Six Sigma for service: how to use lean speed and six sigma quality to improve services and transactions*. McGraw-Hill (New York, N.Y.).
2. Pope D. 2012. Lean Six Sigma in the clinical trial industry: two perspectives. *App Clin Trials*. www.appliedclinicaltrials.com/lean-six-sigma-clinical-trial-industry-two-perspectives



Christine Senn, PhD, CCRC, CPI, (csenn@iacthealth.com) is the chief implementation officer and a member of the Quality Assurance and Compliance Committee with IACT Health in Columbus, Ga.

BECOME THE Compliance expert

- Learn in a program offered in partnership with Northwestern University's Feinberg School of Medicine and from a curriculum informed with the latest insights on healthcare, translational research and regulation.
- Develop the interdisciplinary core competencies needed for leadership roles in the regulatory compliance field.
- Focus on your area of interest by choosing from tracks in healthcare compliance, clinical research and quality systems.
- Earn your Northwestern University master's degree by attending part-time evening courses in Evanston and Chicago.

Apply today — the summer application deadline is April 15.
sps.northwestern.edu/grad • 312-503-2579

Northwestern | REGULATORY COMPLIANCE
 School of Professional Studies

The New European Union Regulation for Clinical Trials

[DOI: 10.14524/CR-16-0017]

PEER REVIEWED
Yves Geysels, PhD
Christopher A. Bamford, PhD
Richard H. Corr





Clinical trials can be defined as investigations made in humans to discover or verify the positive and/or negative effects (effectiveness and safety) of one or more investigational medicinal products.¹ Currently, the conduct of clinical trials in the European Union (EU) must conform with the Directive 2001/20/EC of the European Parliament (the Directive), a document providing trial requirements and guidelines aimed mainly at guaranteeing the highest possible patient safety, enforcing the use of good clinical practice (GCP), and striving for high scientific value and usefulness of the data generated, among other goals.

Upon its initial release, this document was considered an important step toward harmonization of laws in the EU; however, it was each Member State's responsibility to implement the contents of the Directive in their own national laws. Thus, different interpretations of the document resulted in slight discrepancies between the laws of each Member State. Also, the authorization of a clinical trial was specific for each Member State.

Thus, applying for a multicenter trial across different Member States involved, for sponsors, sending largely similar dossiers to each of the concerned Member States and dealing with the different applicable fees in each country. While the 2001/20/EC Directive had noble aims, the results were unsatisfactory, partly because it introduced requirements that ultimately resulted in higher costs for sponsors, and because adequate harmonization had not been achieved.

According to the Council of the European Union, between 2007 and 2011 the number of applications for clinical trials decreased by 25% in the EU.² This is partially attributed to the Clinical Trials Directive of 2001, which ensured a high level of patient safety, but an unfavorable regulatory framework not only for pharmaceutical companies, but also for academic research in general. The Directive caused, for example, increases in staff requirements for sponsors, insurance fees, and administrative costs.

As a result, many pharmaceutical companies and academic researchers felt discouraged to submit new applications within the EU.

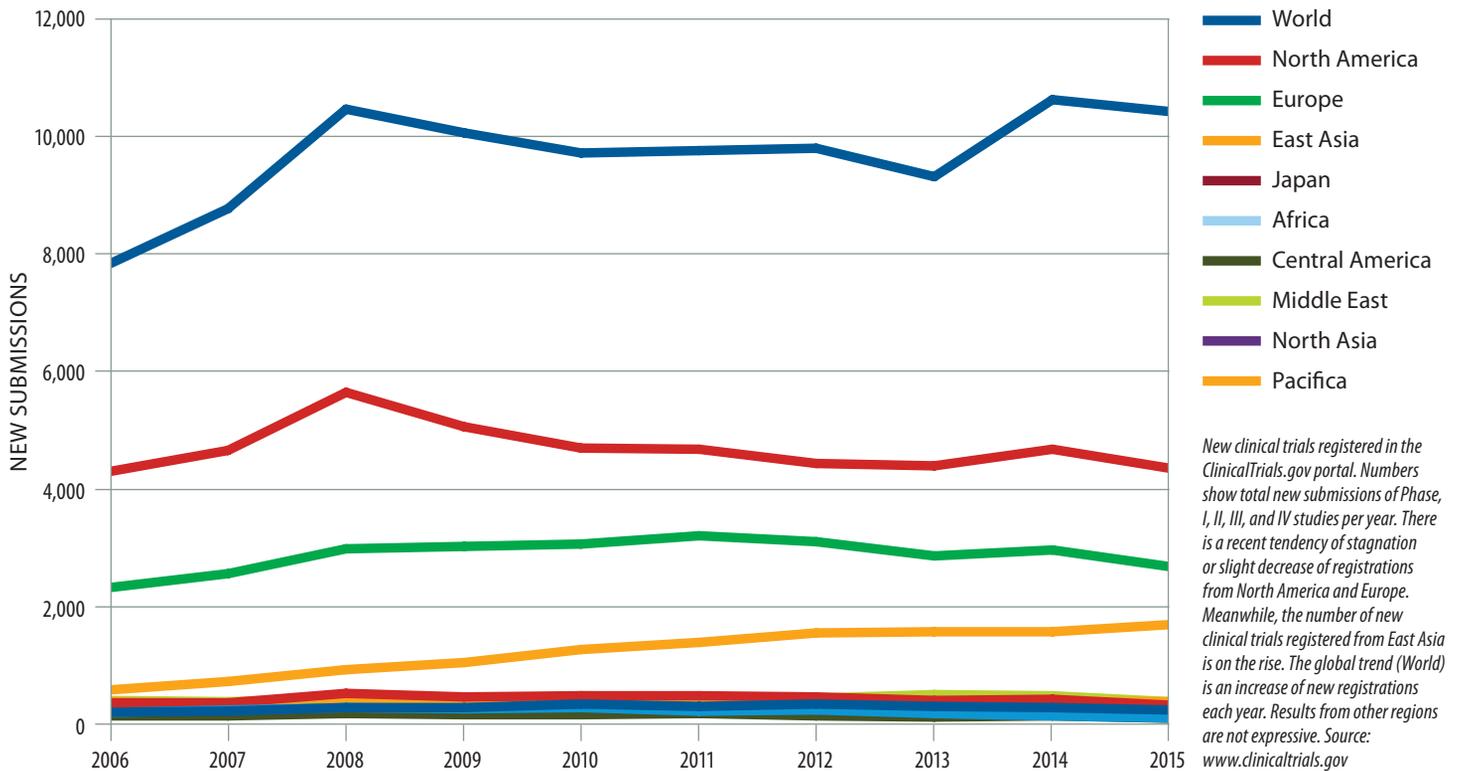
CLINICAL TRIALS TODAY

The number of clinical trials worldwide is increasing rapidly. The total number of registered studies at ClinicalTrials.gov was 5,633 studies in 2000. A decade later in 2010, this number had increased 20-fold to a total of 101,157 studies, and as of May 26, 2016, no less than 216,408 were registered at the portal.³ However, while the number of clinical trials is increasing globally, some regions of the world benefit from the trend more than others, if at all.

When considering data from ClinicalTrials.gov, the number of new registered clinical trials per year in Europe (see Figure 1; green line) shows an apparent stagnation, whereas the global tendency is growth (top blue line). In contrast, the number of new clinical trials registered in East Asia (China, Hong Kong, Korea, and Taiwan; orange line) grew considerably. New clinical trials in East Asia went from a modest 7.3% of global registrations in 2006 to 16.2% in 2015.

These numbers suggest that East Asian countries are becoming increasingly attractive options for pharmaceutical companies that wish to conduct clinical studies. This could be due to a

FIGURE 1: New Clinical Trials Registered Per Year



While the 2001/20/EC Directive had noble aims, the results were unsatisfactory, partly because it introduced requirements that ultimately resulted in higher costs for sponsors, and because adequate harmonization had not been achieved.

sufficiently developed scientific community, robust expenditure for health research, and easy access to a large population, as is the case of China.^{4,5} Another interpretation is that European countries have a higher growth potential than is currently being explored when it comes to clinical studies.

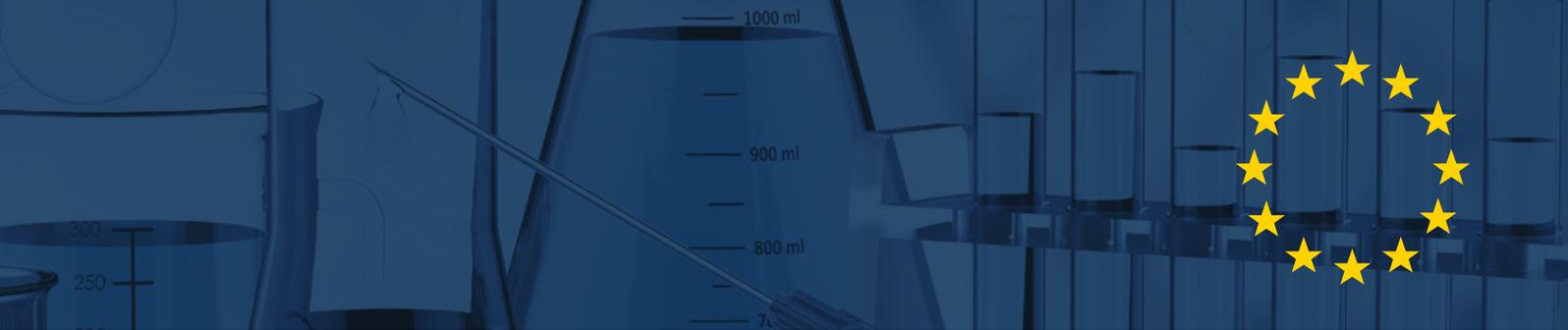
Addressing the issues of the law concerning the authorization and conduct of clinical trials in Europe could help in achieving its full potential of growth. The data on the numbers and geographic distributions of clinical trials shown in Figure 1 are derived from the ClinicalTrials.gov database, which means that these results only apply to U.S. companies and studies under U.S. jurisdiction. Although most pharmaceutical companies submit details about their global clinical trials to this database as well, it still under-represents the number of global trials worldwide.

THE NEW REGULATIONS

The approximation of laws between Member States of the EU is foreseen by the very treaty that establishes the functioning of the EU. In Article 114 of the treaty, it is defined that the European

Parliament and Council shall “adopt measures for the approximation of the provisions laid down by law, regulation or administrative action.” Meanwhile, the treaty also implies, in Article 168, that a high level of human health protection is paramount when defining and implementing a new policy or regulation.⁶

The “new Regulation EU No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC” (the Regulation) was adopted by the European Parliament (on April 2, 2014) and by the Council of Ministers (on April 14, 2014) and signed off on April 16, 2014. This document specifically mentions and respects the previously cited articles. The new Regulation aims to simplify current rules, streamline the application procedure for new clinical trials, provide more transparency in general, and harmonize the process of performing clinical trials throughout all the Member States of the EU. The changes aim to make the EU more attractive for future clinical trials and turn around the decreasing number in new clinical trials observed in recent years.²



The scope of the Regulation is extensive—it covers, in its main text and many appendices, the new authorization procedures, temporal definitions, and conditions for the start of the trial, any suspension or hold on its activities, and any early termination; the protection of subjects; informed consent; the conduct of trials; the reporting of safety issues; insurance requirements; and manufacturing practices (among other subjects). It also contains updated definitions of many key terms for the Regulation, such as the definition of a “clinical trial.”

In the new Regulation, a clinical trial is defined as a type of clinical study that fulfills any of the three following conditions: 1) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; 2) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or 3) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Certain aspects are not directly covered by the new Regulation and remain country-specific considerations, including ethical issues and the involvement of independent ethics committees, legal representative of the subject not able to provide informed consent, rules of liability in the case of damages, requirements for investigators and site qualification, and requirements for country/site-specific documents (including expectations related to the form of notarization and language(s) to be used).

The new Regulation applies directly to all individuals in the EU. It was published in the *Official Journal* on May 27, 2014, but will only become fully applicable when its requirements are met. The time of its implementation is defined to be six months after the European Commission issues a report confirming that the required new information technology infrastructure, namely the EU-portal and the EU-database for clinical trials (discussed below), is fully functional.^{7,8} The portal and the database are being developed by the European Medicines Agency (EMA) in collaboration with the Member States and the European Commission, as defined in Articles 80, 81, and 82 of the 536/2014 Regulation. The current time frame established by the EMA in December 2015 sets October 2018 as the target for when the Regulation will become fully applicable.⁸

In order to prevent inconveniences for the sponsors because of the changes, there will be a transition period of one year, during which

new clinical trial applications can be authorized either according to the old 2001/20/EC Directive or according to the new 536/2014 Regulation, as requested by the sponsor. Also, clinical trials already authorized in accordance with the current Directive will be able to continue following the Directive until up to three years after the new Regulation comes into effect. As established in the EMA time frame, the 2001 Directive will no longer be applicable on October 2021.

MAIN CHANGES

The first change noticeable between the 2001/20/EC Directive and the 536/2014 Regulation is the nature of the document. While a directive is a legislative act that sets out a number of goals that all EU Member States must achieve individually through changes in their own national legislation, a regulation is a binding legislative act, immediately applicable and enforceable in the whole EU, and thus has a legislative power comparable to a law.^{9,10} Sponsors and investigators for clinical trials taking place in multiple Member States can rely directly on the new Regulation, as opposed to dealing with each Member State’s individual approach to an EU directive.

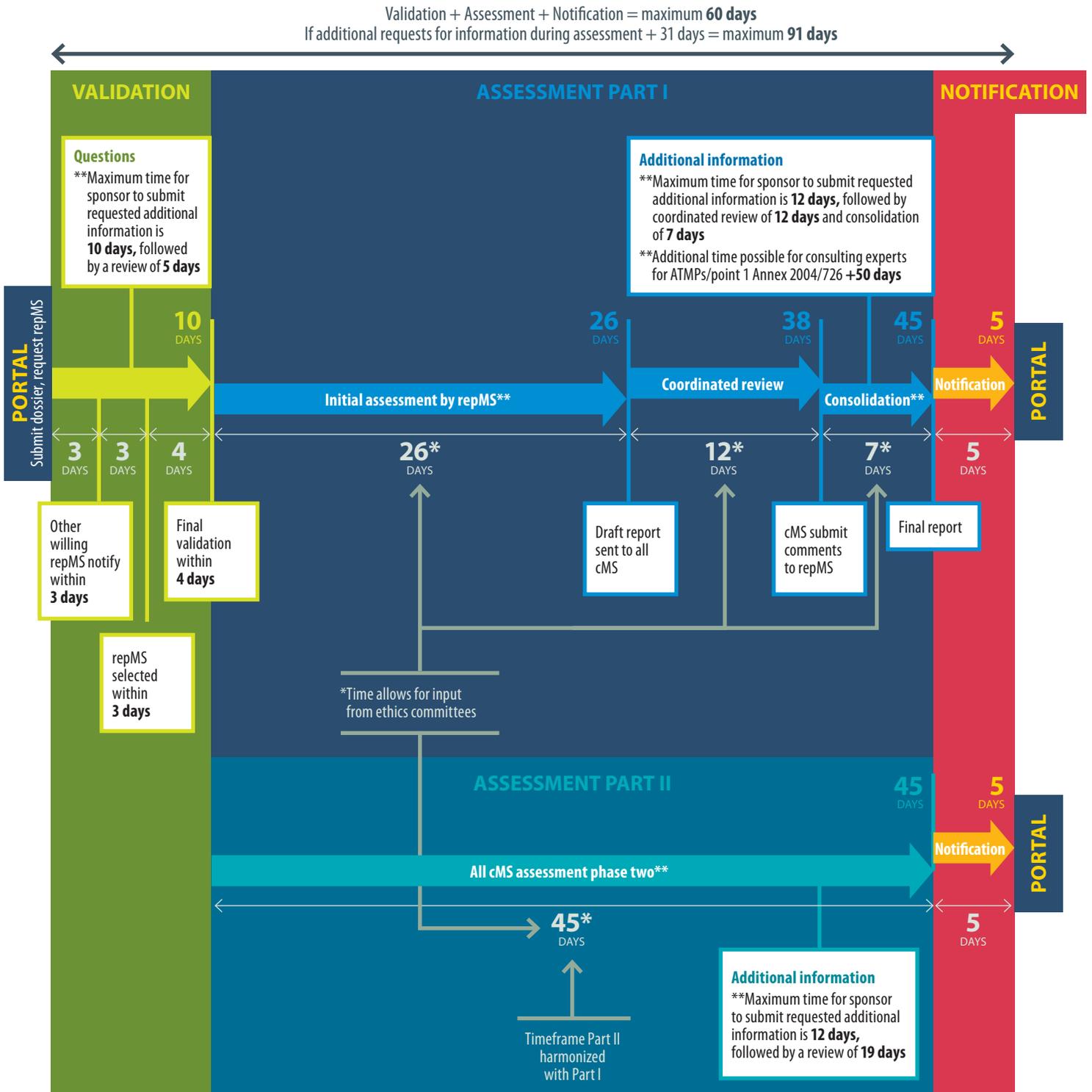
The new Regulation establishes the creation of the EU-portal (Article 80) and the EU-database (Article 81). The EU-portal will be the single entry point for the submission of all data and information relating to clinical trials to be performed in any Member State. These data are to be stored in the EU-database and, unless confidentiality is justified, all non-personal information contained in the database, including the study protocol, will be publicly accessible after the approval of the study, in an “easily searchable format.”⁷

During the authorization process, official communication between sponsors and Member States, such as requests for additional information or notification as to whether a study is authorized, will be made through the EU-portal. It is also the sponsor’s responsibility to permanently update the EU-database with any new relevant information.

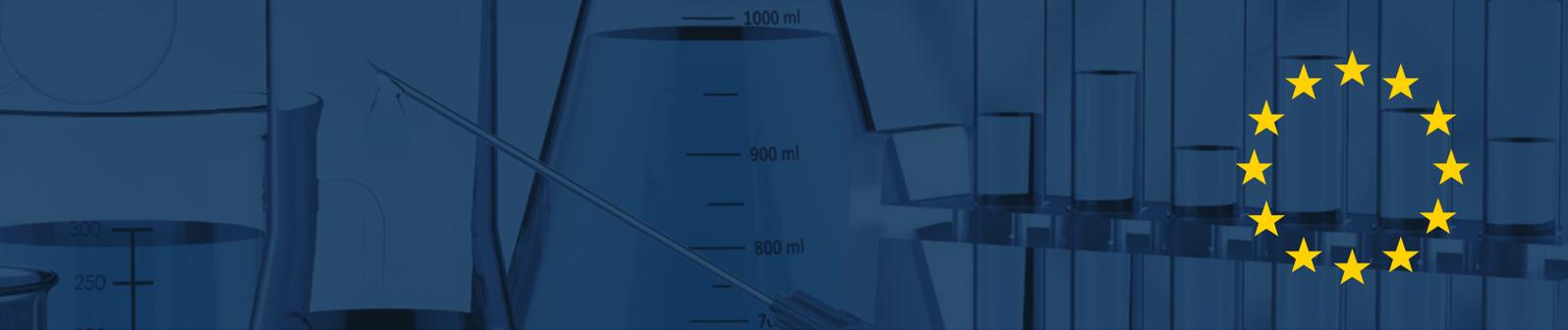
After a trial ends, the sponsor shall also upload, as defined in Annex V of the Regulation, a summary of the trial’s results for laypersons, describing the main aspects of the study, its findings, and comments on its outcome in an accessible way.⁷ In addition, inspection reports for a trial’s investigational sites from the sponsor and any contract research organizations involved will be published on the EU-database.

The new Regulation aims to simplify current rules, streamline the application procedure for new clinical trials, provide more transparency in general, and harmonize the process of performing clinical trials throughout all the Member States of the EU.

FIGURE 2: The New Clinical Trial Authorization Process



Note: cMS = concerned Member States; repMS = reporting Member State; ATMP = advanced therapy medicinal product
 Source: Implementation of the Clinical Trial Regulation at National Level, Late Breaking Clinical Trials News Conference, Brussels, Belgium, October 16, 2014



Another aspect introduced with the new Regulation is the possibility of co-sponsorship (Article 72). This can benefit informal networks of researchers or research institutions that may desire to conduct a clinical trial together. It is defined that, unless decided otherwise in a written contract, all sponsors shall have the full responsibilities of a sponsor as defined in the Regulation. Co-sponsors can jointly establish which sponsor shall be responsible for compliance with the obligations of a sponsor in the authorization procedures; which sponsor will serve as a contact point for receiving all questions from subjects, investigators, or Member States; and which sponsor will carry out corrective measures taken by Member States, such as modification, suspension, or revocation of a clinical trial.

Complying with Chapter II of the new Regulation, the authorization procedure for new clinical trials will be as follows:

- First, the sponsor shall submit the application dossier to all intended Member States through the EU-portal, while proposing one of the Member States to be the “reporting Member State” (see Figure 2). The proposed Member State will be the reporting Member State unless it does not wish to be, or another concerned Member State specifically wishes to be considered for that duty.
- The reporting Member State will, within 10 days of submission of the application dossier to the EU-portal, validate that the application dossier falls within the scope of the 536/2014 Regulation and is in complete accordance with Annex I (application dossier specifications) of the Regulation. It then notifies its decision to the sponsor through the EU-portal. If the application dossier is deemed inappropriate, the sponsor has 10 days to comment on or complete the application through the EU-portal. In this scenario, following the sponsor’s action the reporting Member State will have five days to validate the dossier.
- After validation of the application itself, the reporting Member State shall provide Part I of the Assessment Report, as defined in Article 6 of the Regulation. This report shall contain the reporting Member State’s conclusion as to whether 1) the conduct of the clinical trial is acceptable, 2) it is acceptable but subject to compliance with specific conditions that will be listed in the conclusion of the report, or 3) it is not acceptable. This report has to be submitted through the EU-portal to the sponsor and other

concerned Member States within 45 days from the validation date. For trials involving multiple Member States, the assessment report will consist of an initial phase as described above, a coordinated review involving all Member States concerned, and a consolidation phase again performed by the reporting Member State.

- Simultaneously, in the case of multicenter trials, each other concerned Member State will assess the application for its own territory and draw up Part II of the Assessment Report, with a conclusion as described above, and submit it to the EU-portal within 45 days of the validation date of the dossier. During these 45 days, each concerned Member State, or the reporting Member State, may ask the sponsor for information when deemed necessary. These requests, and the information provided, shall also be submitted to the EU-portal.
- Finally, within five days of the submission of the complete Assessment Report, or on the last day of the assessment time limit (whichever is later), each Member State shall individually notify the sponsor through the EU-portal as to whether the clinical trial is authorized or refused. It is important to note that if the reporting Member State fails to provide the necessary validation of the application dossier, or to provide the Assessment Report, the study is deemed authorized. This concept is called “tacit approval.” Likewise, if the sponsor fails to provide additional information or change its application upon request within the defined time limits, the application is automatically deemed to have lapsed in all Member States.

DISCUSSION

The new 536/2014 Regulation represents changes that are being welcomed by pharmaceutical companies and academic researchers in the EU, and seems to have been elaborated with special consideration toward them. It eases the costs associated with conducting a clinical trial, especially in multiple Member States, in that it reduces the required paperwork, staff, and fees, and simultaneously simplifies the authorization process.

The harmonization of laws was also conducted with consideration given to the future of clinical trials. It is recognized in the new Regulation that, in the near future, studies may be required in specific subgroups of people identified through genetic information. In order to achieve this, it would be

With the benefits of harmonization in mind, it is also important to acknowledge that there are challenges created by the new requirements laid down in the 536/2014 Regulation.



The situation relating to the United Kingdom following the result of the referendum on EU membership will be of particular interest to sponsors, as the implementation date for the 536/2014 Regulation draws near.

vital to include as many Member States as possible for the best possible results. All the changes in the new authorization procedure seem to make multicenter trials an unprecedentedly viable option.

All in all, simpler rules, increased cost effectiveness, and easier access to the European population will probably make the EU more attractive for companies seeking to perform large studies. This change could possibly reverse the recent tendency of pharmaceutical companies to turn to developing countries with large populations, such as China (see Figure 1), as locations for clinical trials.

With the benefits of harmonization in mind, it is also important to acknowledge that there are challenges created by the new requirements laid down in the 536/2014 Regulation. Both sponsors and Phase I trial units have highlighted the potential impediments to the attractiveness of the EU for the conduct of early-phase studies, due to the requirements for increased transparency related to clinical trial design and results, both of which will be required to be published. Concern exists that sponsors may prefer the option of conducting very early-phase studies in Asia, where no such obligations exist.

The EMA has sought to alleviate these concerns by introducing functional specifications that establish extended timelines for the publication of clinical trial registration information relating to early-phase clinical trials. For such trials, sponsors can request deferral of publication of certain protocol-related information, but this information must still be made public at the time of the publication of the results of the trial (the deadline for which would be set at either 12 or 30 months following the end of the trial—as stated in EMA/228383/2015).

While this will offer some reassurances to sponsors, the approval timelines described by the EU 536/2014 Regulation (at up to nearly 100 days for a Clinical Trial Application that elicits questions from Member State authorities) appear particularly unattractive to those familiar with review timelines of less than one month for Phase I clinical trials in some Member States. However, it must be remembered that the timelines stated in the Regulation are all maximum timelines for each step of the process. There has been much communication from the EMA, Member State authorities, and ethics committees at multiple workshops, forums, and stakeholder meetings since the Regulation was published, and through these communications the representatives of some Member States have made it clear that they would hope to review applications

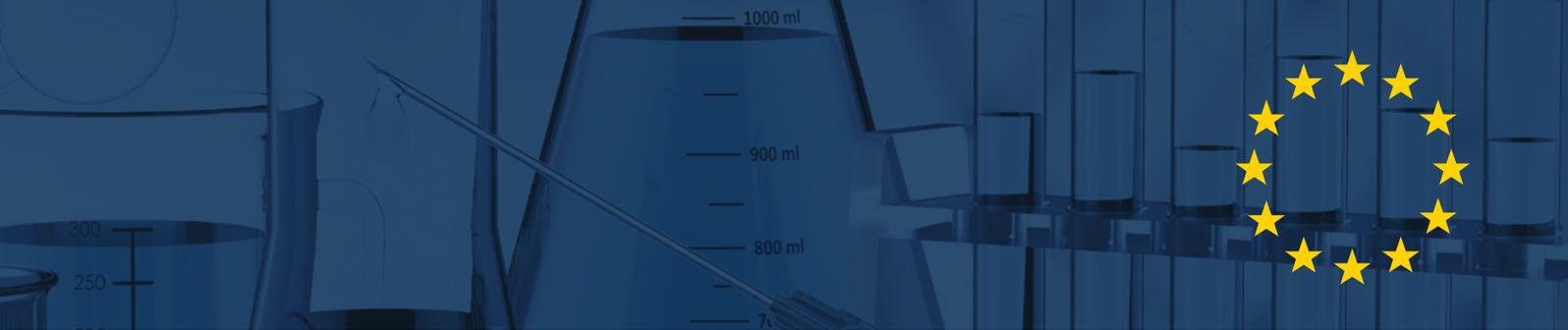
for single-country trials within timelines that are significantly shorter than the maximum timelines described in the Regulation.

The benefits of much greater harmonization of requirements and processes are not limited to high-profile sponsors within the pharmaceutical industries, since the new Regulation also sets the ground for co-sponsorship. This new possibility of study sponsorship can involve smaller research companies or even groups of individual scientists, which should allow for new possibilities for conducting studies independently of big institutions.

In this highly competitive scenario for the EU, it is likely that competition between Member States for patient recruitment will become a priority, together with the identification of investigational sites that excel at study delivery (known as Centers of Excellence). As inspection reports will become public, investigational sites are more than ever pressured to provide high-quality data and guarantee full compliance with the new processes and systems for clinical trials.

The situation relating to the United Kingdom following the result of the referendum on EU membership will be of particular interest to sponsors, as the implementation date for the 536/2014 Regulation draws near. According to media press releases from July and August 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) in the U.K. has stated that the authority will continue to contribute significantly in many areas, including the program for implementing the clinical trial Regulation, as negotiations over the future relationship of the U.K. with the EU continue. The result of these negotiations will obviously have a significant bearing on whether the requirements laid down in the 536/2014 Regulation will apply to the U.K. after implementation in October 2018.

One possible outcome that has been considered is that the U.K. and EU will establish a relationship similar to that applied to the non-EU members of the European Economic Area (EEA). It is fully expected that these EEA countries will apply the requirements of the EU Clinical Trial Regulation, and therefore participate in the approval of clinical trials via the EU-portal and registry of trials within the EU-database (much as the involvement of these countries in clinical trials is recorded in the EudraCT registry at present). This could enable a situation where the new Regulation would apply in a *de facto* manner across the EU, EEA, and the U.K.; however, there are significant political hurdles



to address for this to come to fruition, and an outcome that necessitates the creation of distinct clinical trial submission and regulatory processes in the U.K. cannot be discounted.

Another potential factor of the “Brexit” that should not be discounted is the value of the contribution made by the U.K. authorities, past and at present, in the establishment of harmonized processes across the EU. For example, alongside the authorities in Germany, the MHRA played an active role in the establishment of the Voluntary Harmonized Process, in place for regulatory submissions across participating EU Member States since 2010.

In addition, the MHRA and U.K. Health Research Authority have taken the lead in composing two of the key draft guidance documents that have been developed to facilitate the implementation of the EU Clinical Trials Regulation (“Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)” and “Summary of Clinical Trial Results for Laypersons,” respectively). Although it is acknowledged that 27 Member States will remain involved, it will be to the detriment of the EMA and the representatives of the other Member States if they are, at some future point, forced to proceed with the implementation of the new Regulation with no contributions such as those discussed here from the U.K. authorities.

While considering the impact on sponsors of clinical trials, it must be understood that the changes introduced within Regulation 536/2014 will introduce dramatic alterations to the way that the regulatory authorities, ethics committees, and other bodies assess clinical trial authorizations (for example, radiological committees, bio-banking committees, and other committees established in particular Member States) and interact with one another as they do so (i.e., much greater collaboration will be required in the future). Some authorities in Western Europe have already established pilot programs that will allow them to test their processes for this collaboration, and this can be expected to serve them well as they finalize the processes they will apply when working under the new Regulation starting in October 2018.

However, many Member States are not so advanced in their planning, and it must be hoped that all are able to make progress in this regard, because it will be very difficult to implement the required processes on short notice, and

collaboration within each Member State will be crucial if the authorities are to implement the laws and requirements described within the Regulation.

Finally, one can expect a benefit not only for sponsors in general, but also for the scientific community and the general population, thanks to the increased transparency provided by the new Regulation. The public availability of relevant data, presented in an easily searchable format, and the obligatory inclusion of a layperson’s summary of the study’s protocol and results, when available, will allow citizens not directly involved in the studies to benefit from the results, whether they be patients seeking new treatments or health professionals interested in the new knowledge being produced. Because the summary of the results has to be submitted irrespective of the outcome of the clinical trials, this also avoids publication bias for possibly unfavorable results of a trial.

References

1. Clinical trials – General information. European Commission portal. http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm
2. Council adopts new rules on clinical trials. Council of the European Union press release (April 2014). www.consilium.europa.eu/uedocs/cms_Data/docs/pressdata/en/lsa/142181.pdf
3. Trends, Charts, and Maps. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/resources/trends>
4. Novak T, Payeur G, Belotserkovskiy M. 2014. Decline of clinical trials in central and eastern Europe: fluctuation or trend? www.appliedclinicaltrials.com/decline-clinical-trials-central-and-eastern-europe-fluctuation-or-trend
5. Vieregger RF, Keyang Li. 2015. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. <http://bmjopen.bmj.com/content/5/9/e008932.full>
6. Consolidated version of the treaty on the functioning of the European Union. <http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A12012E%2FTXT>
7. Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and repealing Directive 2001/20/EC. <http://register.consilium.europa.eu/doc/srv?l=EN&f=PE%20%202014%20INIT>
8. Delivery time frame for the EU portal and EU database. 2015. European Medicines Agency. www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199078.pdf
9. Regulations, Directives and other acts. https://europa.eu/european-union/eu-law/legal-acts_en
10. EU Directive vs EU Regulation: what’s the difference? 2014. www.enhesa.com/blog/eu-directive-vs-eu-regulation-whats-difference

Yves Geysels, PhD, (yves.geysels@quintiles.com) is a professor of clinical trials at the University of Namur, Faculty of Medicine, Department of Biomedical Sciences in Belgium, and president of the Belgian Association of Clinical Research Professionals.

Christopher A. Bamford, PhD, is a representative of the Association of Clinical Research Organizations (ACRO), a global CRO trade organization in Washington, D.C.

Richard H. Corr is an exchange student of the Science Without Borders program of the University of Namur, Belgium, and a medical student of the Universidade Federal do Rio de Janeiro, Brazil.

It Ain't Me Babe, *It's My Culture*

If pharmaceutical companies have a special Harry Potter “Defense Against the Dark Arts” class for their management teams, one of the first techniques they must be learning is the Culture Defense. When confronted with evidence of their reluctance to change, they are apparently taught to point their wands out in front of them and say, “It ain’t me, it’s the culture here.” This turns out to be a marvelous, widely applicable spell—the easiest way out of an uncomfortable situation. There’s one problem: *We are* the culture.

To claim that company culture is the reason that operational innovation fails to take root is to deny your own place in the company for which you work. Culture doesn't kill efficiency, people do.

We can't all be the rebels, can we? If so, how would the “culture” ever form with beliefs different from our own? To claim that company culture is the reason that operational innovation fails to take root is to deny your own place in the company for which you work. Culture doesn't kill efficiency, people do.

This common weakness of corporate organizations is particularly obstructive to the introduction of information technology because technology generates so much upheaval, especially in areas of clinical development still untouched, or merely grazed, by the productive use of software. Often standing in the way of that productivity is the Culture Defense.

Let's look at the following examples of flawed process improvement where culture is often blamed as the cause of failure, and let's ask ourselves if there might be other reasons lurking.

The Ubiquitous Culture Defense

We're getting lousy data out of a great tool (an expensive enterprise clinical trials monitoring system [CTMS] for instance, or a state-of-the-art adverse event system [AES]). How does this happen? The old information technology acronym, GIGO (garbage in, garbage out), applies; but why is it happening?

Why are our staff waiting until the last minute to enter trial status information that is supposed to be feeding a highly accurate, real-time CTMS? Or in the case of the AES, why are antique, paper-based data flows being maintained, while the AES is an alien, unwelcome layer imposed on top?

Why are such things allowed to happen? The Culture Defense says, “Well, we're not used to reporting data in real-time,” or “We want to review and double-check the information before anyone sees it.” Or in the safety case, “We won't risk the importance of safety surveillance to software which may not work.” It's a culture thing. Really?

Another example: A major process improvement project is organized into the ubiquitous “workstreams” and comes up with a flood of recommended changes. Several of the most important changes require reorganizing staff, and while the net headcount will stay the same, some people will probably not fit the new skills required. Impossible! Why? Because “we don't (or can't) fire people here—it's our culture.”

Yet another example: We throw resources (human and monetary) at the database lock of our pivotal trial, with no restraint. At that moment, there is nothing more important to the company. If the data management processes are examined, however, you will likely find that the electronic data



capture (EDC) tools you have used for years are being used suboptimally and inefficiently. It's the culture. Perhaps it is, but is that a good thing? Does the Culture Defense make all other options moot?

One last example: "We don't measure here." It's our culture not to measure, or if we do, we don't do it consistently, or with rigor, or learn from the results. There's probably loads of data—indeed, too much—for you to measure from, but it's not in the culture to act on this information. Is that culture or laziness or fear?

More pervasively, it is common to see clinical development executives across the industry turn a blind eye to what really happens at the operational level. Executives announce an impassioned commitment to a particular process improvement initiative, and tiptoe out of the room—leaving the implementation to middle management. In many companies, without the executive watching your back, there is little incentive for middle managers to execute on the vision. Is this disconnect a *culture* problem or a *management* problem?

It is You, Babe

If individual study teams, or even entire therapeutic areas, don't follow company-wide standard operating procedures (but instead make up their own regulatory-compliant "standards"), is that culture or the acts of individual managers? (It may be a justifiable action on the manager's part, but that's logic, not culture, at the source.)

If we put training of the new CTMS tool in an e-learning environment (although most monitors won't really pay attention and only click through it to get certified), can we blame our culture for being anti-training? It was the individual who chose not to pay attention.

In fact, if we rely on individuals' cooperation in using new tools appropriately, and people fail to do so, isn't that a series of individual decisions? If I fail to fill out all the fields in a template-based site visit report in my CTMS, isn't that my choice? The culture didn't make me do it, I chose not to do it.

The damaging side effects of the Culture Defense are legion: It enables us to drag our feet

when it comes to changing the way we are used to working; it gives us permission to abdicate responsibility without penalty; it enables us to stand in the way of progress with impunity for whatever our personal motivation may be (e.g., we're overworked, we're jealous, we want our pet project to get all the attention, we're afraid of learning too many new process details).

Psychologists will tell us that the most powerful realization victims of damaging habits can have is that they have a *choice* to change. The Culture Defense is designed to prevent choice, to *prevent* individual responsibility, even to preclude individual initiative. The Culture Defense is defeated by individuals who choose not to go along with the easy path, to see the executive direction as good for themselves as well as the company, to embrace change as the inevitable condition of modern business, to risk getting information that may reveal true operating conditions quicker because it is better to do so, and to risk measuring because objective data about how we work can make us better workers.

Do the Right Thing

We—as individual pharmaceutical company staff, middle managers, and executives—can **choose** to act in a manner that enables operational improvement to flourish. We can face down the Culture Defense so that our process redesigns are easily learned and pragmatic; so that our CTMS systems actually produce accurate, actionable data on clinical trial program performance; so that our contract research organization vendors are well managed; so that our technology investments are worth the effort to implement them; and so that our diverse and broadly skilled staff can be focused on productive work with urgency.

The eponymous central character of Walt Kelly's famous cartoon strip Pogo once memorably exclaimed, "We have met the enemy and he is us." Culture isn't the enemy, we are. Facing up to this fundamental truth will begin to enable operational innovation to meet our expectations.

The damaging side effects of the Culture Defense are legion: It enables us to drag our feet when it comes to changing the way we are used to working; it gives us permission to abdicate responsibility without penalty; it enables us to stand in the way of progress with impunity for whatever our personal motivation may be.

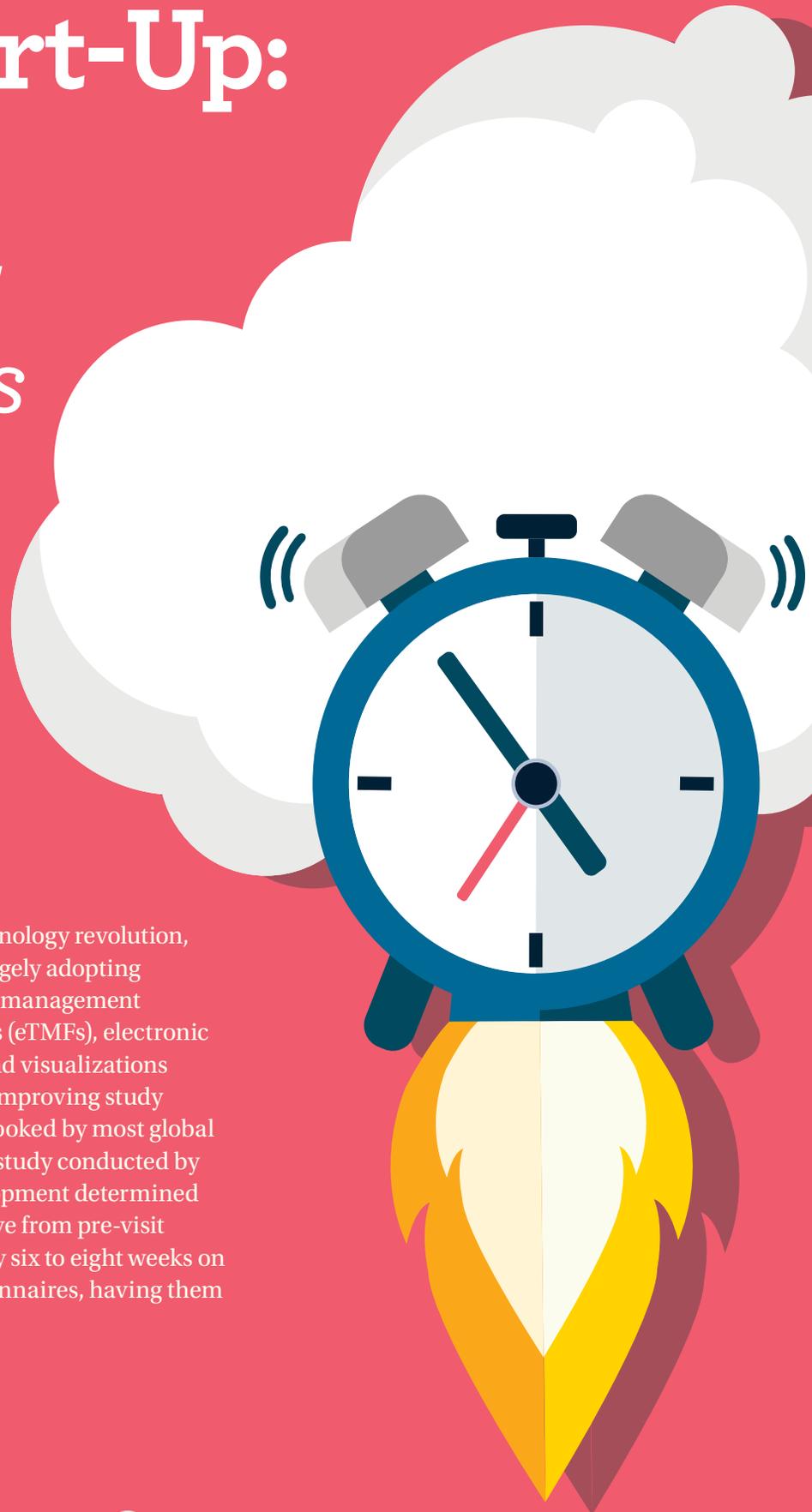


Ronald S. Waife (ronwaife@waife.com) is president of Waife & Associates, Inc. (www.waife.com).

Accelerating Study Start-Up: *The Key to Avoiding Trial Delays*

PEER REVIEWED
Priya Temkar, MSc

In the midst of the current clinical trial technology revolution, although stakeholders in the industry are largely adopting various tools and platforms like clinical trial management systems (CTMSs), electronic trial master files (eTMFs), electronic data capture (EDC), and various analytics and visualizations to aid with ongoing trials, opportunities for improving study start-up (SSU) activities continue to be overlooked by most global pharmaceutical and biotechnology firms. A study conducted by the Tufts Center for the Study of Drug Development determined that it takes eight months, on average, to move from pre-visit through to site initiation,¹ out of which nearly six to eight weeks on an average are for sending feasibility questionnaires, having them completed, and receiving responses.²



72%

of studies run more than one month behind schedule

Quite often, the finalized site selection itself eventually becomes a rushed process, whereby hundreds of investigators/sites across the globe are selected over a short span in an attempt to hasten trial start-up. As a result, poor selection of trial sites becomes a problem during trial conduct, and reportedly increases the cost of clinical trials by at least 20%.³

In a typical Phase III study, this can translate into \$2.25 million in expenses for non-active and under-enrolling sites. According to Cutting Edge Information, 72% of studies run more than one month behind schedule, and such delays can cost sponsors between \$600,000 and \$8 million for each day that a trial delays a product's development and launch.⁴ The cost of initiating a site (which is the largest chunk of SSU cost) has been estimated at \$20,000 to \$30,000, and trial delays can add to this cost.⁵

A U.S. Department of Health and Human Services-sponsored report from 2014 cites key barriers to clinical trials, quite a few of which are related to SSU process, and highlights sponsor-imposed barriers, such as tedious multiple review methods and highly restrictive inclusion/exclusion criteria.⁶ Meanwhile, a research effort funded by the U.S. Food and Drug Administration (FDA) and undertaken by the Clinical Trials Transformation Initiative identified seven SSU cycle times, and concluded that many stakeholders in the U.S. clinical trial enterprise routinely fail to collect standardized measures of SSU cycle times.⁷ This highlights inefficiencies in SSU tracking process and demonstrates the need to implement measures to optimize the same.

The data on elements causing delays in SSU indicate that contract and budget negotiations and approval are responsible for 49% of study delays, followed by patient recruitment, which causes 41% of delays.⁸ A global survey conducted by Center-Watch revealed that 73% of sites use traditional

methods of e-mail, fax, and courier as a primary tool for exchanging clinical trial documents.⁹

Although the results may not be quite the same today, it is interesting to note that a 2005 report found that, despite decades of practice, sponsors underestimated the time required to complete 80% of studies, with the average Phase I study running over by 42%, Phase II study running over by 42%, and Phase III study running over by 30%. The report also found that the average Phase III study was completed more than six months behind schedule.¹⁰

Meanwhile, there are several therapeutic areas that pose particular challenges during the SSU phase. For instance, in oncology, with the emergence of molecular targeted therapy, the complexity of study protocols has increased, allowing for the inclusion of patients with a wide range of tumor types that share a common genetic mutation.¹¹

SSU OVERVIEW AND THE TECHNOLOGY EDGE

The above facts and figures provided by various industry reports help us to put the spotlight on SSU, with an emphasis on the increasing need to accelerate steps in SSU process by utilizing suitable technology options to minimize manual intervention, reduce errors, prevent trial delays, and improve compliance.

If study timelines are not met in the SSU phase itself, this creates a cascading effect in terms of missing later study milestones. That is to say, delays in the determination of study feasibility, site selection, essential document collection, ethics committee submissions, and investigational product release impact site initiation visit timelines, making it tough to meet study conduct milestones and achieve recruitment targets as per the planned dates, which ultimately results in trial delays.

In the midst of the current clinical trial technology revolution, opportunities for improving study start-up activities continue to be overlooked by most global pharmaceutical and biotechnology firms.

FIGURE 1: Overview of Study Start-Up (SSU)



NOTE: The activities highlighted in yellow are areas in which technology can help to speed up SSU.

If study timelines are not met in the SSU phase itself, this creates a cascading effect in terms of missing later study milestones.

Figure 1 depicts a high-level SSU work flow, including the key stages and the respective activities performed under them.

SSU ACCELERATORS

Although appropriate site selection is the most challenging piece in SSU, a probable solution also lies within past site performance data. Lots of data may exist on a site's performance and experience in terms of patient populations, recruitment rates, audit compliance, and more, which could be valuable for gaining insights on site selection. Utilizing these past data of site performance and building predictive analytics tools can enable forecasting of a site's performance on new studies, and has proven to be a smart step toward addressing site selection issues.

To add to the above, use of an electronic feasibility system with a built-in "site scoring" tool for automatic analysis of feasibility responses and categorization of sites as medium, low, or high performers can benefit studies for years to come. Databases built from such online feasibility systems can provide a common platform for real-time

feasibility study status across the globe, and can be utilized further for forecasting and identifying potentially suitable sites for future projects.

By adopting an online feasibility tool, pharmaceutical companies and contract research organizations can reduce the costs and effort devoted to e-mailing feasibility questionnaires, attending to follow-up reminders, and waiting to receive completed questionnaires. Manual tracking and analysis of feasibility responses will be eliminated, and the availability of standard and customizable feasibility status update reports and dashboards will benefit study management teams seeking to keep up with all the activities tied to global trials.

Another large chunk of start-up efforts is spent on coordinating the essential document compilation, review, and reconciliation steps required for various submission packages (e.g., for ethics committees, investigational product release, etc.). This is one of the crucial processes in SSU, and involves a lot of paper-based, manual intervention in many cases. However, a secure, web-based document exchange repository can serve as an effective coordination and communication tool whereby stakeholders from different parts of the globe can

By automating site feasibility studies, pharmaceutical companies can reduce the costs and effort devoted to e-mailing feasibility questionnaires, attending to follow-up reminders, and manual analysis of feasibility responses.

upload, view, and query documents within the tool based on their different access levels. This would enable study management teams to know the real-time status of the start-up documents collected and pending at different sites, along with built-in SSU milestone tracking and auto reminders to concerned stakeholders.

Industry surveys conducted on the use of web-based document exchange tools reveal that 41% of respondents consider time savings to be the biggest benefit, followed by 22% stating better organization of study-related information to be most valuable, and 22% believing easier communication with sponsors comes out ahead.⁸ Implementation of such a document exchange repository will mainly reduce the turnaround time of handling essential documents during SSU (which are otherwise procured via e-mails or in hard copy and stored in various shared drives or online systems), along with reducing the pass-through costs associated with the same.

Data collected on use of web-based communication methods for centralized document exchange on four Phase II-III studies in which a combination of academic medical centers and private hospitals were used revealed up to 27% efficiency gains. In studies involving only private sites, up to 50% efficiency gains were noted (in terms of turnaround time reduction during the SSU document exchange).⁸

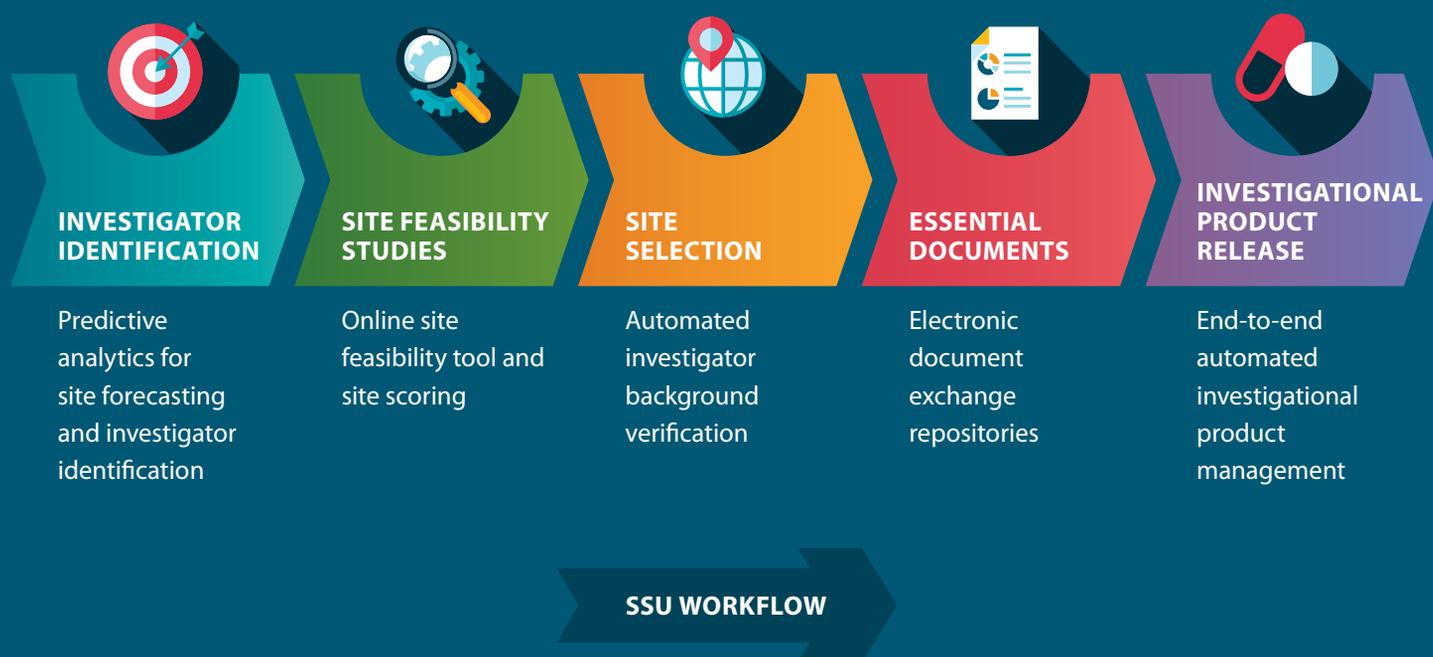
Meanwhile, investigational product release is another vital part of SSU that requires great precision in terms of managing the many details tied to product release packages, in order to meet

specific timelines for drug release to the site and to ensure regulatory compliance in audits. An online document exchange portal can be used to help with package compilation and approval; however, a concept that is emerging in the industry is that of a completely automated investigational product management system. With such a system, an investigational product can be tracked from its arrival at the depot, to its delivery to sites (postapproval of its release package), to being dispensed to patients, to tracking each patient's compliance in terms of drug usage, and finally to the return or destruction of any unused product.

All of the above-mentioned data can be tracked on a single platform and monitored through an application in a smart phone; this can dramatically ease the process of investigational product management, not just in start-up, but also throughout the due course of the study. In fact, a recent case study from a major pharmaceutical company describes the value of deploying technology solutions in SSU at all of its U.S. sites that conduct oncology trials. Prior to implementation, the company reported having no automated task assignment and relying heavily on manual spreadsheets. After eight months of implementation, the company experienced a 32% reduction (in weeks) in the SSU stage.¹²

73% of sites use traditional methods of e-mail, fax, and courier as a primary tool for exchanging clinical trial documents

FIGURE 2: SSU Accelerators—The Technology Edge



In order to target the major SSU bottlenecks, carefully analyzing current processes and making a list of the key problematic areas are essential tasks, to be followed by implementing simple automations within existing processes.

Figure 2 continues the high-level SSU work flow, depicting the key stages and their respective SSU accelerators for giving study leaders the technological edge needed for optimizing their processes, including:

- Predictive analytics and site forecasting, to build efficiencies for investigator identification
- Automated online site feasibility and site scoring system, to facilitate faster turnaround time in feasibility
- Automated investigator background verification, to eliminate manual processes when checking for medical board sanctions and debarments in different states
- Electronic document exchange repositories to optimize and speed up SSU essential document collection
- e-2-e automated investigational product management systems, to gain real-time control of the drug supply and its accountability for greater quality compliance

Examples of initiatives launched by collaborative industry groups and aimed at accelerating SSU include an effort by Johnson & Johnson, Eli Lilly, and Merck,¹³ as well as another by the nonprofit TransCelerate Biopharma Inc.¹⁴

WHERE TO BEGIN?

In order to target the major SSU bottlenecks, carefully analyzing current processes and making a list of the key problematic areas are essential tasks, to be followed by implementing simple automations within existing processes.

For instance, performing state-specific medical board sanction checks for hundreds of investigators in a global megatrial can be a massive manual activity, depending on the number of websites to be checked for each investigator. Automating this process by developing a tool to eliminate manual screening can reduce the time spent on this work and help with the compilation of data from different state board websites into a single file.

Similarly, developing macro solutions for certain manual tracking activities can be another alternative. For example, during the FDA debarment check of different investigators, data are usually checked from three links on the FDA website. Developing a macro solution for automatic comparison of data downloaded from the three links—to check if there have been any additions to the list of investigators from time to time during a study's conduct—is a useful solution for saving manual efforts that also increases compliance related to investigator background verification during the selection process for other studies.

50% efficiency gains were noted in private sites where data were collected using web-based communication methods for centralized document exchange

Once the problematic areas are addressed, study leaders can monitor the improvements in terms of turnaround time and process compliance, and further plan to implement major transformations with the help of customized tools and platforms suitable for their SSU process.

CONCLUSION

Any adoption of new technology brings with it various teething issues and challenges in terms of set-up, training, desired outcomes, and more; hence, progress has been slow in addressing the SSU issues described in this paper through technology solutions, but the trend has been in the right direction. Further, these solutions have proved to be beneficial investments for stakeholders in the clinical research enterprise as it evolves in an era of more powerful tools (CTMSs, eTFMs, EDC, etc.) for core trial conduct. Now it is time for the identification and implementation of the right tools in SSU.

As the staff at study sites and the members of overall clinical trial teams become more and more technologically savvy in their trial conduct, the learning curve necessary for handling new clinical trial systems becomes easier to manage. All stakeholders will need to welcome yet more upcoming technologies, and to make the switch from manual spread sheet-based processes and e-mail communication to secure systems with intelligence, thus enabling the full use of electronic data, automated processes, and dashboards along with a complete audit trail.

Implementing technology within SSU is indeed a challenging task, considering the expedited turnaround timelines to be met at each and every step. However, centralizing SSU via a trusted technology partner who can provide customized SSU solutions for standalone steps, as per the unique needs of each business can help to accelerate SSU.

Acknowledgement

The author would like to thank Dr. Niraj Vyas (AGM Tata Consultancy Service, Clinical Operations and Risk-Based Monitoring) for his review and insights on this article.

References

1. Morgan C. 2015. The need for speed in clinical study startup (citing 2012 presentation by Ken Getz on "Uncovering the drivers of R&D costs"). *Clinical Leader* www.clinicalleader.com/doc/the-need-for-speed-in-study-startup-0001
2. Brennan Z. 2013. Trial site feasibility platform looks to end onerous paper questionnaires. *Outsourcing Pharma* www.outsourcing-pharma.com/Commercial-Services/Trial-Site-Feasibility-Platform-Looks-to-End-Onerous-Paper-Questionnaires
3. Grom T. 2011. Unclogging the patient recruitment bottleneck. *PharmaVOICE* www.pharmavoices.com/article/2182/
4. Cutting Edge Information (press release). 2005. Clinical trial delays cost pharmaceutical companies. www.prnewswire.com/news-releases/clinical-trial-delays-cost-pharmaceutical-companies-55044607.html
5. Miseta E. 2013. Bring down the cost of clinical trials with improved site selection. *Clinical Leader* www.clinicalleader.com/doc/bring-down-the-cost-of-clinical-trials-with-improved-site-selection-0001
6. Sertkaya A, Birkenbach A, Berling A, Eyraud J. 2014. Eastern Research Group, Inc. U.S. Department of Health and Human Services. Examination of clinical trial costs and barriers for drug development. <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>
7. Abbott D, Califf R, Morrison BW, Chakraborty S. 2013. Cycle time metrics for multisite clinical trials in the United States. *ResearchGate. Ther Inn Reg Sci* 47(2):152–60. https://www.researchgate.net/publication/258132214_Cycle_Time_Metrics_for_Multisite_Clinical_Trials_in_the_United_States
8. Farfel GM, Neuer A. 2009. IntraLinks. Faster study start-up and reduced costs through the use of clinical document exchange portals. https://www.intralinks.com/sites/default/files/file_attach/wp_faster_study_startup.pdf
9. Bio-IT World. 2011. IntraLinks survey highlights need for e-Clinical document exchange tools. www.bio-itworld.com/news/06/14/2011/IntraLinks-survey-need-clinical-document-exchange.html
10. Cutting Edge Information. 2005. Trials in the fast lane: accelerating clinical trials: budgets, patient recruitment, and productivity. *J Clin Res Best Pract* 1(3).
11. Joseph SO, Wu J, Muggia FM. 2012. Targeted therapy: its status and promise in selected solid tumours Part II. *Oncology* 26(11):1021–30, 35.
12. goBalto™. Activate reduces cycle time (case study). 2014. http://cdn2.hubspot.net/hubfs/446654/docs/caseStudy_cycleTimes-03JUN2014.pdf?t=1435008341532
13. Beasley D. 2012. J&J, Lilly, Merck plan clinical trial site database. *Reuters* www.reuters.com/article/us-pharmaceuticals-trials-idUSBRE8AE0XS20121115
14. TransCelerate Biopharma Inc. Our initiatives. www.transceleratebiopharmainc.com/initiatives/

Priya Temkar, MSc, (priya.temkar@tcs.com) is a business consultant in the clinical operations services/life sciences area for Tata Consultancy Services Ltd in Mumbai, Maharashtra, India.

Jerry Stein, PhD, is president and owner of Summer Creek Consulting LLC, which provides support for the design and conduct of clinical trials and medical writing, and serves as the current chair of the ACRP Editorial Advisory Board.



Within two years, one of our candidate products was approved by the U.S. Food and Drug Administration and marketed. I was so proud. I could walk into any major retail store that had a drug aisle and literally point to the product I helped develop.

Q: Can you tell us how you first became interested in clinical research, and a little bit about the path you took to get involved in your career?

A: Like most clinical researchers, my path was not direct. My interest in science was influenced by the huge increase in science education funding that followed the launch of Sputnik. This wave impacted an entire generation of scientists. Ultimately, I was trained to conduct preclinical studies as a behavioral neuroscientist. My graduate school training at Syracuse University was unusual, since we spent the majority of our time in the lab conducting studies beginning on the first day. The emphasis on hard work—designing, executing, analyzing, and summarizing studies—had the biggest and longest lasting impact on my career.

I was also exposed to the world of scientific publications, since my advisor was editor-in-chief of several science journals and a publisher. Post-doctoral positions at the University of Washington and University of Iowa were also laboratory-intensive experiences.

So why did I move to clinical research? There were two primary reasons. First, I wanted to see more concrete and quicker results from my efforts. I had become very frustrated with the small, incremental progress we were making in the laboratory—answering one question only to find that two more questions appeared. Second, with a family to support, I wanted a career path that

utilized my education, but offered the potential to earn more money. These reasons don't sound very noble, but I am sure they are common motivators to make a career change.

Q: Was there someone or some experience from your past that significantly impacted your decision to work in clinical research?

A: Early in my career, I served as a clinical monitor as part of a team that evaluated the safety and effectiveness of new over-the-counter lens care formulations. Within two years, one of our candidate products was approved by the U.S. Food and Drug Administration and marketed. I was so proud. I could walk into any major retail store that had a drug aisle and literally point to the product I helped develop. I loved it. I was sold on the career. Over a 30-year span, I've helped develop at least 30 products. The adventure is continuing.

Q: Were there struggles that you had to overcome professionally, or anything you wish you would have done differently?

A: One of the biggest struggles has been the bias against accepting clinical research as a formal area of expertise; a profession. This was exaggerated by my focus on medical device development—an area that includes many products that do not require extensive clinical testing. Unlike other product

development areas, everyone on our project teams seemed to have an opinion on how to design and execute clinical studies. In a cross-functional team, we rarely questioned the plans of pharmacologists, chemists, or microbiologists. However, everyone seemed to have an opinion about clinical.

There was also a general bias against any scientific work generated by personnel working for commercial companies. The assumption was that clinical studies conducted in academic, nonprofit settings were unbiased and believable, while studies conducted by for-profit entities were biased and untrustworthy. I saw this during interactions with regulatory agencies, by the reception we received at scientific/medical meetings, and when we submitted our work to journals. This contrasted greatly with my reality. I have never met a clinical researcher working for any sponsor who was not dedicated to conducting ethical, accurate studies while protecting subject safety and privacy. Any bias in the study design and limitations to our findings were always overtly described in our reports. We continually had to overcome this bias by building bullet-proof designs and exploring every possible confounding variable.

Q: What are your thoughts on formal clinical research programs? How essential is a degree if one wants to develop his or her career in clinical research?

A: One of causes of the biases I cited above is the status of clinical research as a profession. The barriers to entry for investigators are relatively small. If you have a license to perform the tasks required in a clinical protocol, you can easily be designated a principal investigator (PI). The barriers for clinical monitors are also relatively minor, although most monitors receive extensive training. For this reason, I advocate formal training programs as the necessary step toward professionalism. We need government-endorsed standards at the state and national level, similar to those in place in other medical professions. Does it make sense for our society to license real estate agents and plumbers and not PIs, study coordinators, and clinical research associates? Hopefully, we are in a transition period moving toward this goal.

However, training of site personnel, PIs, and their staff continues to lag. I am highly supportive of new and experienced clinical research personnel taking advantage of formal clinical research programs. Ultimately, I would like to see a mandatory, competency-based certification/licensing process that considers the experience and judgment of the individual.

Q: How about your involvement in ACRP? When did you first get involved, and how has your affiliation affected you professionally?

A: During my first five years as a clinical researcher, I spent many hours in training courses learning regulations, standard operating procedures, and company procedures. However, this was primarily internal training, with company supervisors teaching company employees. I was very thirsty to learn how clinical studies were being conducted elsewhere.

When I heard about the Associates of Clinical Pharmacology (the old name for ACRP), I immediately joined. The 1987 Fort Lauderdale meeting was an eye opener. I primarily learned that my company was doing things correctly. This significantly increased my confidence when I returned home. It was also a very lonely professional meeting. I knew no one. Over time, this changed, and every meeting has become more enjoyable as I became more involved with the organization.

I helped organize my local ACRP chapter. I helped organize the national Medical Device Forum (the old name for the Device Interest Group). I helped plan the 2001 San Francisco meeting. I began speaking at local and national meetings. I joined *Clinical Researcher's* Editorial Advisory Board. Through these experiences, I got to know lots of ACRP members. It's my professional home.

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

A: It's exciting to be involved in the clinical research profession at this point in its evolution. I doubt that I can significantly impact national or state politics. However, I am confident that I can positively impact clinical research professionalism, and I believe that ACRP is the perfect vehicle for making a difference.



Jamie Meseke, MSM, CCRA, (jamie.meseke@ppdi.com) is a clinical trial manager for PPD, Inc., and a member of the ACRP Editorial Advisory Board.

I have never met a clinical researcher working for any sponsor who was not dedicated to conducting ethical, accurate studies while protecting subject safety and privacy.

Introducing ACRP'S INAUGURAL CLASS OF FELLOWS



Being named a Fellow of the Association of Clinical Research Professionals (FACRP) is a mark of distinction. By developing a Fellowship program, ACRP recognizes those who have made substantial contributions to the Association and the industry at large, as evidenced by: ACRP certification/ACRP education, leadership contributions to ACRP, and contributions to the field of clinical research. Fellowship highlights excellence and commitment to ACRP, and is suitable for only a small, select number of clinical research professionals who are lauded as global leaders.

ACRP is proud to announce the 2017 Class of Fellows as the first in what aims to be a long and distinguished line.

Janet Ellen Holwell, CCRC, CCRA, TIACR, FACRP

Consultant



Holwell began her career as a clinical research coordinator (CRC) in academia more than 35 years ago. Prior to consulting, she held positions

as a clinical research associate (CRA), site selection specialist, and study manager with oversight of vendor CRAs, clinical operations quality management, and training for several pharmaceutical companies.

Holwell has watched the clinical research industry evolve at the speed of light. ACRP has been there for her every step of the way. "ACRP has done much to help professionalize our roles in clinical research," she says, explaining that, in the early days of the industry, "roles were ambiguous and formal training and certification were not available."

In addition, Holwell praises ACRP for providing a "great environment for learning; it's been my main association through the years." Beyond the valuable networking opportunities and the support ACRP members provide for each other, she benefits from learning and teaching the real impact of potential or new federal regulations.

For Holwell, becoming a Fellow is a great honor and recognition of her years of service via the ACRP Association Board of Trustees, the New York Metropolitan Chapter, committees, and numerous other efforts. "I'm proud and humbled to receive it," she says.

Robert J. Greco, RPh, MPH, CCRA, FACRP

President, Greco Clinical Partners



A pharmacist by training, Greco worked in community pharmacy for a number of years filling prescriptions. "It's a helping profession, so

the patient contact was very rewarding, actually seeing families and children grow up," he says.

Wanting to see more of the clinical picture, Greco eventually joined a contract research organization to be trained as a clinical research associate. "I was really enamored by monitoring and how it allowed you to see first-hand what was working and not working at the site," he explains.

Saying he loves "being part of group continually trying to improve," Greco also reports wanting to help take the profession to the next level, and believing that ACRP is a big part of that effort.

Greco is honored to receive a Fellows designation. "It's wonderful to be recognized for reaching a level of service and experience in an organization known for promoting excellence in clinical research," he says.

Jeff Kingsley, DO, MBA, CPI, FAAFP, FACRP

Founder and CEO, IACT Health; Chair, ACRP Association Board of Trustees



A family physician by training, Kingsley fell in love with research more than 10 years ago and decided to "dedicate the rest of my career"

to it. One of his passions is to help others recognize that research can't be treated as "hobby"—rather, it demands a robust organizational architecture. "It needs to be run like a business—that's why I got an MBA," he notes.

Kingsley's professional passion extends to his long-time involvement with ACRP. "I'm in love with ACRP," he enthuses. Over the years it has furthered his education and helped him meet others in the industry with whom he can swap ideas and best practices.

He applauds the creation of the Fellows Program because it is another step in advancing the concept that research is



a profession. “It is also a recognition that someone has gone above and beyond for the clinical research industry, and I’m honored to receive it,” he says.

Kingsley also served as the 2016 Vice Chair of the ACRP Association Board of Trustees.

Steven Ziemba, PhD, CCRC, CPI, FACRP

Associate Director, Marshfield Clinic Research Foundation; Immediate Past Chair, ACRP Association Board of Trustees



Ironically, Ziemba had no real inclination toward clinical research in the early days of his career as a senior scientist with

Roche Molecular Systems in New Jersey. That changed when he got the opportunity to build a clinical research department.

ACRP was an important partner for Ziemba almost from day one. “It helped me in the education I really needed,” he says. Thanks in part to ACRP, Ziemba learned “what a clinical trial looks like and what regulations and other topics really mean.” He has also benefitted from ACRP’s strong networking program. “You meet with and learn from individuals from all areas of the field—study monitors, contract research organizations, sponsors,” and others among the full spectrum, he says.

Being named a Fellow signifies that you’ve contributed to the field itself, he notes—that’s the distinction. “I’ve taken from industry for my own advancement and improvement, and ACRP has helped me contribute back to industry,” he says.

Barbara Grant Schliebe, MS, CCRA, CCRC, CCRP, FACRP

Clinical Research Monitor



“At some point in one’s life a job becomes a profession,” says Schliebe. Committed to advancing the certification of roles and the professionaliza-

tion of the industry, she took the Certified Clinical Research Coordinator (CCRC) exam in 1997 in part to demonstrate her commitment to the field.

Initially trained as a registered dietitian, she began her clinical research career as a research nutritionist at the University of North Carolina (UNC) at Chapel Hill. She later joined the School of Medicine faculty as a research instructor overseeing projects in colon cancer epidemiology. Following a brief retirement, she returned to UNC and transitioned to a part-time role as a clinical research monitor in the Center of Gastroenterology and Biology. She is also employed as a contract clinical research monitor in the Research Triangle Park area.

Schliebe values ACRP on a number of levels, including its plethora of networking venues and the opportunity to learn about the latest in best practices. While she praises many of the sessions she has attended at previous ACRP conferences, she says “sometimes the individual conversations” after a session have yielded the most benefit to her professionally. “There’s always something new to learn, and ACRP keeps you abreast of trends and makes sure you know what changes are occurring in the profession,” she adds.

Saying that she believes being a Fellow will only help her to connect with more ACRP members working on various parts of clinical trials, she adds that it “demonstrates what you’ve done within the organization and that you’ve made a contribution to ACRP and outside to the broader industry.”

Terri Hinkley, RN, BScN, MBA, CCRC, FACRP

Workforce Innovation Officer, ACRP



In 1995, Hinkley was an emergency room nurse. Tasked with taking a research role in a Phase I clinical trial, she says she initially struggled

because “I had no idea what the field of clinical research was, and I found it to be a difficult transition because of that.” While having a clear and strong identity as a nurse, Hinkley noted that developing an identity as a researcher was much more difficult. A new clinic director introduced her to ACRP in 1997, and Hinkley was hooked. ACRP was the place where she found her professional identity as a researcher.

“I dove in,” Hinkley says. She became a CCRC as soon as she was eligible, in 1999. After attending ACRP’s 2002 conference in Toronto, she became active as a volunteer with the Canada Chapter—first with the education committee, and later as president of the chapter. Hinkley also began volunteering in ACRP-wide positions, through the Membership Committee, the Association Board of Trustees, and the Regulatory Affairs Committee, and otherwise “paying it forward” to an organization that helped her take her career to the next level.

For Hinkley, being named a Fellow is an honor that “recognizes and appreciates my long career and service to ACRP,” she says. “It means a lot.”

Deborah Rosenbaum, CCRC, CCRA, FACRP

Consultant



“I’ve had a similar career path to Janet Holwell, as a CRC, CRA, and industry trainer and subject matter expert,” says Rosenbaum. After a

successful career working in various roles at both sites and pharmaceutical companies, she hung out her consultant shingle. “I sought out ACRP and pursued the certification program in its second year of availability,” she says. She believed adding “those four letters after my name” would demonstrate her professionalism and research knowledge and distinguish her in a crowded field of consultants.

She was elected to the ACRP Association Board of Trustees from 1997 to 2001, and to the Academy Board of Trustees from 2010 to 2015, including serving as the 2014 Chair of the Academy. She has volunteered on various ACRP committees and served as the Standards Officer for the former ACRP Institute’s Educational Standards and Accreditation Committee, as well as given multiple presentations at ACRP conferences, chapter-based symposiums, and other meetings.

For Rosenbaum, joining the first class of Fellows demonstrates her commitment to excellence in the field. It distinguishes a set of individuals “who have dedicated their lives to clinical research,” she says, “and who consider it as more than just a job.”



BETTER TRAINING = BETTER RESULTS

Build competence, improve clinical trial outcomes, and stay focused on your core business with quality team training solutions from ACRP.

Leading Organizations Work with ACRP to

- Build Competence and Improve Team Performance
- Standardize Training Programs Across Organizations
- Easily and Conveniently Manage Training Delivery

Align with the leader in clinical research workforce development and boost your organization's credibility and marketability by putting our 40+ years of experience to work for you.

SOME OF OUR CLIENTS



CONTACT

Jenna Rouse
Director, Business Development
jrouse@acrpnet.org

acrpnet.org/business



On the **CRbeat**

News from the Rest of the World

ACRP's new, weekly e-newsletter—the *CRbeat*—has gotten off to a strong start since its introduction in late October 2016, highlighting the latest articles and columns from *Clinical Researcher* plus ACRP blog entries, press releases, and learning resources. Tucked away near the bottom of each issue, readers can also find links to recent mass media coverage and press releases from the world beyond ACRP about trends, insights, discoveries, and happenings in the clinical research enterprise at large.

Presented here are excerpts from some of those recent “rest of the world” news items that you may have missed.

KEEPING HEART DAMAGE FROM STALKING CHILDHOOD CANCER SURVIVORS

Imagine conquering childhood cancer, only to find out that years down the road your heart may fail. Unfortunately, many children who have battled cancer face this reality. While often lifesaving, the effects of chemotherapy treatment (drugs that kill cancer cells) can take a toll on the developing body of a child, potentially resulting in life-threatening late side effects like cardiac damage.

“You go through terrible chemotherapy, achieve remission, have a new lease on life, and then your heart fails,” said Dr. Todd Cooper, director of the Pediatric Leukemia/Lymphoma Program at Seattle Children’s. “It’s not fair, and we’re determined to change this reality.”

Cooper is leading a new nationwide clinical trial, conducted within the Children’s Oncology Group, for children and adolescents with relapsed acute myelogenous leukemia (AML) to test a drug, CPX-351, which has been designed to kill leukemia cells while minimizing damage to the heart. According to Cooper, up to 30% of patients who undergo chemotherapy for AML will have late-term side effects that affect the heart. For Cooper, that’s 30% too many.

Cooper says previous trials testing the effectiveness and efficacy of CPX-351 have shown tremendous promise in adults, and so he’s hoping to bring that same success to pediatric patients.

(Source: Newswise, www.newswise.com/articles/view/666670/?sc=mwphp)

MISINFORMATION ALL TOO COMMON IN MEDIA REPORTS ON TRIALS

When flawed clinical research is reported in the media with hype and sensationalism, it has the potential to have a devastating effect on patients, physicians, the scientific community, and eventually society as a whole.

In a review article in the journal *EMBO Reports*, the authors question how controversial and weak studies are publicized by the media and often coupled with a narrative that is either false or with little scientific basis. The blame for misleading the public, they believe, should be shouldered equally by journalists, scientists, journal editors, and research institutions.

“We believe that the collaboration between media and scientific journals in communicating advances in science and medicine to the public may result in misinformation and distortion. Unfortunately, this collaboration often exaggerates and allows bad science to be disseminated and shared. Media [are] often drawn to these controversial studies and they promote them with a narrative that is difficult to change, even if it is wrong,” explains lead author Abdulmaged M. Traish, PhD, professor of biochemistry and urology at Boston University School of Medicine.

(Source: Newswise, www.newswise.com/articles/view/666157/?sc=mwphp)



EVALUATION OF SCIENTIFIC RIGOR IN ANIMAL RESEARCH

The “reproducibility crisis” in biomedical research has led to questions about the scientific rigor in animal research, and thus the ethical justification of animal experiments. In research appearing in *PLOS Biology* and *PLOS ONE*, researchers from the University of Bern have assessed scientific rigor in animal experimentation in Switzerland. The study, commissioned by the Swiss Federal Food Safety and Veterinary Office, found widespread deficiencies in the reporting of experimental methodology.

In a first step, PhD student Lucile Vogt and post-doc Thomas Reichlin from the Division of Animal Welfare at the Vetsuisse Faculty in Bern screened all 1,277 approved applications for animal experiments in Switzerland in 2008, 2010, and 2012, as well as a random sample of 50 scientific publications resulting from studies described in the applications. The materials were assessed to determine whether seven basic methods that can help combat experimental bias were reported (including randomization, blinding, and sample size calculation). Appropriate use and understanding of these methods is a prerequisite for unbiased, scientifically valid results, says lead author Prof. Hanno Würbel, director of the Division of Animal Welfare.

Explicit evidence that these methods were used either in the applications for animal experiments or in the subsequent publications was scarce. For example, fewer than 20% of applications and publications mentioned whether a sample size calculation had been performed (8% in applications, 0% in publications), whether the animals had been assigned randomly to treatment groups (13% in applications, 17% in publications), and whether outcome assessment had been conducted blind to treatment (3% in applications, 11% in publications).

Through a separate survey, the authors found that the use of methods against bias is considerably higher than reported in the animal research applications and publications; 86% of the participants claimed to assign animals randomly to treatment groups, but only 44% answered that they had reported this in their latest publication. The same applies to the other measures, for example, for sample size calculation (69% claimed to be doing this, but only 18% say they reported it in their latest publication) and for blinded outcome assessment (47% vs. 27%).

(Source: *Newswise*, www.newswise.com/articles/view/665728/?sc=mwhp)

SEX, GENDER, OR BOTH IN MEDICAL RESEARCH

No one can deny that men and women have different genes, biology, and anatomical features. However, only a minority of medical studies take this into account when analyzing and reporting research results. Time to hold researchers accountable, argue two leading experts on sex and gender, not just for the sake of equity, but mainly for the sake of health.

Dr. Cara Tannenbaum, a professor in the Faculty of Medicine at the University of Montreal and scientific director of the Institute of Gender and Health (Canadian Institutes of Health Research), and Dr. Janine Austin Clayton, director of the Office of Research on Women’s Health at the U.S. National Institutes of Health, have in the *Journal of the American Medical Association* outlined a rationale and new reporting standards for stratifying research data by sex, gender, or both.

These Sex and Gender Equity in Research guidelines are posted on the EQUATOR website, an international network providing medical research guidelines worldwide, and address how the terms “sex” and “gender,” and what they really mean, continue to confuse scientists and the general public.

“We want to put the record straight,” affirms Tannenbaum. “A person’s sex refers to their biology (i.e., their XX or XY chromosomes, their anatomy, and their sex hormones).” Gender, however, is more complex. It encompasses social, behavioral, and cultural interactions, diverse expressions of identity, and the roles and power relations between men and women in society.

(Source: *Newswise*, www.newswise.com/articles/view/665214/?sc=mwh)



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



ready to bring your passion to patient-centered science?

A career in Clinical Trial Management:
Where research meets results

Visit www.novonordiskctmjobs.com
to learn more and apply.

The Novo Nordisk Difference

Novo Nordisk is the world leader in diabetes research, care and treatment, and our passion for helping people is at the heart of everything we do. But our ability to change lives depends on discovering and testing new treatment innovations in a safe and ethical way.

Our Clinical Trial Management team is committed to keeping the patient front and center — never losing sight of the people whose lives are directly affected by our current and future treatments. It's that sense of purpose that drives our success, and motivates clinical trial sites to request to work with Novo Nordisk again and again.

Homegrown research

While the majority of pharmaceutical companies outsource clinical trial staffing to a contract research organization (CRO), Novo Nordisk is unique in that we conduct our own research. Our team of Lead, Field and In-House Clinical Research Associates (CRAs) work together to ensure the highest standards of safety and service to our investigative sites. A low turnover rate of 5% for NNI CRAs, which is atypical in the industry, means that sites have a consistent and known contact for whatever they need.

Sponsor of choice

Our dedication to providing consistent support and fast responses to sites' needs is one of the many reasons that investigative sites have ranked Novo Nordisk among the top company sponsors of clinical trials. In fact, Novo Nordisk was ranked as the best large biopharmaceutical company to work with in the 2015 CenterWatch Global Investigative Site Relationship Survey.

Ready to bring your passion to patient-centered science?

If you're inspired by the opportunity to do meaningful research that yields promising results, Novo Nordisk is a great place to grow your career in clinical trial management.

In a 2015 survey of nearly 2,000 global investigative sites, Novo Nordisk was rated **the best biopharmaceutical company to work with.**

— CenterWatch